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- (54) **NEUROLOGICAL MONITORING AND ALERTS**
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CPC *A61N 1/37258* (2013.01); *A61B 5/4094* (2013.01); *A61N 1/00* (2013.01); *A61N 1/0529* (2013.01)

(58) **Field of Classification Search**
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See application file for complete search history.

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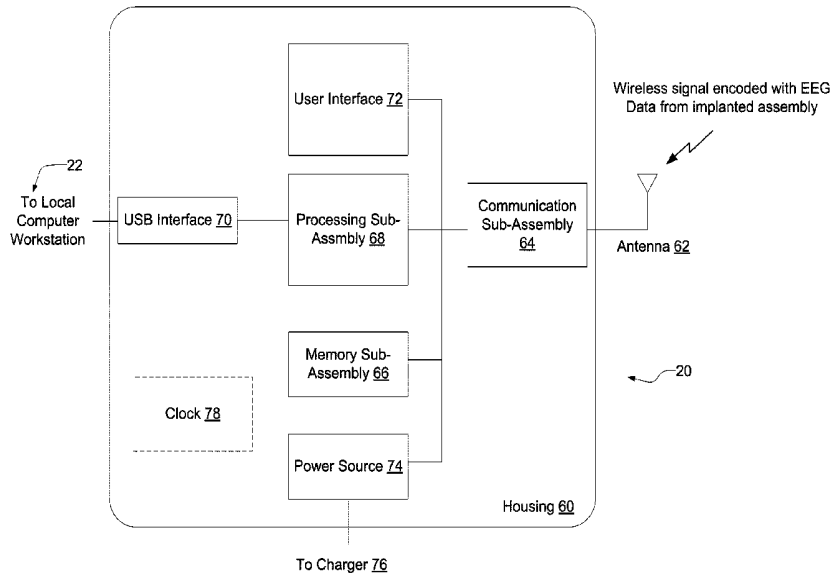
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(57) **ABSTRACT**

A system for providing alerts of neurological events occurring in a human subject is provided. The system includes: a monitoring module adapted to detect and sample a neurological signal; an event detection module coupled to the monitoring module for detecting one or more types of predetermined reportable events based on the detected neurological signal; and an alert module coupled to the event detection module, wherein upon the detection of a reportable event by the event detection module, said alert module selects a first alert contact from a plurality of contacts contained in a contact list, and generates a first alert communication to the first alert contact.

40 Claims, 20 Drawing Sheets



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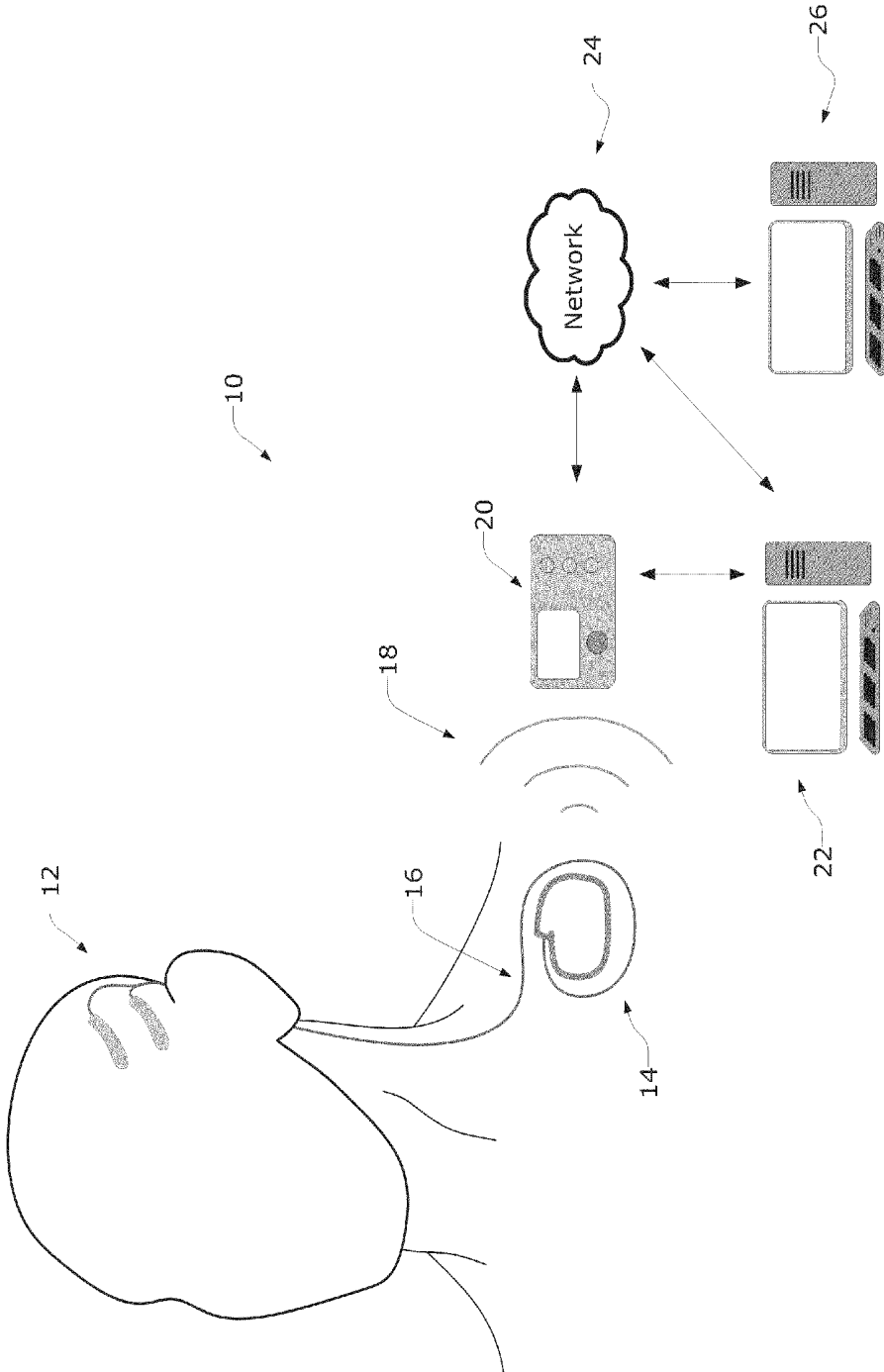


FIG. 1

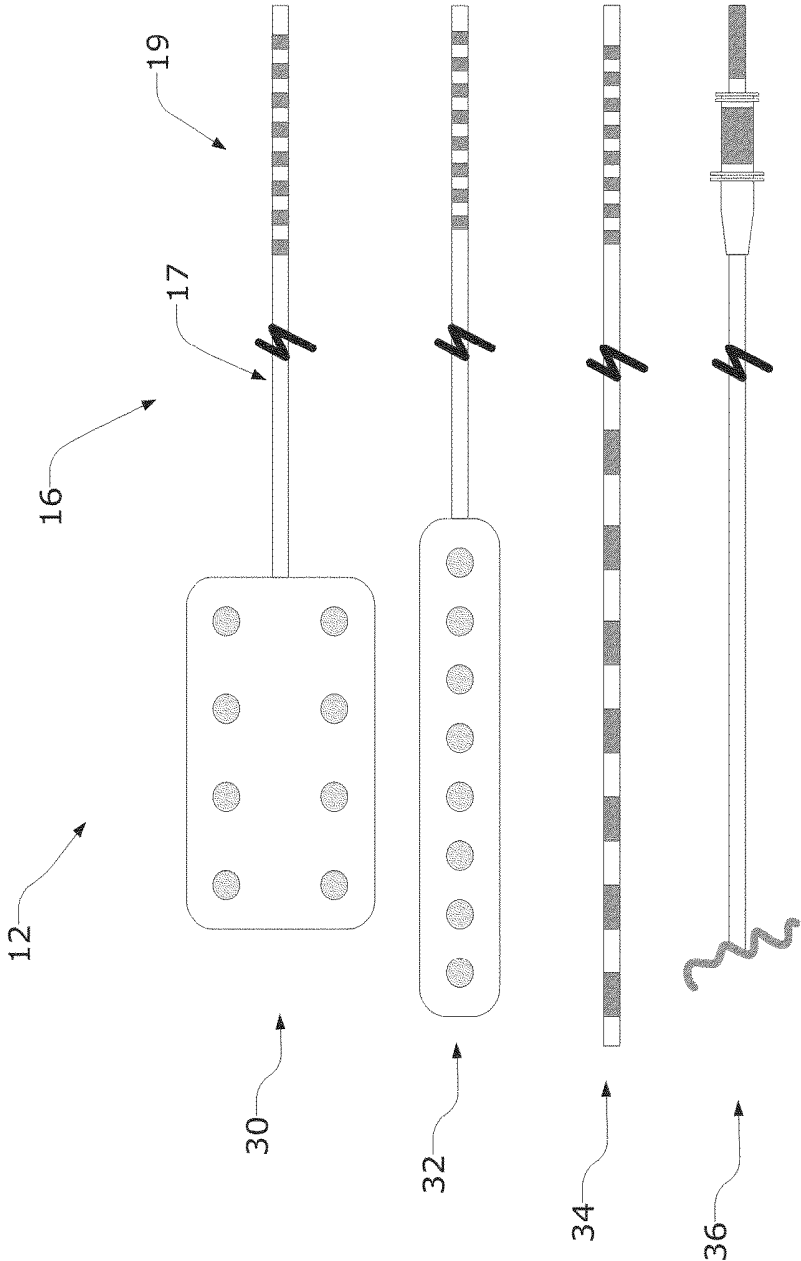


FIG. 2

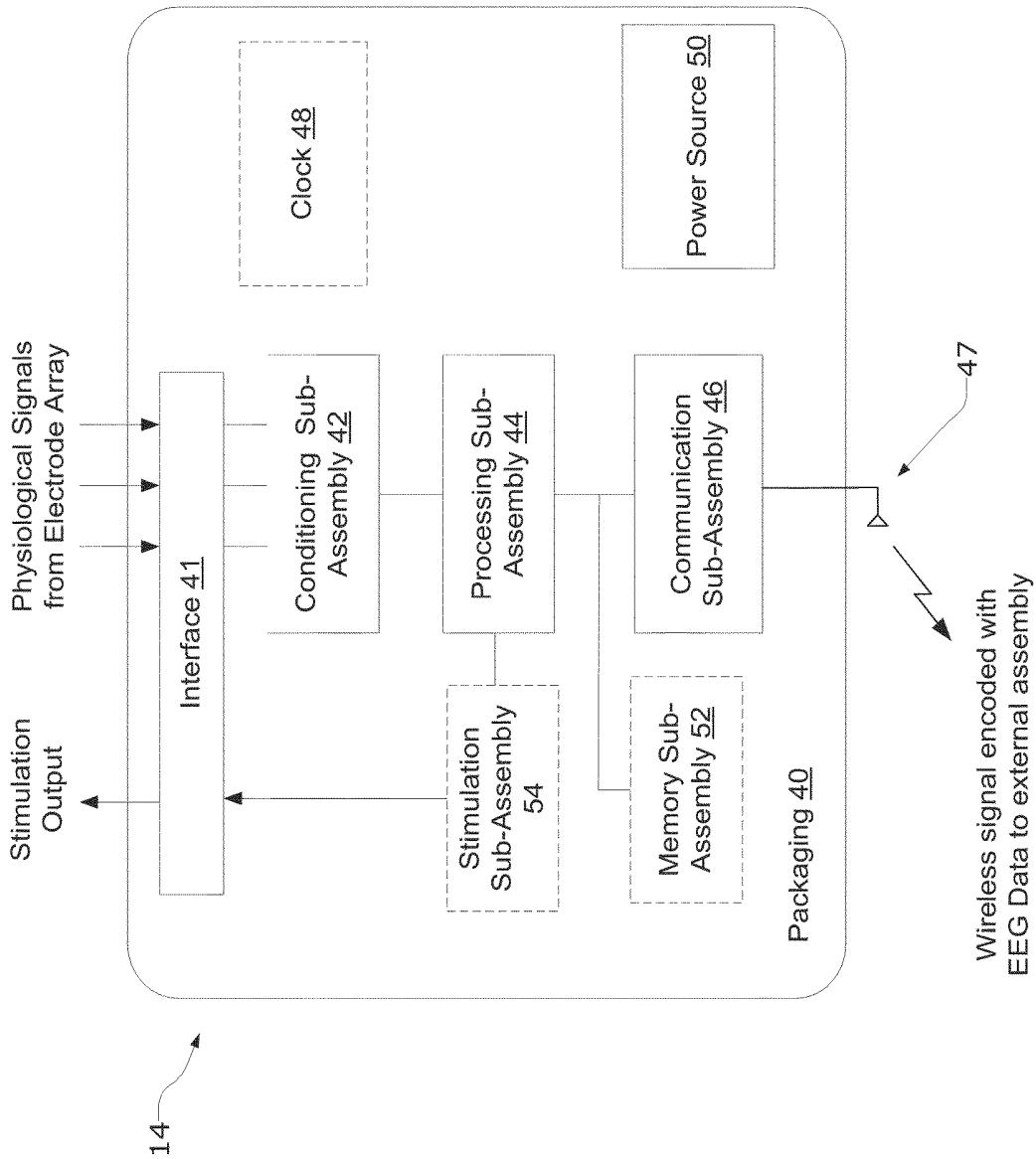


FIG. 3

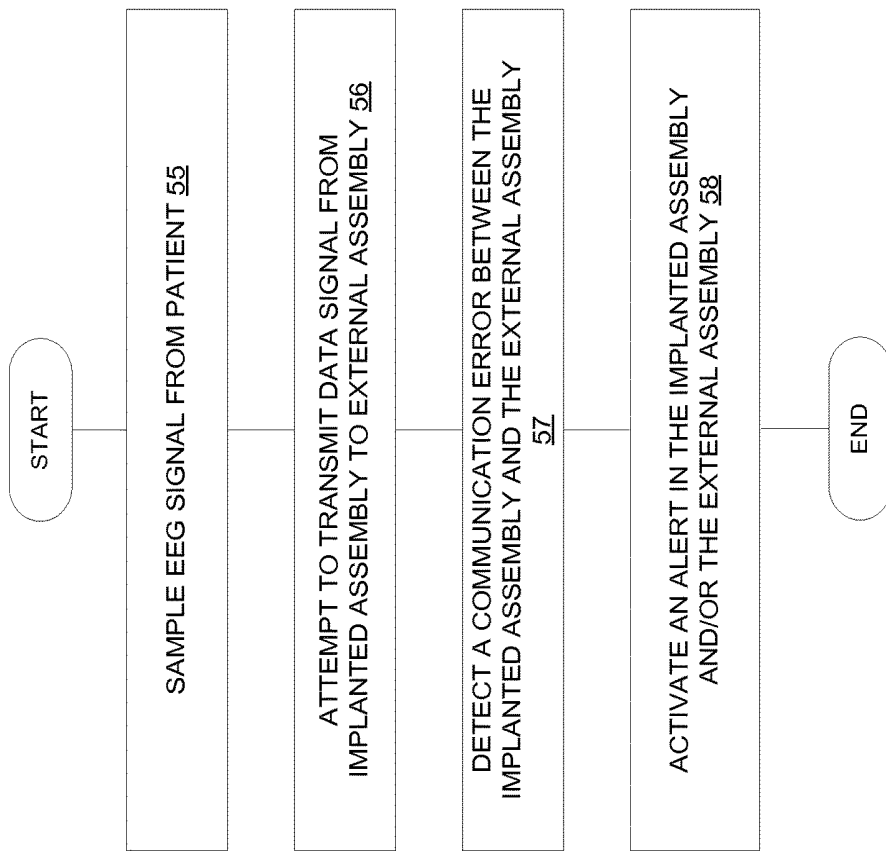


FIG. 4

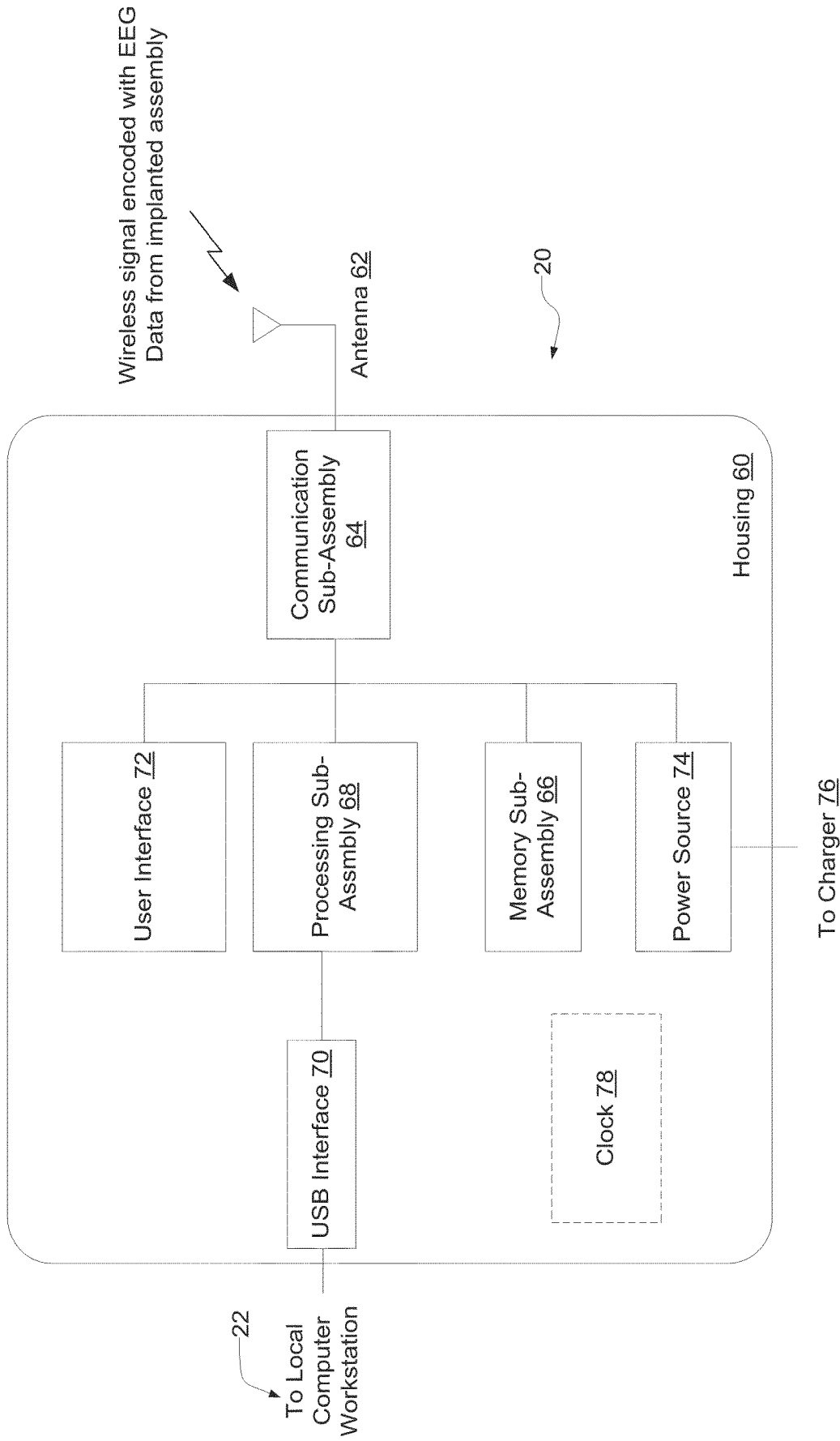


FIG. 5

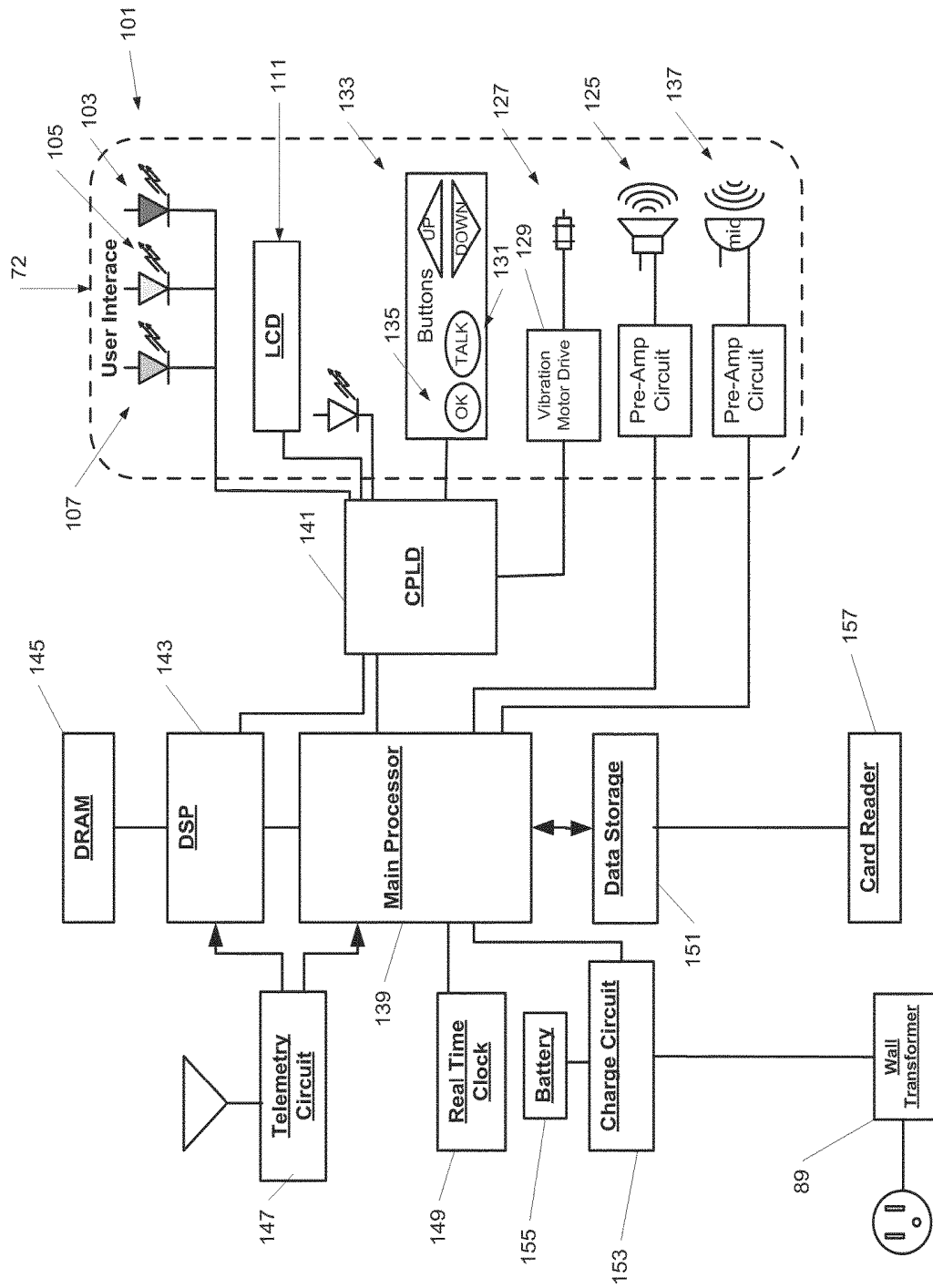


FIG. 6

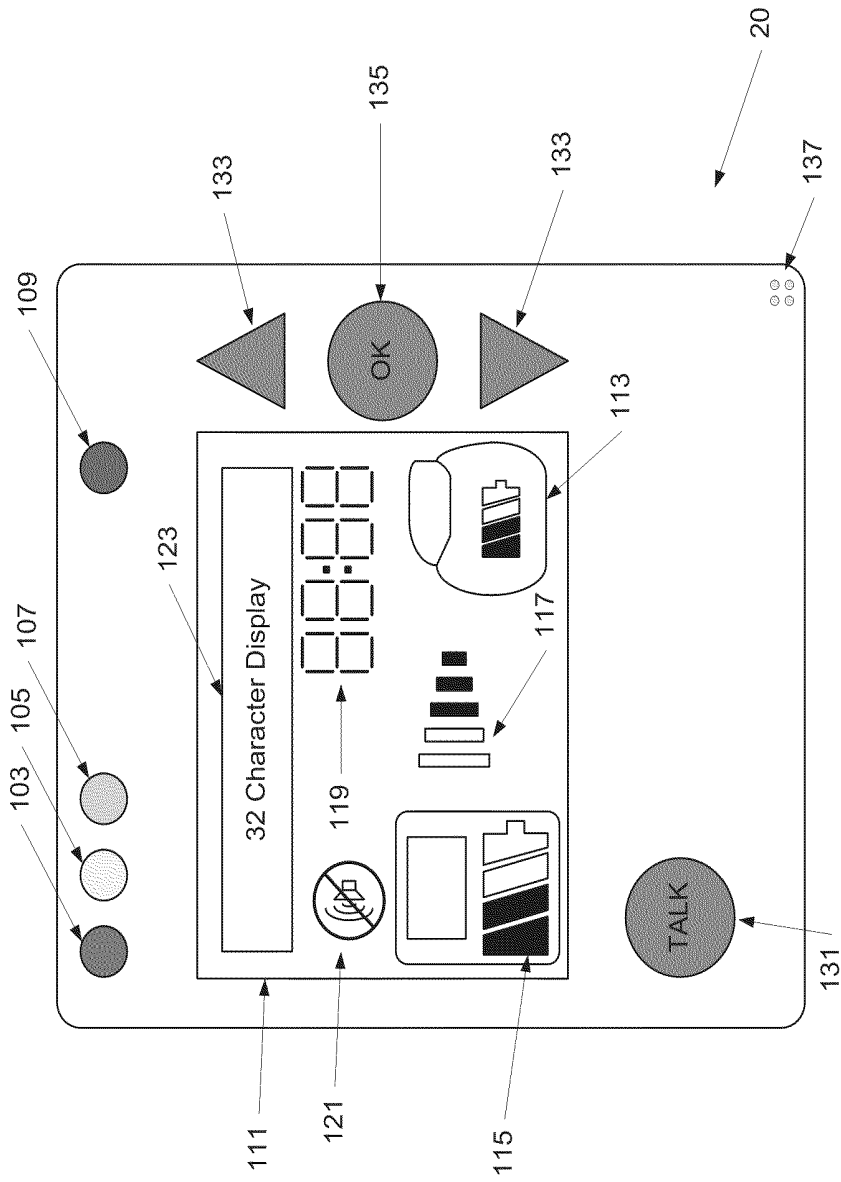
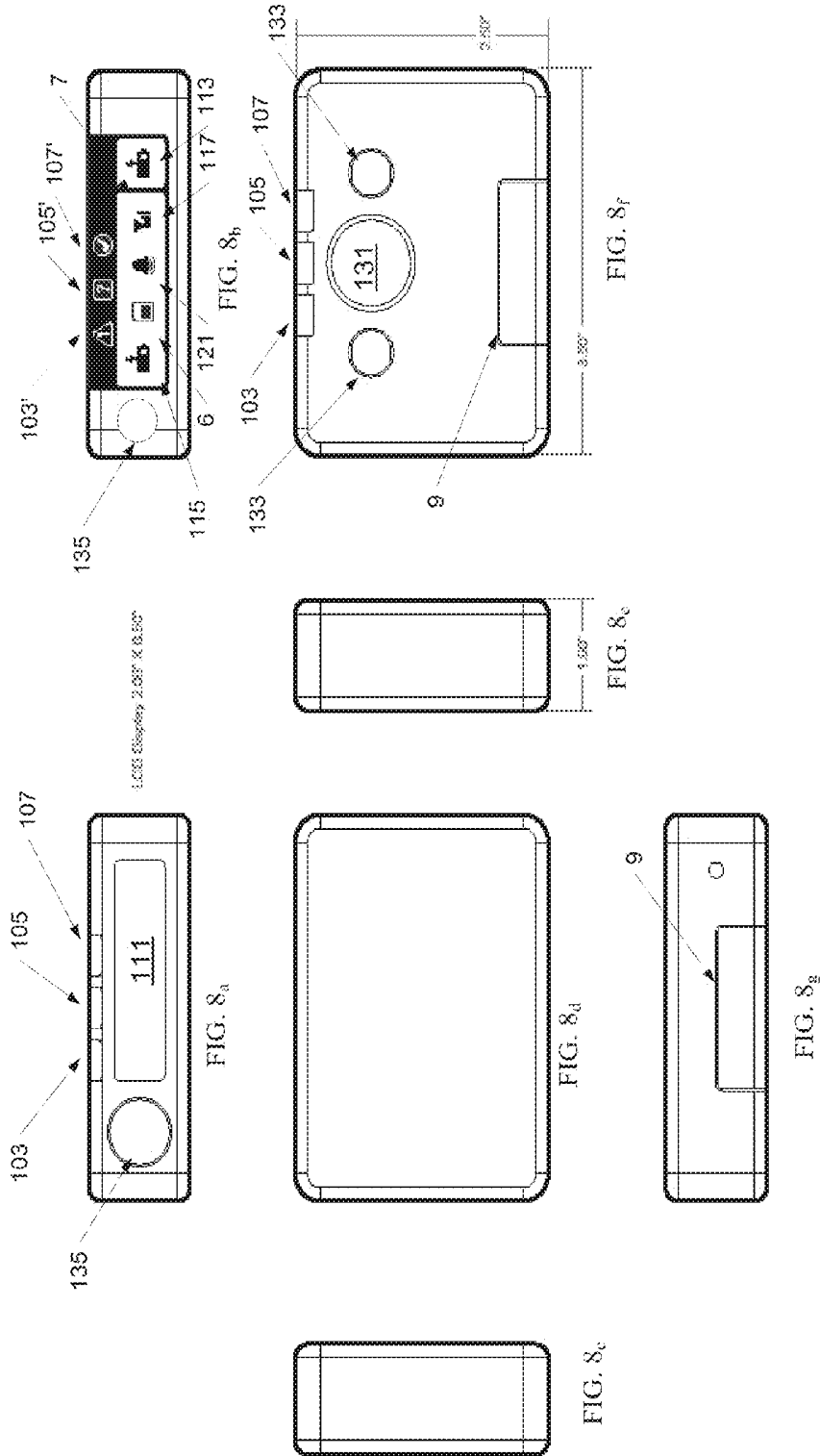


FIG. 7



FIGS. 8a - 8g

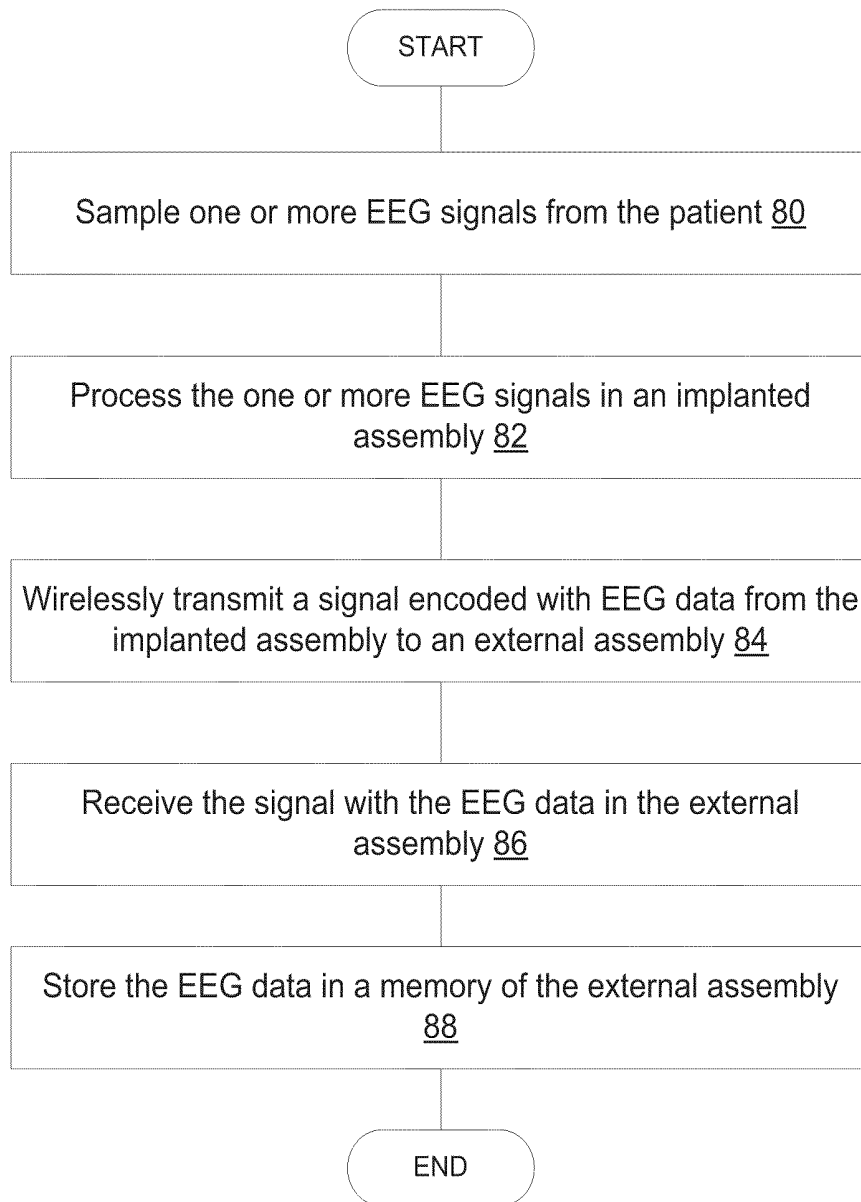


FIG. 9

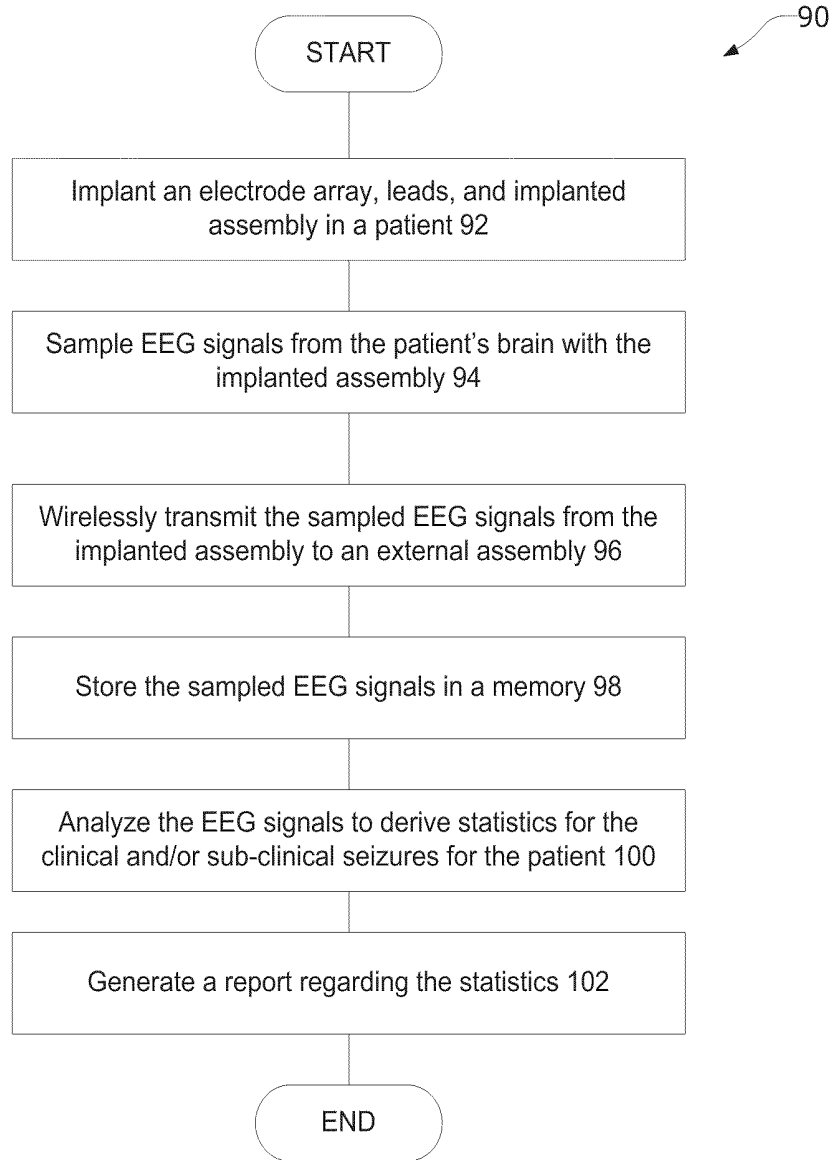


FIG. 10

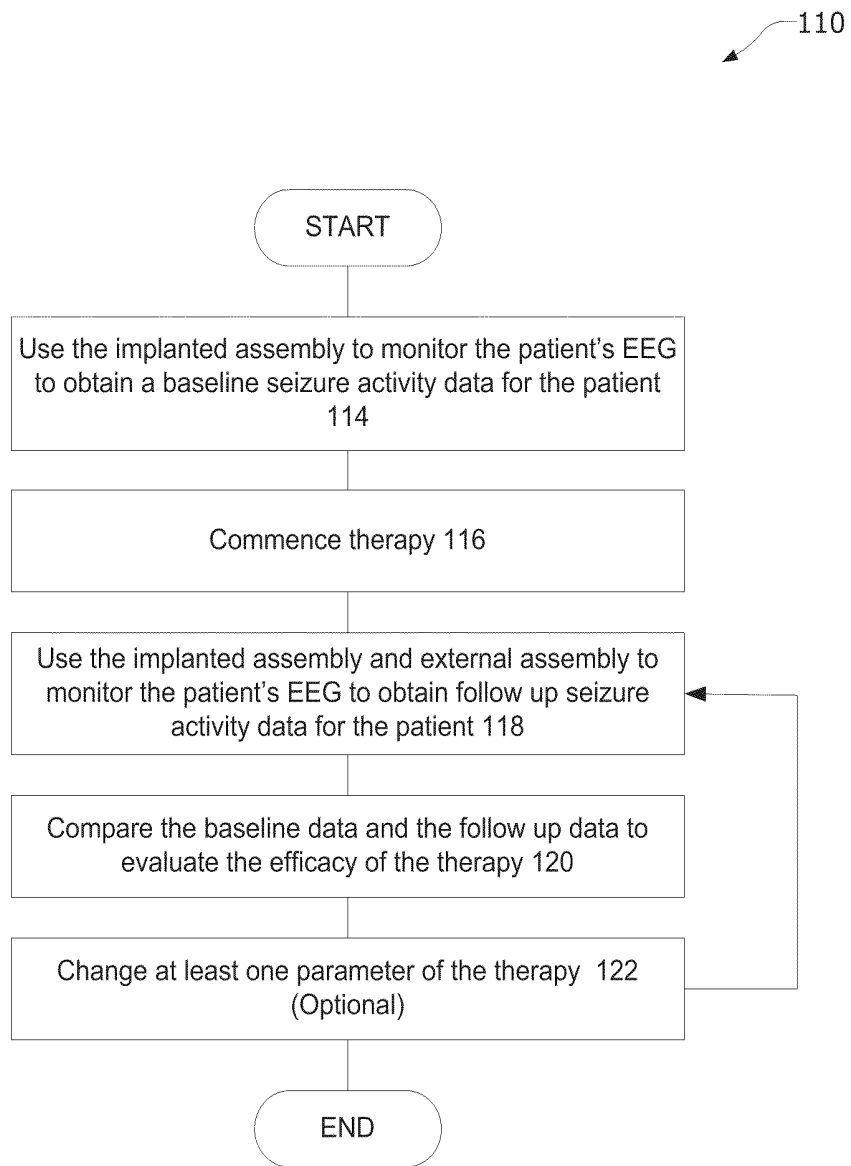


FIG. 11

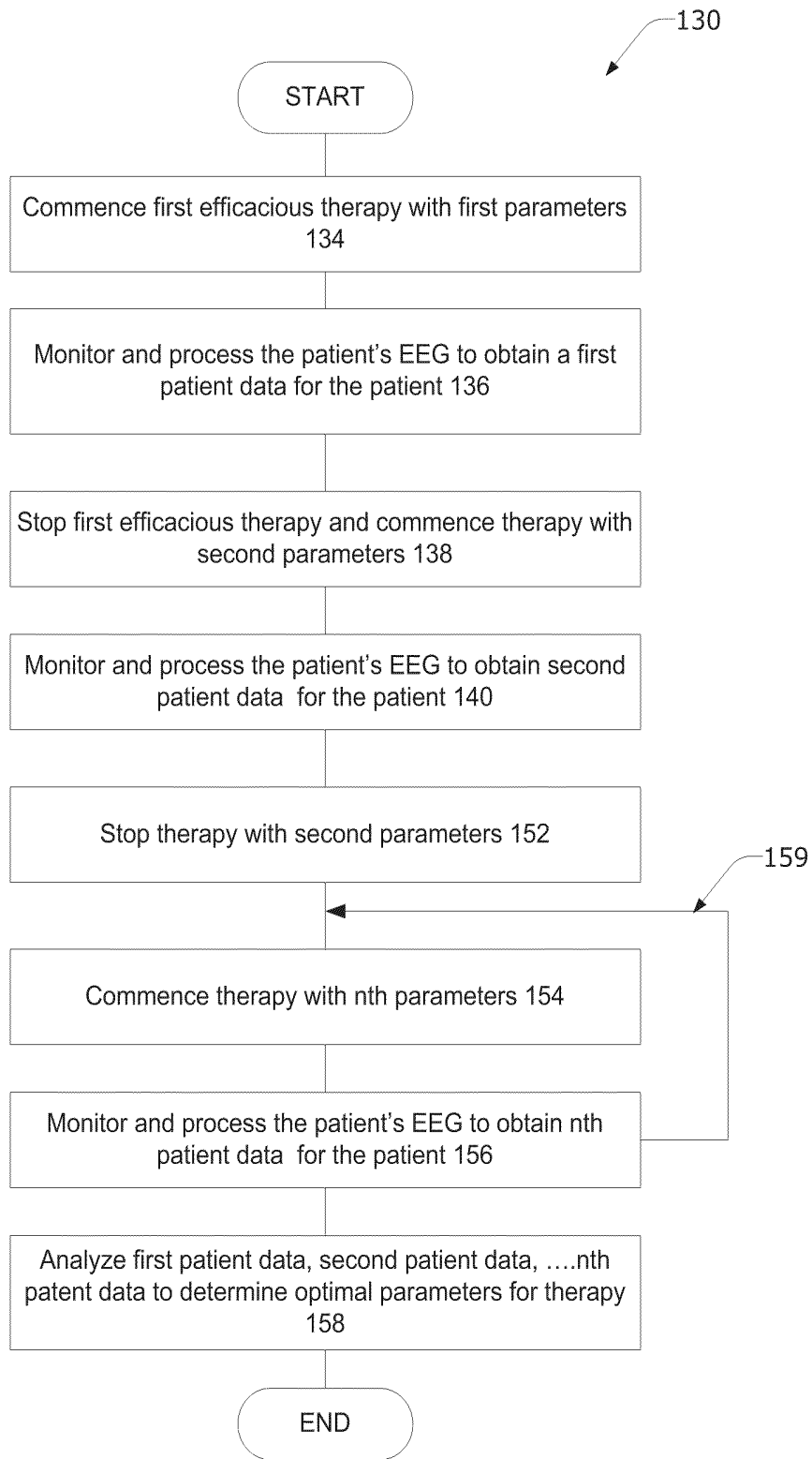


FIG. 12

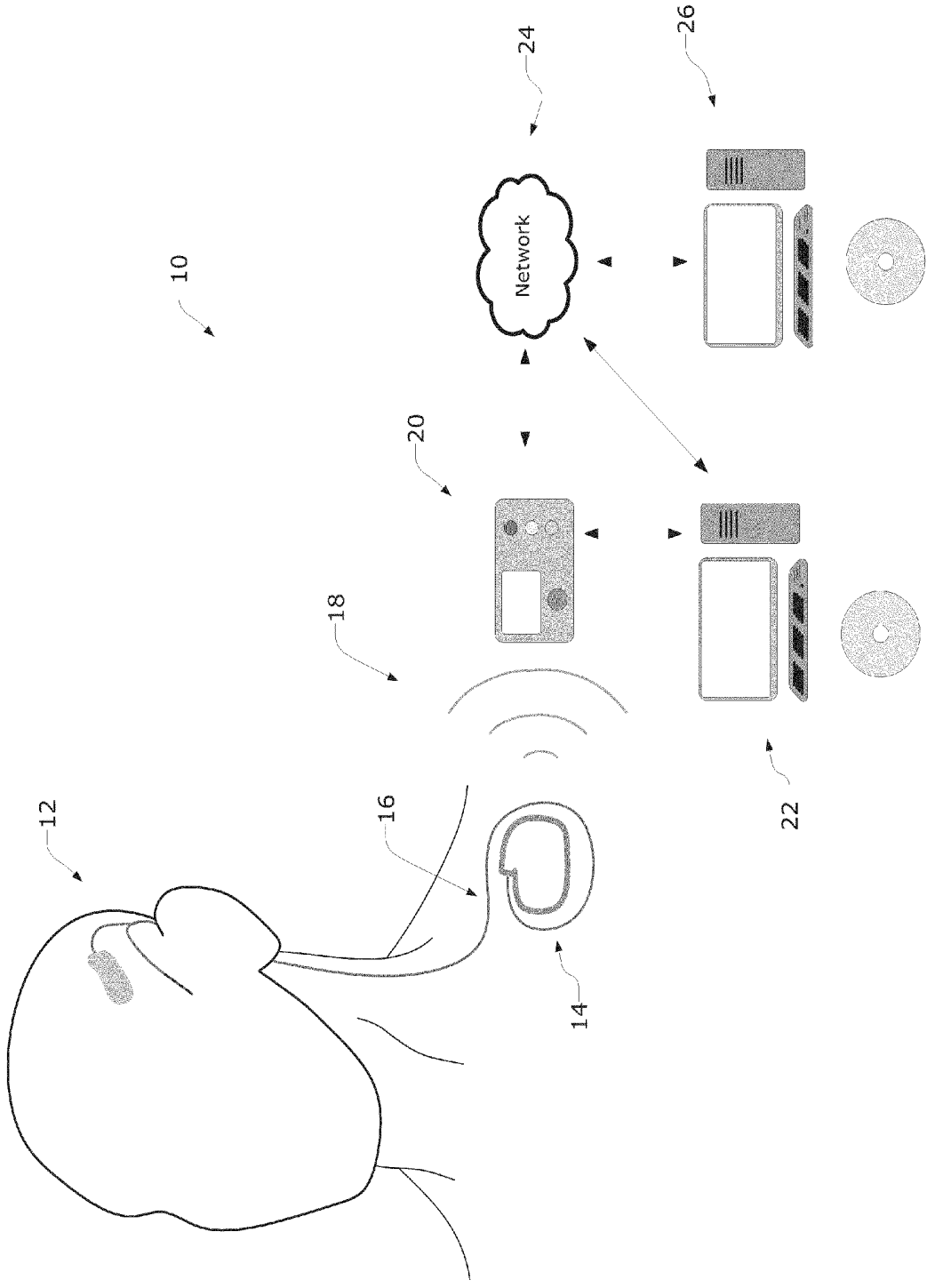


FIG. 13

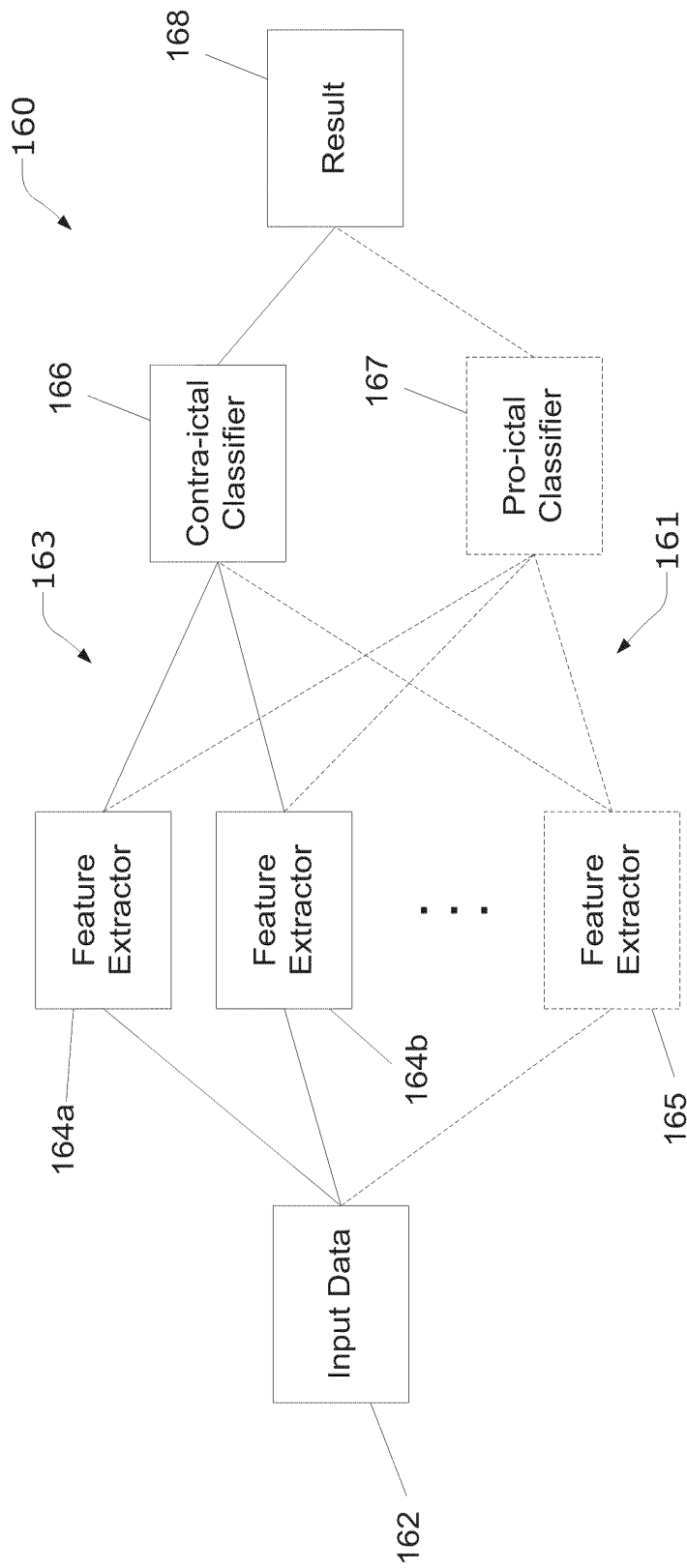
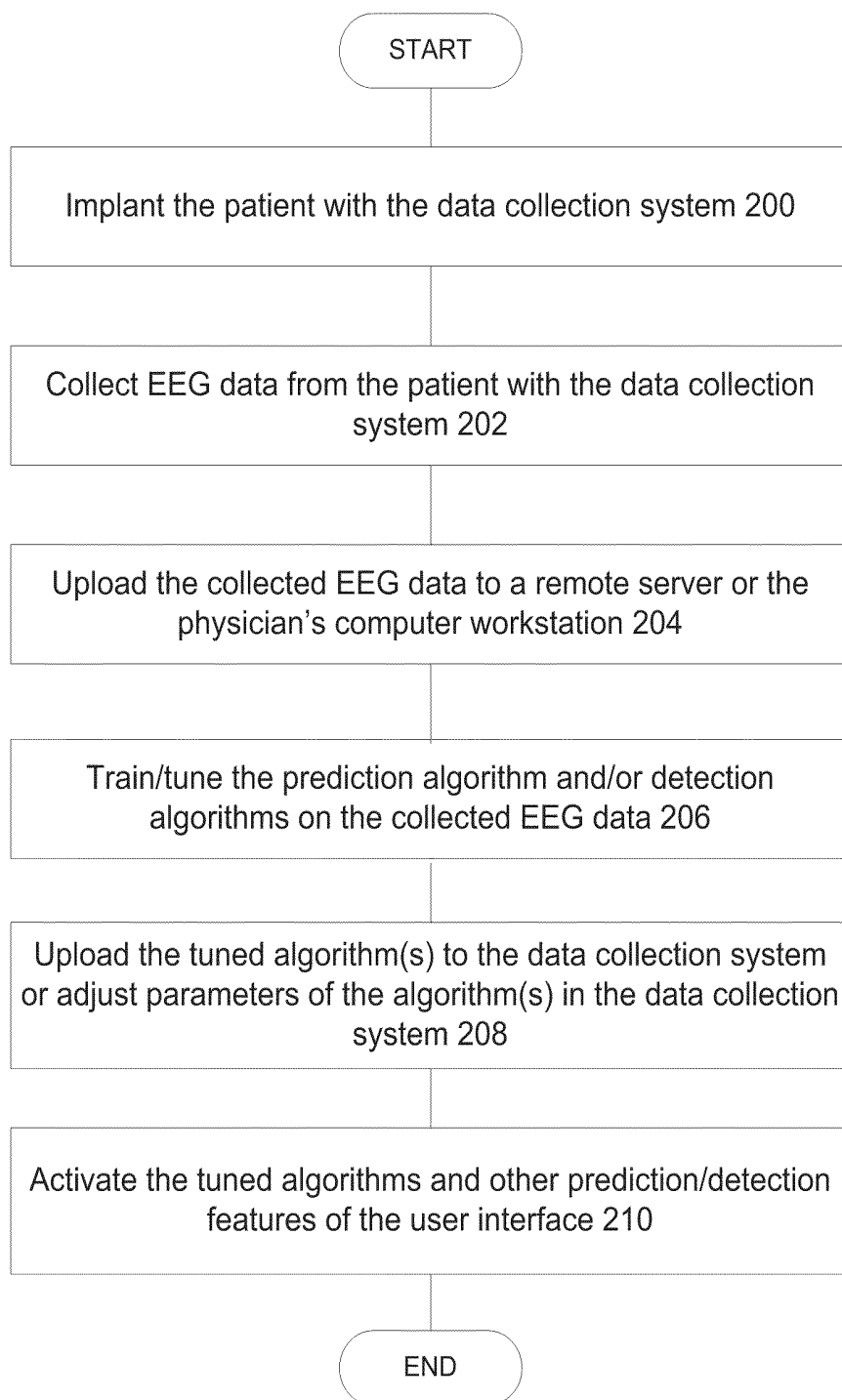


FIG. 14

**FIG. 15**

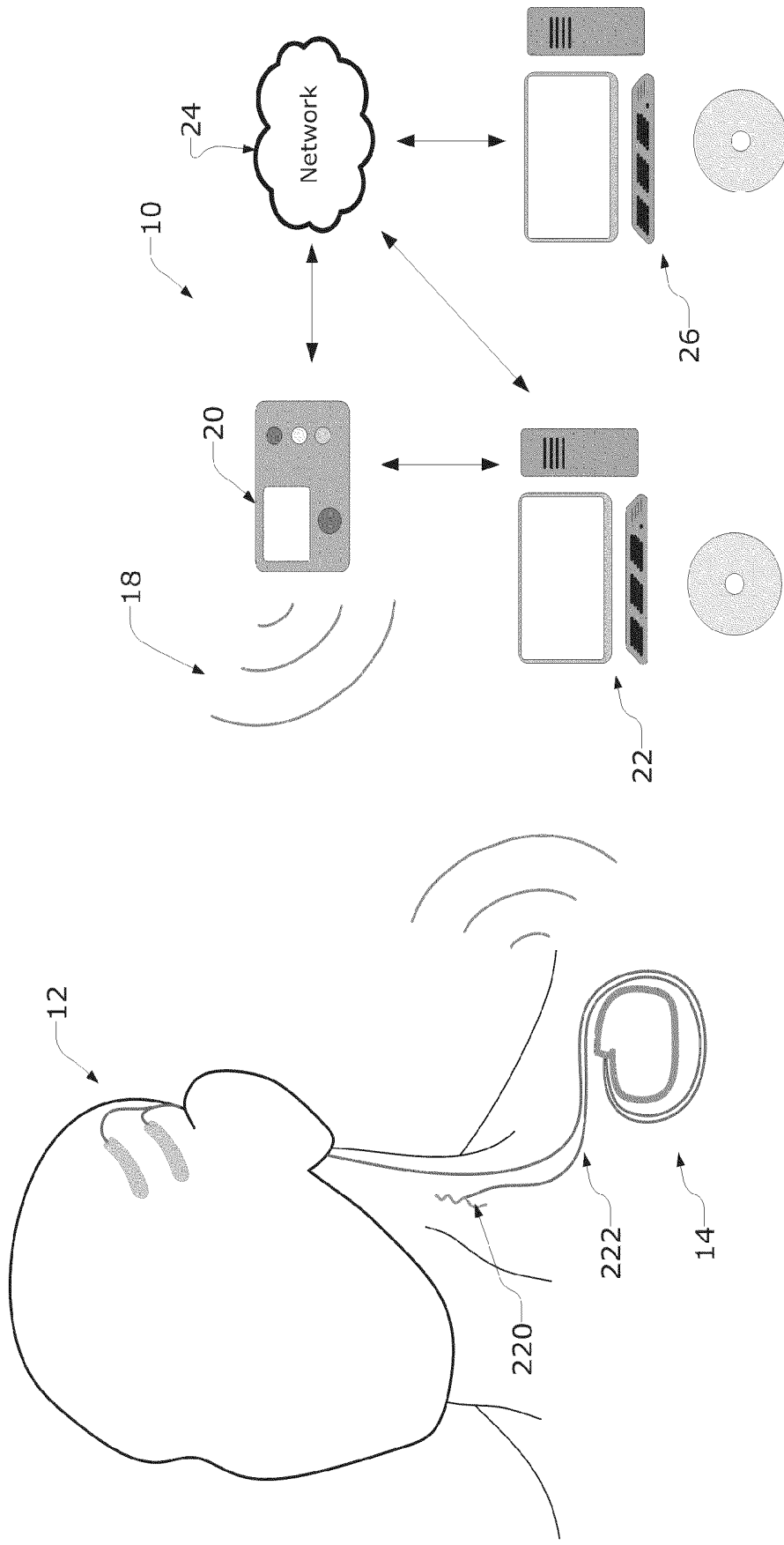


FIG. 16

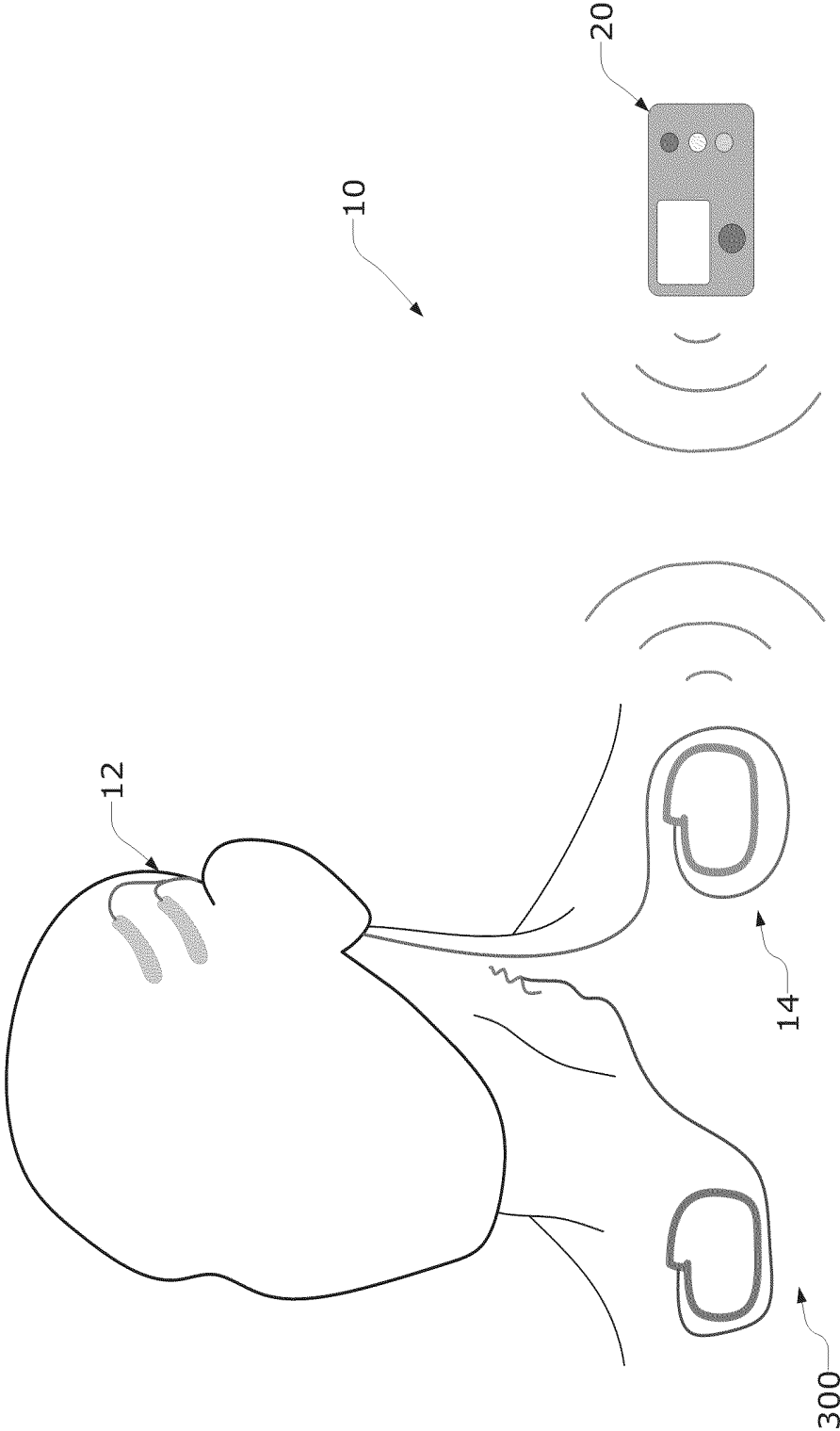


FIG. 17

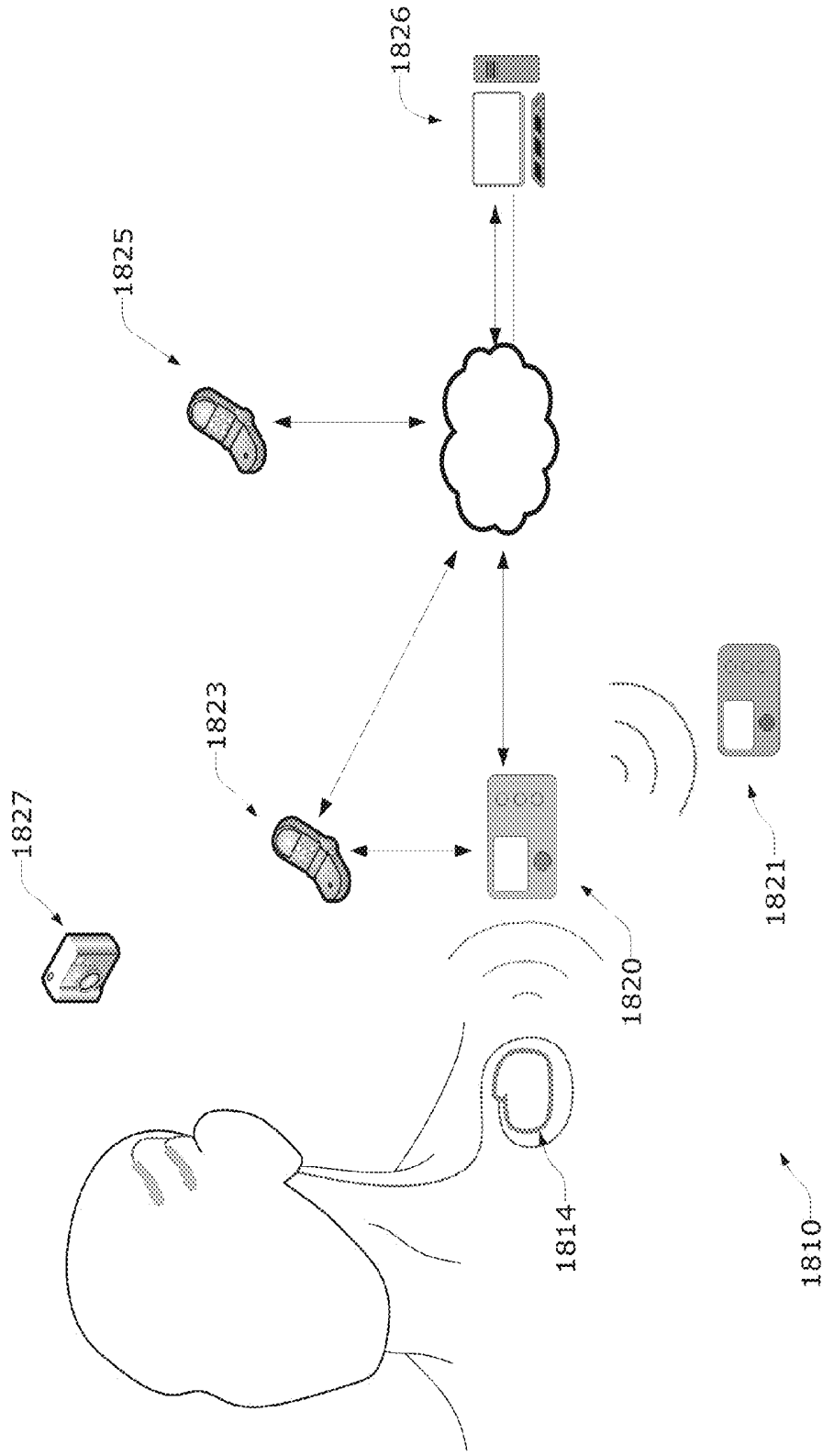


FIG. 18

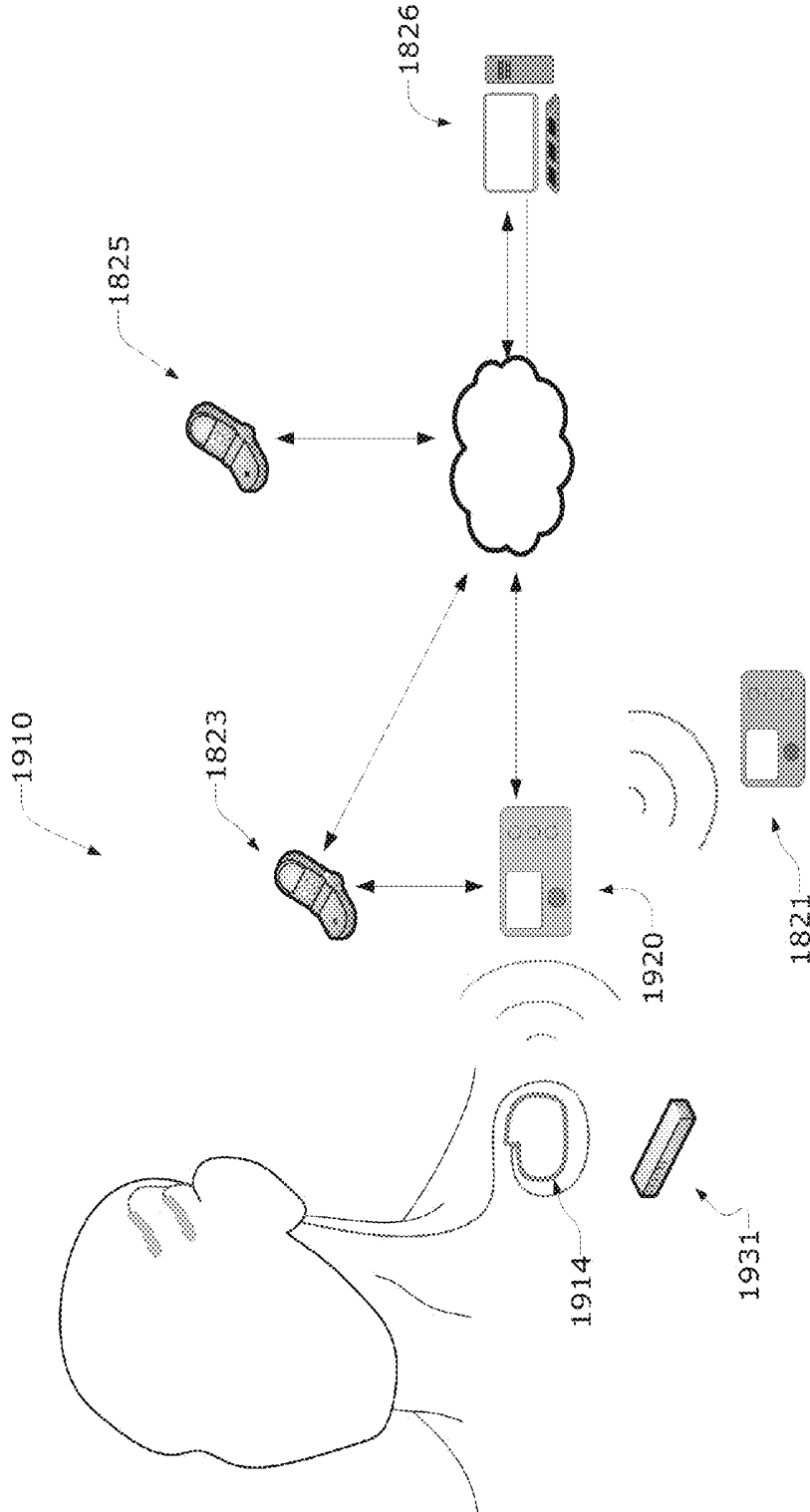


FIG. 19

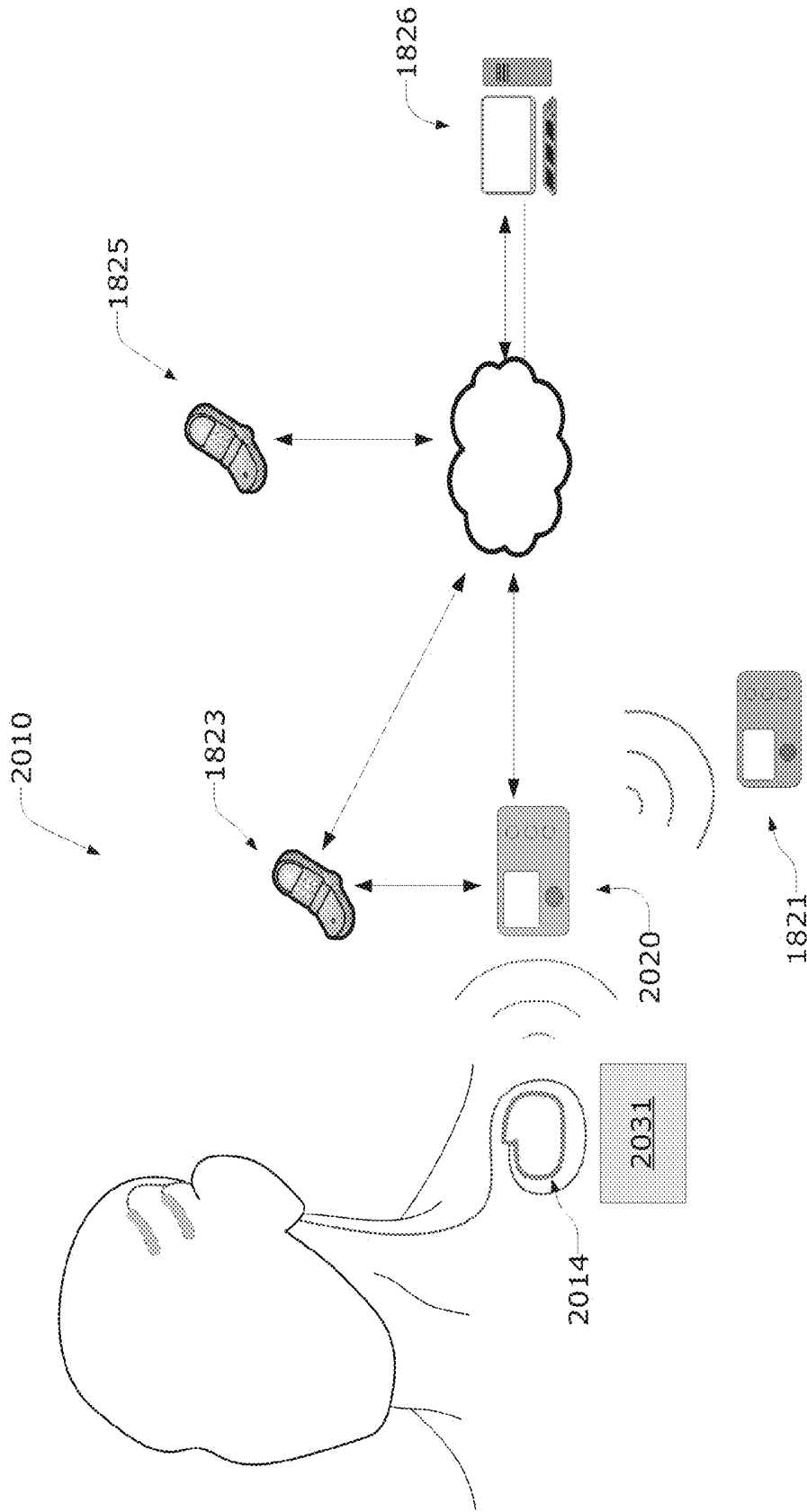


FIG. 20

NEUROLOGICAL MONITORING AND ALERTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. Provisional Patent Application No. 61/304,263, filed Feb. 12, 2010, the disclosure of which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

The present invention relates generally to systems and methods for sampling and processing one or more physiological signals from a subject. More specifically, the present invention relates to monitoring of one or more neurological signals from a subject.

Epilepsy is a neurological 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 attention, loss of consciousness, and voiding of urine or stool.

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 subjects. 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.

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), stroke, or from neoplastic, vascular or developmental abnormalities of the brain. Approximately 70% of epileptic subjects, 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.

Demographic studies have estimated the prevalence of epilepsy at approximately 1% of the population, or approximately 2.5 million individuals in the United States alone. In order to assess possible causes and to guide treatment, epileptologists (both neurologists and neurosurgeons) typically evaluate subjects with seizures with brain wave electrical analysis and imaging studies, such as magnetic resonance imaging (MRI).

While there is no known cure for epilepsy, chronic usage of anticonvulsant and antiepileptic medications can control seizures in most people. For most cases of epilepsy, the disease is chronic and requires chronic medications for treatment. The anticonvulsant and antiepileptic medications do not actually correct the underlying conditions that cause seizures. Instead, the anticonvulsant and antiepileptic medi-

cations manage the subject's epilepsy by reducing the frequency of seizures. There are a variety of classes of anti-epileptic drugs (AEDs), each acting by a distinct mechanism or set of mechanisms.

AEDs generally suppress neural activity by a variety of mechanisms, including altering the activity of cell membrane ion channels and the susceptibility of action potentials or bursts of action potentials to be generated. These desired therapeutic effects are often accompanied by the undesired side effect of sedation, nausea, dizziness, etc. Some of the fast acting AEDs, such as benzodiazepine, are also primarily used as sedatives. Other medications have significant non-neurological side effects, such as gingival hyperplasia, a cosmetically undesirable overgrowth of the gums, and/or a thickening of the skull, as occurs with phenytoin. Furthermore, some AED are inappropriate for women of child bearing age due to the potential for causing severe birth defects.

An estimated 70% of subjects will respond favorably to their first AED monotherapy and no further medications will be required. However, for the remaining 30% of the subjects, 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 subject's seizures. For those that fail the second AED, a third AED will be tried, and so on. Subjects who fail to gain control of their seizures through the use of AEDs are commonly referred to as “medically refractory.” This creates a scenario in which 750,000 subjects or more in the United States have uncontrolled epilepsy. These medically refractory subjects account for 80% of the \$12.5 billion in indirect and direct costs that are attributable to epilepsy in the United States.

A major challenge for physicians treating epileptic subjects 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 subject or for the subject's caregiver to keep a diary of seizure activity. However, it is well recognized that such self-reporting is often of poor quality because subjects often do not realize when they have had a seizure, or fail to accurately record seizures.

If a subject is refractory to treatment with chronic usage of medications, surgical treatment options may be considered. If an identifiable seizure focus is found in an accessible region of the brain, which does not involve “eloquent cortex” or other critical regions of the brain, then resection is considered. If no focus is identifiable, there are multiple foci, or the foci are in surgically inaccessible regions or involve eloquent cortex, then surgery is less likely to be successful or may not be indicated. Surgery is effective in more than half of the cases in which it is indicated, but it is not without risk and is irreversible. Because of the inherent surgical risks and the potentially significant neurological sequelae from respective procedures, many subjects or their parents decline this therapeutic modality.

Some non-respective functional procedures, such as corpus callosotomy and subpial transection, sever white matter pathways without removing tissue. The objective of these surgical procedures is to interrupt pathways that mediate spread of seizure activity. These functional disconnection procedures can also be quite invasive and may be less effective than resection.

An alternative treatment for epilepsy that has demonstrated some utility is open loop Vagus Nerve Stimulation (VNS). This is a reversible procedure which introduces an electronic device which employs a pulse generator and an

electrode to alter neural activity. The vagus nerve is a major nerve pathway that emanates from the brainstem and passes through the neck to control visceral function in the thorax and abdomen. VNS uses open looped, intermittent stimulation of the left vagus nerve in the neck in an attempt to reduce the frequency and intensity of seizures. See Fisher et al., "Reassessment: Vagus nerve stimulation for epilepsy, A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology," *Neurology* 1999; 53:666-669. While not highly effective, it has been estimated that VNS reduces seizures by an average of approximately 30-50% in about 30-50% of subjects who are implanted with the device. Unfortunately, a vast majority of the subjects who are outfitted with the Cyberonics® VNS device still suffer from un-forewarned seizures and many subjects obtain no benefit whatsoever.

Another alternative electrical stimulation therapy for the treatment of epilepsy is deep brain stimulation (DBS). Open-loop deep brain stimulation has been attempted at several anatomical target sites, including the anterior nucleus of the thalamus, the centromedian nucleus of the thalamus, and the hippocampus. The results have shown some potential to reduce seizure frequency, but the efficacy leaves much room for improvement.

Another type of electrical stimulation therapy for the treatment epilepsy has been proposed by NeuroPace, Inc., in which an implanted device is designed to detect abnormal electrical activity in the brain and respond by delivering electrical stimulation to the brain.

There have also been a number of proposals described in the patent literature regarding the use of predictive algorithms that purportedly can predict the onset of a seizure. When the predictive algorithm predicts the onset of a seizure, some type of warning is provided to the subject regarding the oncoming seizure or some sort of therapy is initiated. For example, see U.S. Pat. No. 3,863,625 to Viglione et al., U.S. Pat. No. 5,995,868 to Dorfmeister et al., and U.S. Pat. No. 6,658,287 to Litt et al., which describe a variety of proposed seizure prediction systems.

SUMMARY

Systems for providing alerts of neurological events occurring in a human subject are provided. The systems include: a monitoring module adapted to detect and sample a neurological signal; an event detection module coupled to the monitoring module for detecting one or more types of predetermined reportable events based on the detected neurological signal; and an alert module coupled to the event detection module, wherein upon the detection of a reportable event by the event detection module, said alert module selects a first alert contact from a plurality of contacts contained in a contact list, and generates a first alert communication to the first alert contact.

Methods for providing alerts of neurological events occurring in a human subject are provided. The methods comprise: detecting a neurological signal from an ambulatory subject; detecting one or more types of predetermined reportable events based on the detected neurological signal; and upon the detection of a reportable event, selecting a first alert contact from a plurality of contacts contained in a contact list, and generating a first alert communication to the first alert contact.

Systems for providing alerts of neurological events occurring in a human subject are described. The systems include: a monitoring module adapted to detect a neurological signal; an event detection module for detecting one or more types

of predetermined reportable events based on the detected neurological signal; and an alert module coupled to the event detection module, said alert module containing a plurality of predetermined alert types, each alert type being associated with one or more of the predetermined reportable event types; wherein upon the detection of a reportable event by the event detection module, said alert module selects a first alert type from the plurality of predetermined alert types, said first alert type being associated with the type of detected reportable event, and said alert module generates an alert communication of the first alert type to an alert recipient.

Methods for providing alerts of neurological events occurring in a human subject are described. The methods include: monitoring a neurological signal using an implanted device; analyzing the neurological signal to detect one or more types of predetermined reportable events; and upon the detection of a reportable event, selecting a first alert contact from a plurality of contacts contained in a contact list and transmitting a first alert communication to the first alert contact.

BRIEF DESCRIPTION OF THE DRAWINGS

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:

FIG. 1 illustrates one embodiment of a monitoring or data collection system which comprises one or more intracranial electrodes in communication with an external assembly through an implanted assembly.

FIG. 2 illustrates examples of electrode arrays that may be used with the system of FIG. 1.

FIG. 3 is a simplified illustration of an implanted assembly that may be used with the system of FIG. 1.

FIG. 4 is a simplified illustration of a method of alerting a subject of a communication error between the implanted assembly and external assembly

FIG. 5 is a simplified illustration of an external assembly that may be used with the system of FIG. 1.

FIG. 6 is an alternative illustration of an external assembly that may be used with the system.

FIG. 7 illustrates an exemplary user interface including outputs of an exemplary external assembly that may be used with the system.

FIG. 8 illustrates an exemplary external assembly that may be used with the system.

FIG. 9 is a simplified flow chart that illustrates one method of storing EEG data.

FIG. 10 illustrates a method of measuring seizure activity data for clinical and/or sub-clinical seizures.

FIG. 11 illustrates a method of evaluating efficacy of a therapy.

FIG. 12 illustrates a method of titrating an efficacious therapy.

FIG. 13 illustrates one embodiment of a simplified seizure advisory system which comprises an array of epidural or subdural electrodes and an array of depth electrodes in communication with an external assembly through an implanted assembly.

FIG. 14 schematically illustrates a plurality of algorithms that may be embodied by the present invention.

FIG. 15 illustrates a method of using a seizure advisory system.

FIG. 16 illustrates another variation to the system of FIG. 6 which includes a pulse generator that is coupled to a vagus nerve electrode array.

FIG. 17 illustrates a separate vagus nerve stimulator that is used in conjunction with a seizure advisory system.

FIG. 18 illustrates an embodiment of a system that provides alerts of neurological events.

FIG. 19 illustrates an embodiment of a system that incorporates a drug delivery device that can be triggered to deliver a medication upon detection of a certain event or sequence of events.

FIG. 20 illustrates an embodiment of a system that includes a transdermal drug delivery patch that may be activated by the system upon detection of a certain event or sequence of events.

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 subject’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 a categorical approximation of a point (or group of points) along a single or multi-variable state space continuum of the subject’s condition. The estimation of the subject’s state does not necessarily constitute a complete or comprehensive accounting of the subject’s total situation. As used in the context of the present invention, state typically refers to the subject’s state within their neurological condition. For example, for a subject suffering from an epilepsy condition, at any point in time the subject may be in a different states along the continuum, such as an ictal state (a state in which a neurological event, such as a seizure, is occurring), a pro-ictal state (a state in which the subject has an increased risk of transitioning to the ictal state), an inter-ictal state (a state in between ictal states), a contra-ictal state (a state in which the subject has a low risk of transitioning to the ictal state within a calculated or predetermined time period), or the like. A pro-ictal state may transition to either an ictal or inter-ictal state.

The estimation and characterization of “state” may be based on one or more subject dependent parameters from the a portion of the subject’s body, such as electrical signals from the brain, including but not limited to electroencephalogram signals and electrocorticogram signals “ECoG” or intracranial EEG (referred to herein collectively as EEG); brain temperature, blood flow in the brain, concentration of AEDs in the brain or blood, changes thereof, etc.). While parameters that are extracted from brain-based signals are preferred, the present invention may also extract parameters

from other portions of the body, such as the heart rate, respiratory rate, blood pressure, chemical concentrations, etc.

An “event” is used herein to refer to a specific event in the subject’s condition. Examples of such events include transition from one state to another state, e.g., an electrographic onset of seizure; end of seizure, or the like. For conditions other than epilepsy, the event could be an onset of a migraine headache, onset of a depressive episode, a tremor, or the like.

The occurrence of a seizure may be referred to as a number of different things. For example, when a seizure occurs, the subject is considered to have exited a “pro-ictal state” and has transitioned into the “ictal state”. However, the electrographic onset of the seizure (one event and/or the clinical onset of the seizure (another event) have also occurred during the transition of states.

A subject’s “susceptibility” for a seizure is a measure of the likelihood of transitioning into the ictal state. The subject’s susceptibility for seizure may be estimated by determining which “state” the subject is currently in. As noted above, the subject is deemed to have an increased susceptibility for transitioning into the ictal state (e.g., have a seizure) when the subject is determined to be in a pro-ictal state. Likewise, the subject may be deemed to have a low susceptibility for transitioning into the ictal state when it is determined that the subject is in a contra-ictal state.

While the discussion below focuses on measuring electrical signals generated by electrodes placed near, on, or within the brain or nervous system (EEG signals) of subjects and subject populations for the determination of a subject’s susceptibility for having a seizure, it should be appreciated that the invention is not limited to measuring EEG signals or to determining the subject’s susceptibility for having a seizure. For example, the invention could also be used in systems that measure one or more of a blood pressure, blood oxygenation indicator e.g. via pulse oximetry, temperature of the brain or of portions of the subject, blood flow measurements, ECG/EKG, heart rate signals, respiratory signals, chemical concentrations of neurotransmitters, chemical concentrations of medications, pH in the blood, or other physiological or biochemical parameters of a subject in addition to or instead of monitoring EEG signals.

Furthermore, while much of the discussion herein focuses on systems and method for measuring a subject’s susceptibility for having a seizure or detecting seizures as they occur, embodiments of the present invention may also be applicable to monitoring other neurological or psychiatric disorders and determining the susceptibility for such disorders. For example, embodiments of the present invention may also be applicable to monitoring and management of sleep apnea, Parkinson’s disease, essential tremor, Alzheimer’s disease, migraine headaches, depression, eating disorders, cardiac arrhythmias, bipolar spectrum disorders, or the like. Embodiments of the present invention may also be applicable to non-medical monitoring and management of events such as storms, earthquakes, social unrest, or other episodic events from which identification of a low susceptibility state may be useful. As can be appreciated, the features extracted from the signals and used by the algorithms will be specific to the underlying disorder that is being managed. While certain features may be relevant to epilepsy, such features may or may not be relevant to the state measurement for other disorders.

Embodiments of the methods and systems of the present invention can be used for long-term, ambulatory sampling and analysis of one or more physiological signals, such as a subject’s brain activity (e.g., EEG). In some embodiments,

the systems and methods incorporate brain activity analysis algorithms that extract one or more features from the brain activity signals (and/or other physiological signals) and classifies, or otherwise processes, such features to determining the subject's susceptibility for having a seizure.

Some systems may also be used to facilitate delivery of a therapy to the subject to prevent the onset of a seizure and/or abort or mitigate a seizure. Facilitating the delivery of the therapy may be carried out by outputting a warning or instructions to the subject or automatically initiating delivery of the therapy to the subject (e.g., pharmacological, electrical stimulation, focal cooling, etc.). The therapy may be delivered to the subject using an implanted assembly that is used to collect the ambulatory signals, or it may be delivered to the subject through a different implanted or external assembly.

A description of some systems that may be used to monitor and/or deliver a therapy to the subject are described in the following commonly-owned patents and patent applications: U.S. Pat. No. 6,366,813 (issued Apr. 2, 2002); U.S. Pat. No. 6,819,956, (issued Nov. 16, 2004); U.S. Pat. No. 7,209,787 (issued Apr. 24, 2007); U.S. Pat. No. 7,242,984 (issued Jul. 10, 2007); U.S. Pat. No. 7,277,758 (issued Oct. 2, 2007); U.S. Pat. No. 7,231,254 (issued Jun. 12, 2007); U.S. Pat. No. 7,403,820 (issued Jul. 22, 2008); U.S. Pat. No. 7,324,851 (issued Jan. 29, 2008); U.S. Pat. No. 7,747,325 (issued Jun. 29, 2010); U.S. Pat. No. 7,623,928 (issued Nov. 24, 2009); U.S. Pat. No. 7,676,263 (issued Mar. 9, 2010); U.S. Pat. No. 7,747,551 (issued Jun. 29, 2010); U.S. Pat. No. 7,840,507 (issued Nov. 23, 2010); U.S. Pat. No. 7,853,329 (issued Dec. 14, 2010); and U.S. patent application Ser. No. 11/282,317 (filed Nov. 17, 2005); Ser. No. 11/321,897 (filed Dec. 28, 2005, and published as U.S. Patent Publication No. 2007/0150024); Ser. No. 11/321,898 (filed Dec. 28, 2005, and published as U.S. Patent Publication No. 2007/0150025); Ser. No. 11/322,150 (filed Dec. 28, 2005 and published as U.S. Patent Publication No. 2007/0149952), Ser. No. 12/343,376 (filed Dec. 23, 2008, and published as U.S. Patent Publication No. 2009-0171168); Ser. No. 12/630,300 (filed Dec. 3, 2009, and published as U.S. Patent Publication No. 2010/0145176); Ser. No. 12/053,312 (filed Mar. 21, 2008, and published as U.S. Patent Publication No. 2008/0234598); Ser. No. 12/020,450 (filed Jan. 25, 2008, and published as U.S. Patent Publication No. 2008/0183096); Ser. No. 12/180,996 (filed Jul. 28, 2008 and published as U.S. Patent. Publication No. 2009/0062682); Ser. No. 12/035,335 (filed Feb. 21, 2008, and published as U.S. Patent Publication No. 2008/0208074); U.S. patent application Ser. No. 12/020,507 (filed Jan. 25, 2008 and published as U.S. Patent Publication No. 2008/0183097) the complete disclosures of which are incorporated herein by reference in their entireties.

For subjects suspected or known to have epilepsy, embodiments of the present invention may be used to collect data and quantify metrics for the subjects that heretofore have not been accurately measurable. For example, the data may be analyzed to (1) determine whether or not the subject has epilepsy, (2) determine the type of epilepsy, (3) determine the types of seizures, (4) localize or lateralize one or more seizure foci or seizure networks, (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, deep brain or cortical stimulation, peripheral nerve stimulation, and/or cranial nerve stimulation, (8) assess the

effect of adjustments of the parameters of the AED treatment, (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., peripheral nerve stimulation, cranial nerve stimulation, deep brain stimulation (DBS), cortical stimulation, etc.), (11) determine the effect of and the adjustment of parameters of focal cooling (e.g., use of cooling fluids, Peltier devices, etc., to diminish or reduce seizures (see, for example, "Rothman et al., "Local Cooling: A Therapy for Intractable Neocortical Epilepsy," *Epilepsy Currents*, Vol. 3, No. 5, September/October 2003; pp. 153-156, (12) determine "triggers" for the subject's seizures, (13) assess outcomes from surgical procedures, (14) provide immediate biofeedback to the subject, (15) screen subjects for determining if they are an appropriate candidate for a seizure advisory system or other neurological monitoring or therapy system, or the like.

In accordance with some embodiments, a data collection system is provided that is adapted to collect long term ambulatory brain activity data from the subject. In some embodiments, the data collection system is able to sample one or more channels of brain activity from the subject with one or more implanted electrodes. The electrodes are in wired or wireless communication with one or more implantable assemblies that are, in turn, in wired or wireless communication with an external assembly. The sampled brain activity data may be stored in a memory, of the implanted assembly, external assembly and/or a remote location such as a physician's computer system. In alternative embodiments, it may be desirable to integrate the electrodes with the implanted assembly, and such an integrated implanted assembly may be in communication with the external assembly.

Unlike other systems which have an implanted memory that is able to only store small epochs of brain activity before and after a seizure, some embodiments described herein are configured to substantially continuously sample the physiological signals over a much longer time period (e.g., anywhere between one day to one week, one week to two weeks, two weeks to a month, several months, or more) so as to be able to monitor fluctuations of the brain activity (or other physiological signal) over the entire time period. In alternative embodiments, however, the implantable assembly may only periodically sample the subject's physiological signals or selectively/aperiodically monitor the subject's physiological signals. Some examples of such alternative embodiments are described in commonly owned U.S. patent application Ser. No. 11/616,788 (filed Dec. 27, 2006, and published as U.S. Patent Publication No. 2008/0161712) and Ser. No. 11/616,793 (filed Dec. 27, 2006, and published as U.S. Patent Publication No. 2008/0161713), the complete disclosures of which are incorporated herein by reference in their entireties.

When the memory is almost full, the system may provide the subject a warning so that the subject may manually initiate uploading of the collected brain activity data or the system may automatically initiate a periodic download of the collected brain activity data from the memory to another storage device with greater capacity, such as a hard drive, flash-drive, local computer workstation, remote server or computer workstation, or other larger capacity memory system. In alternative embodiments, the external assembly may be configured to automatically stream the stored EEG data over a wireless link to a remote server or database. Such a wireless link may use existing WiFi networks, cellular networks, pager networks or other wireless network communication protocols. Advantageously, such embodiments

would not require the subject to manually upload the data and could reduce the down time of the system and better ensure permanent capture of substantially all of the sampled data.

Another aspect is a system for monitoring a subject's susceptibility to a seizure. The system includes an electrode and an implanted communication assembly in communication with the electrode. The implanted communication assembly samples a neural signal with the electrode and substantially continuously transmits a data signal from the subject's body. The system also comprises an external assembly positioned outside the subject's body that is configured to receive and process the data signal to measure the subject's susceptibility to having a seizure. In alternative embodiments the implanted assembly processes the data and measures the subject's susceptibility of having a seizure, in which case only data indicative of the measured susceptibility is transmitted to the external assembly.

FIG. 1 illustrates an exemplary embodiment of a either a data collection system or monitoring system. System 10 includes one or more electrode arrays 12 that are configured to be implanted in the subject and configured to sample electrical activity from the subject's brain. The electrode array 12 may be positioned anywhere in, on, and/or around the subject's brain, but typically one or more of the electrodes are implanted within in the subject. For example, one of more of the electrodes may be implanted adjacent or above a previously identified epileptic network, epileptic focus or a portion of the brain where the focus is believed to be located. While not shown, it may be desirable to position one or more electrodes in a contralateral position relative to the focus or in other portions of the subject's body to monitor other physiological signals. Other placement schemes are described in U.S. patent application Ser. No. 12/630,300 (filed Dec. 3, 2009 and published as 2010/0145176), the disclosure of which is incorporated herein by reference in its entirety.

The electrode arrays 12 may be intracranial electrodes (e.g., epidural, subdural, and/or depth electrodes), extracranial electrodes (e.g., spike or bone screw electrodes, subcutaneous electrodes, scalp electrodes, dense array electrodes), or a combination thereof. Although monitoring signals directly from the brain generally provides the highest quality signal, in some embodiments, it may be desirable to monitor brain activity elsewhere, such as by using sphenoidal electrodes, foramen ovale electrodes, intravascular electrodes, peripheral nerve electrodes, cranial nerve electrodes, or the like. While some of the disclosure herein focuses on intracranial electrodes for sampling intracranial EEG, it should be appreciated that various embodiments may use other types of electrodes capable of detecting any type of physiological signal from the subject.

In the configuration illustrated in FIG. 1, two electrode arrays 12 are positioned in an epidural or subdural space, but as noted above, in various embodiments, other types of electrode placements may be used to monitor brain activity of the subject. For example, in a minimally invasive embodiment, the electrode array 12 may be implanted between the skull and any of the layers of the scalp. Specifically, the electrodes 12 may be positioned between the skin and the connective tissue, between the connective tissue and the epicranial aponeurosis/galea aponeurotica, between the epicranial aponeurosis/galea aponeurotica and the loose aerolar tissue, between the loose aerolar tissue and the pericranium, and/or between the pericranium and the calvarium. To improve signal-to-noise ratio, such subcutaneous electrodes may be rounded to conform to the curvature of the outer

surface of the cranium, and may further include a protuberance that is directed inwardly toward the cranium to improve sampling of the brain activity signals. Furthermore, if desired, the electrode may be partially or fully positioned in openings disposed in the skull. Additional details of exemplary wireless minimally invasive implantable devices and their methods of implantation can be found in U.S. patent application Ser. No. 11/766,742 (filed Jun. 21, 2007, and published as U.S. Patent Publication No. 2008/0027515), the disclosure of which is incorporated by reference herein in its entirety.

Some exemplary configurations of the electrode arrays 12 are shown in FIG. 2. Each of the illustrated electrode arrays has eight electrode contacts so as to provide sixteen 16 channels for monitoring the EEG signals. The electrode contacts may be bipolar or referential. It should be appreciated however, that while FIG. 2 illustrates sixteen 16 channels that are distributed over two electrode arrays, any number electrode arrays that have any number of contacts may be used. In most embodiments, however, the system typically includes between about 1 and about 256 channels, and preferably between about 1 and about 32 channels, and more preferably between 8 and 32 channels that are distributed over, e.g., between one array and four arrays. The array pattern and number of contacts on each array may be configured in any desirable pattern.

FIG. 2 specifically illustrates a 2x4 grid electrode array 30, a 1x8 strip electrode array 32, or a 1x8 depth electrode array 34. Each of the electrode arrays 12 will be coupled to the implanted assembly 14 with leads 16. Alternatively, the electrode arrays 12 may transmit the physiological signals to the implanted assembly 14 wirelessly. The leads of each of the electrode arrays 12 may have a common lead body 17 and connector 19 for coupling with the implanted assembly 14. The connector 19 may take any conventional or proprietary form, but in some embodiments is similar to connectors used in commercial spinal cord stimulation (SCS) or internal cardioverter defibrillator (ICD) systems. The electrode arrays could be used in either a bipolar or monopolar configuration.

If the system 10 includes the capability of providing stimulation of a peripheral nerve, such as the vagus nerve, the system 10 may include a vagus nerve cuff 36. The cuff 36 may be similar to the IS1 connector used by Cyberonics Inc. of Houston, Tex. Some systems 10 may also be configured to provide electrical stimulation to other portions of the nervous system (e.g., cortex, deep brain structures, cranial nerves, etc.). Stimulation parameters are typically about several volts in amplitude, 50 microsec to 1 milisc pulse duration, and at a frequency between about 2 Hz and about 1000 Hz.

As shown in FIG. 1, the electrode arrays 12 are in wired communication with an implanted assembly 14 via the lead body 17. The lead wires for each individual contact (not shown) are carried through lead body 17, which is tunneled between the cranium and the scalp and subcutaneously through the neck to the implanted assembly 14. The implanted assembly 14 may be implanted in a sub-clavicular pocket in the subject, or may be disposed elsewhere in the subject's body. For example, the implanted assembly 14 may be implanted in the abdomen or underneath, above, or within an opening in the subject's cranium (not shown).

Implanted assembly 14 can be used to pre-process EEG signals sampled by the electrode array 12 and transmit a data signal that is encoded with the sampled EEG data over a wireless link 18 to an external assembly 20, where the EEG data is permanently or temporarily stored. FIG. 3 illustrates

a simplified embodiment of an exemplary implanted assembly **14**. Implanted assembly **14** may comprise a cast epoxy packaging **40** that hermetically encapsulates the sub-assemblies of the implanted assembly **14**. In other embodiments, the packaging **40** may include (i) biocompatible metals such as platinum, niobium, titanium, tantalum, and various alloys of these metals, (ii) biocompatible ceramics such as Aluminum Oxide (Al₂O₃), Zirconium Oxide (ZrO₂), and Boron Nitride (BN), (iii) and any combination of ceramic, metal, and epoxy.

Packaging **40** is preferably as small as possible and may have a similar packaging footprint as a spinal cord stimulator. Thus, the packaging typically has a volume between about 10 cubic centimeters to about 70 cubic centimeters and preferably about 30 cubic centimeters, but may be larger, or smaller, depending on what components are disposed therein. Packaging **40** comprises an interface **41** for the connectors **19** of leads **16**. The interface **41** will have at least the same number of input channels as the number of contacts in the electrode array, and may have more input channels than active contacts. Interface **41** may also have one or more bipolar output channels for delivering electrical stimulation to a peripheral nerve, brain tissue, cranial nerves, or other portions of the subject's body. Further details of an exemplary housing structure for the implanted assembly and embodiments of the packaging **40** can be found in U.S. patent application Ser. No. 12/343,386 (filed Dec. 23, 2008, and published as U.S. Patent Publication No. 2009-0171420), the complete disclosure of which is incorporated herein by reference in its entirety.

The interconnections between the components of implanted assembly **14** and external assembly **20** may be wired, wireless, digital, analog, or any combination thereof and such electronic components may be embodied as hardware, software, firmware, or any combination thereof. While FIG. 3 shows one preferred embodiment of the electronic components of implanted assembly **14**, it should be appreciated that the functionality performed by each of the sub-assemblies shown in FIG. 3 may be embodied in multiple sub-assemblies and the functionality carried out by multiple sub-assemblies of FIG. 3 may be combined into a single sub-assembly. Furthermore, some embodiments of the implanted assembly **14** may have additional functionalities not illustrated, while other embodiments may not have all of the functionality and/or electronic components that are illustrated in FIG. 3.

The electronic components of the implanted assembly will typically comprise a signal conditioning sub-assembly **42** that conditions the one or more EEG signals received from the interface **41**. The signal conditioning sub-assembly **42** may perform amplification, combined to reduce common mode signal, filtering (e.g., lowpass, highpass, bandpass, and/or notch filtering), digital-to-analog conversion, or some combination thereof.

The electronic components of the implanted assembly **14** may optionally comprise dedicated circuitry and/or a microprocessor (referred to herein collectively as "processing sub-assembly **44**") for further processing of the EEG signals prior to transmission to the external assembly **20**. The further processing may include any combination of encryption, forward error correction, checksum or cyclic redundancy checks (CRC), or the like. The processing sub-assembly may comprise an ASIC, discrete components, or the like. In one embodiment processing sub-assembly **44** includes one or more multiple-core processors for processing data. Such multiple-core microprocessors provide faster

processing, while consuming less power than multiple single core processors. Consequently, the life of the power source **44** may be prolonged.

Of course, while FIG. 3 illustrates a separate conditioning assembly **42** and processing sub-assembly, the two assemblies may be embodied in a single component, such as an ASIC, that performs the functionality of both assemblies **42**, **44**.

The implanted assembly **14** will also typically include both a clock **48** and a power source **50**. The clock **48** is typically in the form of an oscillator and frequency synthesizer to provide synchronization and a time base for the signals transmitted from internal assembly and for signals received from external assembly **20**. Power source **50** may be a non-rechargeable battery, a rechargeable battery, a capacitor, etc. One preferred power source is a medical grade rechargeable Li-Ion battery that is commonly used in other implantable devices. The rechargeable power source **50** may also be in communication with the communication sub-system **46** so as to receive power from outside the body by inductive coupling, radiofrequency (RF) coupling, etc. Such rechargeable power sources typically have a lifespan of between about 3 years and about 5 years. Power source **50** will generally be used to provide power to the other components of the implantable assembly **14**.

In some embodiments, the implanted assembly **14** may optionally include a memory sub-system **52** (e.g., RAM) for permanently or temporarily storing or buffering the processed EEG signal. For example, memory sub-assembly **52** may be used as a buffer to temporarily store the processed EEG data if there are problems with transmitting the data to the external assembly. For example, if the external assembly's power supply is low, the memory in the external assembly is removed, or if the external assembly is out of communication range with the implantable assembly **14**, the EEG data may be temporarily buffered in memory sub-assembly **52** and the buffered EEG data and the current sampled EEG data may be transmitted to the external assembly when the problem has been corrected. The buffer may be any size, but it will typically be large enough to store between about 1 megabyte and 100 megabytes of data. As can be appreciated, as technology improves and the capacity of memory cards improve, it is likely that many hundreds of gigabytes or hundreds of gigabytes of data may be buffered in the internal memory. Of course, in embodiments that do not have a memory sub-system **52** in the implanted assembly **14**, any data that is sampled during the times in which the external assembly **20** is out of communication range with the implanted assembly **14**, there may simply be gaps in the stored data.

In some embodiments, the system **10** may incorporate an alert that is activated to indicate that there is a communication error between the implanted assembly and the external assembly. Exemplary communication errors include, without limitation, when (1) the external assembly **20** is out of communication range with the internal assembly **14** such that the transmitted data signals are not received by the external assembly, (2) there is some other error in the transmission and receipt of data signals between the internal assembly **14** and external assembly, (3) self test error has been encountered, (4) memory card is full (or nearly full), or some combination thereof. Additional exemplary causes for an alert are discussed below in the more detailed discussion of the external assembly.

Typically, the alert is incorporated in the external assembly **20** so that the external assembly can provide a visual, audible, and/or tactile alert. Such an alert can indicate to the

subject (or third party) that the external assembly **20** is not able to receive the RF signal from the implanted assembly **14** and/or that appropriate data transfer is not occurring. Moreover, the alert may reduce the likelihood of misplacing the external assembly **20**, since in most embodiments, once the data transfer is interrupted, the alert may be activated by the system. In such a case, if the subject were to walk away from the external assembly **20** (e.g., leave the external assembly **20** on a table), the subject would not be advised of their susceptibility for seizure. If the subject did not realize that they did not have their external assembly **20** with them, the subject may assume that they are in a low susceptibility and perform activities on the assumption that their external assembly **20** would warn them of a changing to a state in which they were in a higher susceptibility to a seizure.

Additionally or alternatively, it may be possible to incorporate an alert in the implanted assembly **14** and the alert may provide a tactile warning (e.g., vibration) and/or audible alert to warn the subject that there is a data transmission error between the external assembly **20** and the implanted assembly **14**.

In some embodiments the external assembly can be adapted so that it will expect to receive a data signal from the implanted assembly, and if it does not, the alert will be activated. The external assembly can be programmed to expect to receive a substantially continuous data signal from the implanted assembly, such that if the external assembly stops receiving a signal the alert will be activated. The external assembly can also be programmed to expect to receive a data signal periodically rather than substantially continuously. For example, the external assembly could expect to receive a signal every two seconds, and if it fails to receive a signal after a two second period of time, the alert will be activated. Thus, when the external assembly is adapted to expect a data signal periodically, the alert will be activated after a specified period of time passes without the external assembly receiving the data signal.

In some embodiments the communication error comprises a gap in the communication stream. For example, if the data signal comprises a numbered sequence of packets of information, and the external assembly receives a signal with missing packets of information within the sequence, the alert would be activated. The implanted assembly can be adapted to temporarily store the data signal so that if the external assembly detects a gap in the communication, the implanted assembly can attempt to retransmit the complete data signal data.

In some embodiments the communication error can include data formatting errors. An exemplary formatting error is an invalid cyclic redundancy check, but formatting errors as described herein include any other alteration of data during transmission or storage.

FIG. 4 illustrates an exemplary method of activating an alert when there is an error transmitting a data signal between the implanted assembly and the external assembly. First, a brain signal, such as an EEG signal, is sampled from the subject at step **55**. The implanted assembly then attempts to transmit a data signal which is indicative of the brain signal to the external assembly at step **56**. If there is a communication error between the implanted assembly and the external assembly, step **57**, the alert is activated, step **58**, to notify the subject of the communication error. The implanted assembly can also attempt to retransmit the data signal between the implanted assembly and the external assembly if there is a communication error.

In some situations, the subject may be able to temporarily disable the alert and/or change the mode or parameters of the

alert using a subject input. Such functionality may be carried out through providing a manual subject input—such as pressing a button on the external assembly **20**.

In some embodiments, external assembly **20** may be programmed to allow the subject to disable the alert if the subject is in one or more different neurological states. For example, if the subject is in a contra-ictal state in which the subject is at a low susceptibility to transitioning into an ictal state and/or a pro-ictal state in a period of time and did not want to carry the external assembly **20** with them (e.g., to take a shower and leave the external assembly **20** in the bedroom), the subject may disable the alert by using the buttons **131**, **133**, **135** or other user inputs on the external assembly **20** (FIG. 6). The disabling of the alert could last for a predetermined time period and then automatically be re-enabled, or the disabling of the alert may be continued until the subject manually re-enables the alert.

The subject and/or the physician may also customize the alert parameters to the subject. For example, some subjects may want to be immediately alerted if there is a communication error, while others may want a time delay before the alert is sounded.

Furthermore, if there is a prolonged alert (e.g., the subject leaves the house without the external assembly), the external assembly **20** may automatically disable the alert after a predetermined time and/or the alert may be manually disabled by a third party. To further reduce the likelihood of misplacing the external assembly **20** and ensuring that the subject is being monitored and advised, the external assembly **20** may comprise a communication assembly that facilitates the wireless communication with a remote party, such as the subject's caregiver, spouse, or friend (described in more detail below as the caregiver advisory device). Thus, if an alert is sounded that indicates a communication error, the communication assembly may send a wireless communication to the remote party to alert the third party that the subject is not being advised of their susceptibility to seizure. Typically, the wireless communication to the caregiver will be sent only after a predetermined time period has elapsed.

Tuning or reprogramming of the components of implanted assembly **14** may be carried out in vivo through communication sub-assembly **46**. For example, the external assembly **20** and/or a dedicated programmer (controlled by physician) may be brought into communication range with the communication sub-assembly **46** and the reprogramming instructions may be uploaded into the processing sub-assembly.

Communication sub-assembly may include a magnetic reed switch (not shown) similar to those found in the Cyberonics® Vagus Nerve Stimulator or spinal cord stimulators. The magnetic reed switch would enable initiation of an electrode impedance check, self test, RAM check, ROM check, power supply checks, computer operating properly checks, electrode impedance check, or the like.

Implantable assembly **14** can be configured to substantially continuously sample the brain activity of the groups of neurons in the immediate vicinity of each of the contacts in the electrode array **12**. The communication range between the implanted assembly **14** and the external assembly **20** may be, e.g., about 5 meters, but could be so short as to require that the external assembly **20** contact the skin of the subject, or may be as long as 10 meters or more. Sampling of the brain activity is typically carried out at a sampling rate above about 200 Hz, and preferably between about 200 Hz and about 1000 Hz, and most preferably between about 400 Hz and about 512 Hz, but it could be higher or lower, depending on the specific condition being monitored, the

subject, and other factors. Each sample of the subject's brain activity will typically contain between about 8 bits per sample and about 32 bits per sample, and preferably between about 12 bits and 16 bits per sample. The wireless communication link **18** may have an overall data transfer rate between approximately 5 Kbits/sec and approximately 500 Kbits/sec, and preferably about approximately 50 kbits/sec. As can be appreciated, the over air data transfer rate of the implanted assembly could be considerably higher (e.g., 2 Mbts/sec), which would allow for a lower transmit duty cycle which will result in power savings.

For example, if each communication transmission to the external assembly 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 assembly **14** to the external assembly **20** is at least about 6.4 Kbits/second/channel. If there are 16 channels, the total data transfer rate for the wireless communication link **18** between the implanted assembly **14** and the external assembly **20** would be about 102 Kbits/second.

While substantially continuous sampling and transmission of brain activity is preferred, in alternative embodiments, it may be desirable to have the implantable assembly **14** sample the brain activity of the subject in a non-continuous basis or the sampling rate may vary over the period of monitoring. In such embodiments, the implantable assembly **14** may be configured to sample the brain activity signals periodically (e.g., a burst of sampling every 5 seconds) or aperiodically. For example, it may be desirable to reduce or increase the sampling rate when a subject has gone to sleep.

To enable the high data transfer rates of the present invention, the wireless communication link **18** provided by the communication sub-assembly **46** is typically in the form of an electromagnetic radiofrequency communication link. Conventional devices typically use a slower communication link (e.g., that is designed for low data transfer rates and long link access delays) and transmit data out on a non-continuous basis. Instead, a fast access communication link may be used that transmits smaller bursts of data (e.g., single or small number of EEG samples from each of the channels at a time) on a substantially continuous basis so as to allow for substantially real-time analysis of the EEG data. The frequency used to transfer data between the implantable assembly **14** and external assembly **20** may be, e.g., between 13.56 MHz and 10 GHz, between about 900 MHz and about 2.4 GHz, at about 2.4 GHz, or between about 900 MHz and about 928 MHz. One potentially useful communication sub-assembly is a 900 MHz ISM telemetry transmitter. If it is desired to avoid FCC regulations, it may be desirable to use telemetry at low frequency, such as below 9 KHz.

As can be appreciated, while the aforementioned frequencies are examples of preferred frequencies, other frequencies that are higher and lower may also be used. For example, it may be desirable us use the MICS (Medical Implant Communication Service band) that is between 402-405 MHz to facilitate the communication link.

In order to facilitate data transmission from the implanted assembly **14** to the external assembly **20**, the antennas **47** and **62** of the implantable assembly **14** and external assembly **14**, respectively, must be maintained 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 typically 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; but if higher frequencies are used, the communication range may be larger than twenty feet.

While not illustrated in FIGS. **1** to **4**, various embodiments 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 assembly **14** to the external assembly **20**. Such forward error correction methods may include such conventional implementations such as cyclic redundancy check ("CRC"), checksums, or the like.

In some situations, instead of a wireless link between the implanted assembly **14** and the external assembly **20**, it may be desirable to have a wired connection from the subject-worn data collection assembly **20** to an interface (not shown) that could link to an implanted assembly **14** positioned below the subject's skin. For example, the interface may utilize an extremely short range wireless communication, such as a magnetically attached transducer, as with cochlear implants. This could enable higher rates of data transmission between the implanted assembly **14** and the external assembly **20**.

FIG. **5** illustrates a simplified embodiment of external assembly **20**. For example, in alternative embodiments the functionality performed by a single sub-assembly shown in FIG. **5** may be embodied in multiple sub-assemblies, and/or the functionality carried out by multiple sub-assemblies of FIG. **5** may be combined into a single sub-assembly. Furthermore, other embodiments of the external assembly **20** may have additional functionalities not illustrated, while other embodiments may not have all of the functionality and/or electronic components that are illustrated in FIG. **5**. External assembly **20** is typically portable and comprises a housing **60** that is of a size that allows for storage in a purse or pocket of the subject. The handheld housing **60** typically has a form factor of a MP3 player (e.g., Apple iPod), cellular phone, personal digital assistant (PDA), pager, or the like. In some embodiments, the components of the external assembly **20** may be integrated within a housing of such consumer electronics devices.

FIGS. **6**, **7**, and **8** illustrate alternative embodiments of external assembly **20**.

The illustrated external assembly shows a user interface **72** that includes a variety of indicators for providing system status and alerts to the subject. User interface **72** may include one or more indicators **101** that indicate the subject's brain state. In the illustrated embodiment, the output includes light indicators **101** (for example, LEDs) that comprise one or more (e.g., preferably two or more) discrete outputs that differentiate between a variety of different brain states. In the illustrated embodiment, the brain state indicators **101** include a red light **103**, yellow/blue light **105**, and a green light **107** for indicating the subject's different brain states (described more fully below). In some configurations the lights may be solid, blink or provide different sequences of flashing to indicate different brain states. If desired, the light indicators may also include an "alert" or "information" light **109** that is separate from the brain state indicators so as to minimize the potential confusion by the subject.

External assembly **20** (one embodiment of which is referred to as a Patient Advisory Device or PAD) may also include a liquid crystal display ("LCD") **111** or other display for providing system status outputs to the subject. The LCD **111** may display the system components' status and prompts

for the subject. For example, as shown in FIG. 7, LCD 111 can display indicators, in the form of text or icons, such as, for example, implantable device battery strength 113, external assembly battery strength 115, and signal strength 117 between the implantable device and the external assembly 20. If desired, the LCD may also display the algorithm output (e.g., brain state indication) and the user interface 72 may not require the separate brain state indicator(s) 101. The output on the LCD is preferably continuous, but in some embodiments may appear only upon the occurrence of an event or change of the system status and/or the LCD may enter a sleep mode until the subject activates a user input. LCD 111 is also shown including a clock 119, audio status 121 (icon shows PAD is muted), and character display 123 for visual text alerts to the subject—such as an estimated time to seizure or an estimated “contra-ictal” time. While not shown in FIG. 7, the LCD 111 may also indicate the amount of free memory remaining on the memory card.

FIGS. 8_a-8_g illustrate a variety of different views of another embodiment of the external assembly. FIGS. 8_a and 8_b are two alternative top plan views of the external assembly. FIGS. 8_c and 8_e are opposing side views. FIG. 8_d is a back view. FIG. 8_f is a front view. FIG. 8_g is a bottom view. The illustrated embodiment of FIG. 8 is a pager-style external assembly that may be carried on a clip (not shown) that may be used to couple the external assembly to the subject's belt or bag. The typical dimensions of this embodiment of the external assembly are typically 1.00"×2.50"×3.50", but may be larger or smaller as desired.

Similar to the other embodiments, the external assembly of FIG. 8 comprise a plurality of user inputs 131, 133, 135, brain state indicators 101 and outputs that indicate a state of the system (e.g., LCD 111). As shown in FIG. 8_b, the LCD may comprise a plurality of different icons on the LCD 111 to indicate the state of the system. For example, the illustrated embodiment includes an external assembly battery indicator 115, implanted device battery indicator 113, telemetry signal strength indicator 117, volume indicator 121, and a memory card status indicator 6. To differentiate between the implanted device system state and external assembly system state, it may be desirable to provide a physical separation 7 between the icons. The physical separation element 7 could be a physical barrier that overlays the LCD, two separate LCDs that are spaced from each other, or simply a discernable separation between icons on the LCD.

The LCD 111 and brain state indicators 101 are typically viewable by the subject when it is attached to the subject's belt. As such, the subject need only glance down onto the top surface of the PAD when an audible or tactile indication is provided that indicates a subject's brain state or change thereof.

In the embodiment of FIG. 8.sub.a, the brain state indicators 103, 105, 107 may be positioned along the junction of the top surface and front surface so as to be viewable from multiple angles. In another embodiment shown in FIG. 8.sub.b, either in addition to the brain state indicators 103, 105, 107 on the front surface (FIG. 8.sub.f) or as an alternative to the brain state indicator on the front surface, the top surface may have brain state indicators 103', 105', 107' that are viewable from the top surface. In the embodiment shown in 8.sub.b, the brain state indicators 103', 105', 107' on the top surface may be different colored and different shaped to further differentiate between the different brain states. In both embodiments of FIGS. 8.sub.a and 8.sub.b the acknowledgement input 135 may be positioned along a top surface of the external assembly so that the acknowledge-

ment input 135 is readily accessible to the subject when the brain state indicator 101 is activated.

The front surface of the external assembly may also comprise a door 9 that houses the removable data storage card and on/off input button (not shown). When opened, the subject may replace the full (or defective) data card with a new card. Alternatively, if the subject desires to turn on or off the external assembly, the subject may activate the on/off input. Typically, the subject will keep the external assembly on at all times, but in instances which require the external assembly to be off (e.g., on an airplane), the subject may have the ability to turn off the external assembly and stop the transmission of the data signal from the implanted device—which may help to conserve battery power of the external assembly and implanted device.

Referring again to FIG. 6, external assembly 20 may also include a speaker 125 and a pre-amp circuit to provide audio outputs to the subject (e.g., beeps, tones, music, recorded voice alerts, etc.) that may indicate brain state or system status to the subject. User interface 72 may also include a vibratory output device 127 and a vibration motor drive 129 to provide a tactile alert to the subject, which may be used separately from or in conjunction with the visual and audio outputs provided to the subject. The vibratory output device 127 is generally disposed within external assembly 20, and is described in more detail below. Depending on the desired configuration any of the aforementioned outputs may be combined to provide information to the subject.

The external assembly 20 preferably comprises one or more subject inputs that allow the subject to provide inputs to the external assembly. In the illustrated embodiment, the inputs comprise one or more physical inputs (e.g., buttons 131, 133, 135) and an audio input (in the form of a microphone 137 and a pre-amp circuit).

Similar to conventional cellular phones, the inputs 131, 133, 135 may be used to toggle between the different types of outputs provided by the external assembly. For example, the subject can use buttons 133 to choose to be notified by tactile alerts such as vibration rather than audio alerts (if, for example, a subject is in a movie theater). Or the subject may wish to turn the alerts off altogether (if, for example, the subject is going to sleep). In addition to choosing the type of alert, the subject can choose the characteristics of the type of alert. For example, the subject can set the audio tone alerts to a low volume, medium volume, or to a high volume.

Some embodiments of the external assembly 20 will allow for recording audio, such as voice data. A dedicated voice recording user input 131 may be activated to allow for voice recording. In preferred embodiments, the voice recording may be used as an audio subject seizure diary. Such a diary may be used by the subject to record when a seizure has occurred, when an aura or prodrome has occurred, when a medication has been taken, to record subject's sleep state, stress level, etc. Such voice recordings may be time stamped and stored in data storage of the external assembly and may be transferred along with recorded EEG signals to the physician's computer. Such voice recordings may thereafter be overlaid over the EEG signals and used to interpret the subject's EEG signals and improve the training of the subject's customized algorithm, if desired.

The one or more inputs may also be used to acknowledge system status alerts and/or brain state alerts. For example, if the external assembly provides an output that indicates a change in brain state, one or more of the LEDs 101 may blink, the vibratory output may be produced, and/or an audio alert may be generated. In order to turn off the audio alert,

turn off the vibratory alert and/or to stop the LEDs from blinking, the subject may be required to acknowledge receiving the alert by actuating one of the user inputs (e.g., button 135).

While the external assembly is shown having inputs 131, 133, 135, any number of inputs may be provided on the external assembly. For example, in one alternate embodiment, the external assembly may comprise only two input buttons. The first input button may be a universal button that may be used to scroll through output mode options. A second input button may be dedicated to voice recording. When an alert is generated by the external assembly, either of the two buttons may be used to acknowledge and deactivate the alert. In other embodiments, however, there may be a dedicated user input for acknowledging the alerts.

External assembly 20 may comprise a main processor 139 and a complex programmable logic device (CPLD) 141 that control much of the functionality of the external assembly. In the illustrated configuration, the main processor and/or CPLD 141 control the outputs displayed on the LCD 111, generates the control signals delivered to the vibration device 127 and speaker 125, and receives and processes the signals from buttons 131, 133, 135, microphone 137, and a real-time clock 149. The real-time clock 149 may generate the timing signals that are used with the various components of the system.

The main processor may also manage a data storage device 151, provides redundancy for a digital signal processor 143 (“DSP”), and manage the telemetry circuit 147 and a charge circuit 153 for a power source, such as a battery 155.

While main processor 139 is illustrated as a single processor, the main processor may comprise a plurality of separate microprocessors, application specific integrated circuits (ASIC), or the like. Furthermore, one or more of the microprocessors 139 may include multiple cores for concurrently processing a plurality of data streams.

The CPLD 141 may act as a watchdog to the main processor 139 and the DSP 143 and may flash the LCD 111 and brain state indicators 101 if an error is detected in the DSP 143 or main processor 139. Finally, the CPLD 141 controls the reset lines for the main microprocessor 139 and DSP 143.

A telemetry circuit 147 and antenna may be disposed in the PAD 10 to facilitate one-way or two-way data communication with the implanted device. The telemetry circuit 147 may be an off the shelf circuit or a custom manufactured circuit. Data signals received from the implanted device by the telemetry circuit 147 may thereafter be transmitted to at least one of the DSP 143 and the main processor 139 for further processing.

The DSP 143 and DRAM 145 receive the incoming data stream from the telemetry circuit 147 and/or the incoming data stream from the main processor 139. The brain state algorithms process the data (for example, EEG data) and estimate the subject’s brain state, and are preferably executed by the DSP 143 in the PAD. In other embodiments, however, the brain state algorithms may be implemented in the implanted device, and the DSP may be used to generate the communication to the subject based on the data signal from the algorithms in the implanted device.

The main processor 139 is also in communication with the data storage device 151. The data storage device 151 preferably has at least about 7 GB of memory so as to be able to store data from about 8 channels at a sampling rate of between about 200 Hz and about 1000 Hz. With such parameters, it is estimated that the 7 GB of memory will be

able to store at least about 1 week of subject data. Of course, as the parameters (e.g., number of channels, sampling rate, etc.) of the data monitoring change, so will the length of recording that may be achieved by the data storage device 151. Furthermore, as memory capacity increases, it is contemplated that the data storage device will be larger (e.g., 10 GB or more, 20 GB or more, 50 GB or more, 100 GB or more, etc.). Examples of some useful types of data storage device include a removable secure digital card or a USB flash key, preferably with a secure data format.

“Subject data” may include one or more of raw analog or digital EEG signals, compressed and/or encrypted EEG signals or other physiological signals, extracted features from the signals, classification outputs from the algorithms, etc. The data storage device 151 can be removed when full and read in card reader 157 associated with the subject’s computer and/or the physician’s computer. If the data card is full, (1) the subsequent data may overwrite the earliest stored data or (2) the subsequent data may be processed by the DSP 143 to estimate the subject’s brain state (but not stored on the data card). While preferred embodiments of the data storage device 151 are removable, other embodiments of the data storage device may comprise a non-removable memory, such as FLASH memory, a hard drive, a micro-drive, or other conventional or proprietary memory technology. Data retrieval off of such data storage devices 151 may be carried out through conventional wired or wireless transfer methods.

The power source used by the external assembly may comprise any type of conventional or proprietary power source, such as a non-rechargeable or rechargeable battery 155. If a rechargeable battery is used, the battery is typically a medical grade battery of chemistries such as a lithium polymer (LiPo), lithium ion (Li-Ion), or the like. The rechargeable battery 155 will be used to provide the power to the various components of the external assembly through a power bus (not shown). The main processor 139 may be configured to control the charge circuit 153 that controls recharging of the battery 155.

In addition to being able to communicate with the implanted device, the external assembly may have the ability to communicate wirelessly with a remote device—such as a server, database, physician’s computer, manufacturer’s computer, or a caregiver advisory device (all of which can be herein referred to as “CAD”). In the exemplary embodiment, the external assembly may comprise a communication assembly (not shown) in communication with the main processor 139 that facilitates the wireless communication with the remote device. The communication assembly may be a conventional component that is able to access a wireless cellular network, pager network, wifi network, or the like, so as to be able to communicate with the remote device. The wireless signal could be transfer of data, an instant message, an email, a phone call, or the like.

In one particular embodiment, the external assembly is able to deliver a signal through the communication assembly that is received by the CAD so as to inform the caregiver of the subject’s brain state or change in brain state. The CAD would allow the caregiver to be away from the subject (and give the subject independence), while still allowing the caregiver to monitor the subject’s brain state and susceptibility for seizure. Thus, if the subject’s brain state indicates a high susceptibility for a seizure or the occurrence of a seizure, the caregiver would be notified via the CAD, and the caregiver could facilitate an appropriate treatment to the subject (e.g., small dosage of an antiepileptic drug, make the subject safe, etc). A signal may be provided to the caregiver

only if the subject has a high susceptibility for a seizure or if a seizure is detected, or it may provide the same indications that are provided to the subject.

In yet other embodiments, the communication assembly could be used to inform the caregiver that there is a communication error between the subject's implanted assembly and external assembly, so as to indicate that the subject is not being properly monitored and advised. Such a communication would allow the caregiver to intervene and/or inform the subject that they are not being monitored.

In other embodiments, the communication assembly could be used to facilitate either real-time or non-real time data transfer to the remote server or database. If there is real time transfer of data, such a configuration could allow for remote monitoring of the subject's brain state and/or EEG signals. Non-real time transfer of data could expedite transfer and analysis of the subject's recorded EEG data, extracted features, or the like. Thus, instead of waiting to upload the brain activity data from the subject's data storage device, when the subject visits their physician, the physician may have already had the opportunity to review and analyze the subject's transferred brain activity data prior to the subject's visit.

The external assembly may be configured to perform a self hardware/software test to detect system errors such as power failures, software failures, impedance change, battery health of the implanted device and external assembly, internal clock and voltage reference, hardware (processors, memory, and firmware) checks, or the like. The self test may be performed periodically, upon initial startup, upon a system reset, or some combination thereof. The system preferably runs a self-test on the external assembly, implanted device, electrode array and the communication links. The external assembly may emit a tone and/or display information on the LCD at the initiation of the self-test(s). If the external assembly, implanted device, electrode array and/or communication link pass the self-test, the subject may be notified with an alert indicating the respective devices passed the self-test. If any of the components do not pass the self-test, the subject can be alerted with an output that indicates which component did not pass (for example, an icon on the LCD representing the component which did not pass the test flashes). There may also be an audio alert, such as a voice alert, that one or some of the devices failed the test. The external assembly may also indicate these failures with information or alert light **109** (FIG. 7). The system may then wait for input from the subject to acknowledge the system failure(s) by depressing a button on the external assembly (such as the "OK" button **135** in FIG. 6), which indicates the user is aware of the alert. Additionally or alternatively, there may be a text display on the LCD notifying the subject to contact the manufacturer or physician to receive further instructions.

The external assembly may be configured to be toggled between two or more different modes of operation. In one embodiment, the physician may toggle the external assembly between three different modes of operations. Of course, it should be appreciated that the external assembly may have as little as one mode of operation, or more than three different modes of operations.

In one example, a first mode of operation of the external assembly may be merely data collection, in which data signals from the implanted device are stored in the data storage **151** of the external assembly. In such a mode, the user interface **72** may be modified to only provide system status indications to the subject via the LCD **111**, and the brain state indicators **101** may be temporarily disabled.

In a second mode of operation, after the brain state algorithms have been trained on the subject's data that was collected during the first mode of operation, the brain state algorithms may be implemented to process substantially real-time data signals and the brain state indicators **101** may be enabled so as to inform the subject of their substantially real-time brain state.

In a third mode of operation, it may be desirable to only receive and process the data signals from the implanted device, but no longer store the substantially continuous data signals in a memory of the external assembly. For example, if the brain state algorithms are performing as desired, the brain data signals from the implanted device will not have to be stored and analyzed. Consequently, the subject would not have to periodically replace the data card as frequently. However, it may still be desirable to store the data signals that immediately precede and follow any detected seizure. Consequently, in the third mode such seizure data signals may optionally be stored.

As noted above, in some embodiments the system comprises one or more brain state algorithms. In one embodiment, the brain state algorithms embodied in the present invention will generally characterize the subject's brain state as either "Low Susceptibility," "Unknown," "Elevated Susceptibility" or "Detection." It is intended that these are meant to be exemplary categories and are in no way to be limiting and additional brain states or fewer brain state indicators may be provided. There may be different types of algorithms which are configured to characterize the brain state into more or less discrete states. "Contra-ictal" generally means that brain activity indicates that the subject has a low susceptibility to transition to an ictal state and/or a pro-ictal state for an upcoming period of time (for example, 60 minutes to 90 minutes). This is considered positive information and no user lifestyle action is required. A pro-ictal state generally means that the algorithm(s) in the PAD are determining that the subject has an elevated susceptibility for a seizure (possibly within a specified time period). A "detection" state generally means that brain activity indicates that the subject has already transitioned into an ictal state (e.g., occurrence of an electrographic seizure) or that there is an imminent clinical seizure. User actions should be focused on safety and comfort. An "unknown" state generally means the current type of brain activity being monitored does not fit within the known boundaries of the algorithms and/or that the brain activity does not fit within the contra-ictal state, pro-ictal state, or ictal state. Therefore no evaluation can be reliably made. "Unknown" can also indicate there has been a change in the status of the brain activity and while the subject does not have an elevated susceptibility and no seizure has been detected, it is not possible to reliably tell the subject that they may not transition into an ictal state and/or pro-ictal state for a period of time. This state is considered cautionary and requires some cautionary action such as limiting exposure to risk. The two different types of "unknown" may have separate brain state indicators, or they may be combined into a single brain state indicator, or the user interface may not provide the "unknown" state to the subject at all.

The external assembly preferably comprises visual indicators, such as LEDs, notifying the subject of the determined brain state. In one preferred embodiments, the visual indicators for the brain state alerts will comprise a green, yellow/blue, and red lights. The green light will be illuminated when the PAD determines that the brain state is in a "low susceptibility to seizure" state. The yellow or blue light will be illuminated when the subject is in an "unknown"

state. The PAD will emit a solid red light when the subject is in the “high susceptibility” state. The PAD will emit a blinking red light when the subject is in the “detection” state. The light colors or number of light indicators are not intended to be limiting. Any color may be used. It may be desirable to include additional lights or colors (e.g., orange) to further delineate the subject’s estimated condition. In yet other embodiments, it may be desirable to display only a green light and red light.

Further exemplary details of external assembly 20 can be found in U.S. patent application Ser. No. 12/180,996 (filed Jul. 28, 2008, and published as U.S. Patent Publication No. 2009/0062682) the disclosure of which is incorporated by reference herein in its entirety.

FIG. 9 illustrates an exemplary simplified method of storing EEG data. The implantable assembly 14 samples the brain activity signals with the contacts on the electrode array 12 (step 80). The sampled brain activity signals are carried to the implantable assembly 14 over leads 16 (or alternatively may be wirelessly transmitted). The implantable assembly 14 may then pre-process the sampled brain activity signals as desired (step 82), and then use the communication sub-assembly to transmit a substantially continuous wireless RF signal to the external assembly 20 that is encoded with EEG data (step 84). The RF signal emitted by the internal assembly 14 is received by an antenna in the external assembly, and the RF signal is decoded to extract the EEG data (step 86). The sampled EEG data may thereafter be stored in a memory of the external assembly 20 (step 88). Rather than storing the data in a memory in the external assembly (step 88), the data can also be transmitted to a remote device in substantial real time without storage in the external assembly.

In some embodiments, the wireless signal is transmitted substantially immediately after sampling of the EEG signal to allow for substantially continuous real-time transfer of the subject’s EEG data to the external assembly 20. In alternate embodiments, the sampled EEG data may be temporarily buffered in an internal memory 52 (FIG. 4) of the implanted assembly 14 and the communication transmission to the external assembly 20 may be delayed by any desired time period and such transmissions may include the buffered EEG data and/or a real-time sampled EEG data. In yet other embodiments, the sampled EEG data may be stored for extended periods of time in the implanted assembly 14 (e.g., hours, days, weeks, or months of EEG data may be stored before transmission to the external assembly 20).

As noted above, the data signals that are wirelessly transmitted from implanted assembly 14 may be encrypted so as to help ensure the privacy of the subject’s data prior to transmission to the external assembly 20. Alternatively, the data signals may be transmitted to the external assembly 20 with unencrypted EEG data. The EEG data may then be encrypted prior to the storage of the EEG data in the memory of external assembly 20 or prior to transfer of the stored EEG data to the local computer workstation 22 or remote server 26.

The download of brain activity data may be manually carried out by the subject or automatically initiated by a component of system 10. After a time period of collecting EEG data (e.g., one day to one week, one week to two weeks, two weeks to one month, etc.), the external assembly 20 may be manually put in communication with a local computer workstation 22 through either a wireless link or wired link to download the stored data to a memory of the local computer workstation 22. For example, in one embodiment, a wired USB 2.0 connection (improvements thereof or

other conventional interface) may be used to upload the stored EEG data to the local computer workstation 22. Alternatively, instead of downloading the data directly to a local or remote computer workstation 22, 26, the data may be downloaded to a portable hard drive or flash drive for temporary storage. In such embodiments, the drive may thereafter be brought or delivered into the physician’s office for download and analysis.

Furthermore, as shown in FIG. 1, the communication sub-assembly of external assembly 20 may have the capability to continuously or periodically communicate wirelessly with a broadband, high speed communication network 24—such as a cellular network, pager network, the Internet (Wifi, WiMAX); or the like, to automatically and wirelessly transmit the stored and/or real-time data over the network 24 to a remote server (not shown) or remote computer workstation 26.

For example, the local computer workstation 22 (or remote computer workstation 26) may periodically command the external assembly to upload the data from the memory of the external assembly, or the external assembly may be programmed to automatically upload the EEG data according to a predetermined schedule or upon reaching a threshold level memory usage. By incrementally downloading days or weeks of stored brain activity data periodically, the subject’s physician may be able to start analysis of the brain activity data and possibly complete the analysis of the long term data prior to the subject going to the physician’s office. If a subject were to bring in a week or month of stored brain activity data for analysis by the physician, the subject would have to wait hours, days or even weeks for the analysis of the data to be completed. Consequently, instead of waiting for the analysis, analysis of the data may be substantially completed and therapy or diagnosis decisions may be made prior to the office visit and the subject would be able to immediately implement any changes or start therapy immediately after visiting the office.

Once implanted in the subject, embodiments of the present invention may be used for a variety of different data collection and monitoring purposes. For example, in one usage the systems may be used to quantify seizure activity statistics for the subject. Currently, the most common method of quantifying a subject’s seizure activity is through subject self reporting using a seizure diary. However, it has been estimated that up to 63% of all seizures are missed by subjects. The missed seizures may be the result of the subjects being amnesic to the seizures, unaware of the seizures, mentally incapacitated, asleep during the seizures, or otherwise unaware that a seizure is occurring. FIG. 10 illustrates a simplified method 90 of measuring a subject’s seizure activity statistics. At step 92, the electrode arrays 12, leads 16, and implanted assembly 14 are implanted in the subject. At step 94, the implanted assembly is activated to substantially continuously sample EEG signals from the subject. At step 96, the sampled EEG signals are wirelessly transmitted from the implanted assembly 14 to an external assembly 20. At step 98, the sampled EEG signals are stored in a memory—either in the external assembly 20 or in one of the computer workstations 22, 26. At step 100, the stored EEG signals are manually analyzed by the physician and/or analyzed with EEG analysis software, typically using a seizure advisory algorithm(s) or spike detector, to derive statistics for the clinical seizures and/or the sub-clinical seizures for the subject based on the long-term, ambulatory EEG data. For example, the following statistics may be quantified using the present invention: (1) Seizure count over a time period—How many clinical and sub-clinical

seizures does the subject have in a specific time period? (2) Seizure frequency—How frequent does the subject have seizures? What is the seizure frequency without medication and with medication? Without electrical stimulation and with electrical stimulation? (3) Seizure duration—How long do the seizures last? Without medication and with medication? Without electrical stimulation and with electrical stimulation? (4) Seizure timing—When did the subject have the seizure? Do the seizures occur more frequently at certain times of the day? (5) Seizure patterns—Is there a pattern to the subject's seizures? After certain activities are performed? What activities appear to trigger seizures for this particular subject?

Finally, at step 102, 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, and may also include the EEG signals 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 subject in an actionable format.

As noted above, embodiments of the present invention can enable the quantification, documentation and long term monitoring of sub-clinical seizures in a subject. Because the subject is unaware of the occurrence of sub-clinical seizures, heretofore 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, may provide important additional information relevant to the effectiveness of subject therapy, and may further enhance the development of additional treatments for epilepsy.

FIG. 11 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 subject or stopping the usage of ineffective therapies. Currently, effectiveness of the AED therapy is based on self-reporting of the subject, in which the subject makes entries in a diary regarding the occurrence of their seizure(s). If the entries in the subject diary indicate a reduction in seizure frequency, the AED is deemed to be effective and the subject continues with some form of the current regimen of AEDs. If the subject entries in the subject 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 subject on ineffective AEDs and exposes the subject to unnecessary side-effects.

By way of example, a medically refractory subject 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 subject's medications and have the subject 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 subject 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 subjects to make informed decisions on the effectiveness and non-effectiveness of the medications.

FIG. 11 schematically illustrates this method 110. At step 114, the implantable assembly and external assembly are used to monitor the subject's EEG to obtain a baseline measurement for the subject. The baseline measurement is typically seizure activity statistics for a specific time period 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 subject is not taking any AEDs or using any other therapy. In other embodiments, however, the subject may be taking one or more AEDs and the baseline measurement will be used to evaluate adjustments to dosage or other add-on therapies.

At step 116, the therapy that is to be evaluated is commenced. The therapy will typically be an AED and the subject 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 assembly and external assembly will be used to substantially continuously sample the subject's EEG. The sampled EEG may thereafter be processed to obtain a follow-up measurement for the subject (Step 118). 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 120, 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 subject's baseline, the therapy may be stopped, and other therapies may be tried.

Currently, the primary metric in evaluating the efficacy of an AED is whether or not the AED reduces the subject'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 subject was having a large number of sub-clinical seizures, spike bursts, or other epileptiform activity (which the subject 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 subject diary "metrics", the subject and physician would not be aware of such a reduction, and such an AED would be determined to be non-efficacious for the subject. However, because the present invention is able to provide metrics for the sub-clinical seizures, the efficacious medication could be continued.

At step 122, 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" up measurements and/or the baseline measurements.

Of course, the therapy is not limited to AED therapy. Therapies that can be assessed may include cooling therapy, electrical stimulation (such as vagus nerve stimulation, deep brain stimulation, cortical stimulation), or the like. Various embodiments may be used to screen the subjects for determining appropriate therapy for their condition and/or to determine the appropriate parameters for the selected therapy.

In addition to evaluating an efficacy of a therapy for an individual subject, the metrics that may be provided also enable an intelligent titration of a subject's medications. As shown in FIG. 12, if the subject is on a treatment regimen of an efficacious therapy, the system may be used to reduce/titrate a dosage or frequency of intake of the AED (or AEDs) 130. Typically, the subject 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 134). At step 136, the subject's EEG (and/or other physiological signal) is monitored for a desired time period to obtain a first subject data measurement for the subject (e.g., the baseline measurement). Similar to previous embodiments, the first subject data measurement may be any desired metrics, but will typically be selected from clinical seizure frequency, clinical seizure duration, sub-clinical seizure frequency, sub-clinical seizure duration, medication side effects. At step 138, 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. 12). 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.

At step 140, the subject's EEG is monitored and processed to obtain a second subject data measurement for the subject (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 142), and a therapy with N^{th} parameters (e.g., third, fourth, fifth . . .) is commenced (step 144). Monitoring and processing of the subject's EEG signals are repeated (step 146), and the process is repeated a desired number of times (as illustrated by arrow 147). Once the desired numbers of modifications to the therapy have been made, the various subject data measurements may be analyzed and compared to each other to determine the most desirous parameters for the therapy (step 148).

With the instrumentation provided by the present invention, the process of selecting appropriate AEDs and the dosages of such AEDs could occur much faster and with much greater insight than ever before. Further, the chance of a subject remaining on an incremental AED that was providing little incremental benefit would be minimized. Once a subject was under control, the subject could cease the use of the system, but the implantable assembly could remain. In the future, the subject might be asked to use the system again should their condition change.

In addition to or as an alternative to the above data collection uses, some embodiments may be used to analyze EEG data substantially in real-time and provide an output to

the subject and/or provide a therapy to the subject based on the analysis of the EEG data. In some embodiments, the systems may be used as seizure advisory systems that measure the subject's susceptibility to a seizure and/or to detect the onset of the seizure prior to the clinical manifestation of the seizure and provide an appropriate warning to the subject. In some embodiments, the systems may be used to detect the onset of a known event (such as an electrographically identified seizure) and to warn the subject or other individual of the detection.

The platform of system 10 used for data collection described above and the system used for determining the subject's susceptibility for having a seizure may have the same general components, so that the same system may be used for both data collection and advising of susceptibility to seizure. However, when the system is used for data collection during a training period, the algorithms that determine the subject's susceptibility of having a seizure may be disabled or not yet programmed in the system so as to not be accessible to the subject. If and when seizure advising is desired, such algorithms may be enabled and/or added into the system.

For example, EEG data may be collected as noted above. The collected EEG data may be analyzed off-line (e.g., in a separate computer, such as workstation 22) and, if desired, algorithms may be customized or otherwise tuned to the subject specific EEG data. Thereafter, the parameters of the disabled algorithm(s) may be modified or the entire tuned algorithm may be uploaded to a memory of system 10 and the aspects of the system relevant to seizure advising may be enabled. Finally, the seizure advising functionality in the system 10 may be enabled and used by the subject in real-time on a substantially continuous basis.

FIG. 13 illustrates an embodiment of the seizure advisory system in which the electrode array 12 includes at least one depth electrode array, but otherwise contains similar components as the system of FIG. 1. Typically, the depth electrode will be only for sampling EEG signals, but as will be described below, the electrode arrays 12 may be used to deliver electrical stimulation directly to the brain. The system 10 shown in FIGS. 1 and 13 will include algorithms that process the EEG in substantially real-time to determine the subject's susceptibility for having a seizure. When a high susceptibility to a seizure is determined, a user interface of the external assembly 20 will provide an output to the subject that is indicative of the high susceptibility to the seizure. In the illustrated embodiment, the output to the subject may be a visual display on the LCD, a light display on the LED, a vibratory signal, and/or an audio output, etc., as described above.

FIG. 14 depicts an example of the overall structure of a system for performing substantially real-time assessment of the subject's brain activity and for determining the communication output that is provided to the subject. The system may comprise one or more algorithms or modules that process input data 162. The algorithms may take a variety of different forms, but typically comprises one or more feature extractors 164a, 164b, 165 and at least one classifier 166 and 167. The embodiment illustrated in FIG. 14 shows a contralateral algorithm 163 and a pro-ictal algorithm 161 which share at least some of the same feature extractors 164a and 164b. In alternative embodiments, however, the algorithms used in the system may use exactly the same feature extractors or completely different feature extractors.

The input data 162 is typically EEG, but may comprise representations of physiological signals obtained from monitoring a subject and may comprise any one or combi-

nation of the aforementioned physiological signals from the subject. The input data may be in the form of analog signal data or digital signal data that has been converted by way of an analog to digital converter (not shown). The signals may also be amplified, preprocessed, and/or conditioned to filter out spurious signals or noise. For purposes of simplicity the input data of all of the preceding forms is referred to herein as input data **162**. In one preferred embodiment, the input data comprises between about 1 channel and about 64 channels of EEG from the subject.

The input data **162** from the selected physiological signals is supplied to the one or more feature extractors **164a**, **164b**, **165**. Feature extractor **164a**, **164b**, **165** may be, for example, a set of computer executable instructions stored on a computer readable medium, or a corresponding instantiated object or process that executes on a computing device. Certain feature extractors may also be implemented as programmable logic or as circuitry. In general, feature extractors **164a**, **164b**, **165** can process data **162** and identify some characteristic of interest in the data **162**. Such a characteristic of the data is referred to herein as an extracted feature.

Each feature extractor **164a**, **164b**, **165** may be univariate (operating on a single input data channel), bivariate (operating on two data channels), or multivariate (operating on multiple data channels). Some examples of potentially useful characteristics to extract from signals for use in determining the subject's propensity for a neurological event, include but are not limited to, bandwidth limited power (alpha band [8-13 Hz], beta band [13-18 Hz], delta band [0.1-4 Hz], theta band [4-8 Hz], low beta band [12-15 Hz], mid-beta band [15-18 Hz], high beta band [18-30 Hz], gamma band [30-48 Hz], high frequency power [>48 Hz], bands with octave or half-octave spacings, wavelets, etc.), second, third and fourth (and higher) statistical moments of the EEG amplitudes or other features, spectral edge frequency, decorrelation time, Hjorth mobility (HM), Hjorth complexity (HC), the largest Lyapunov exponent $L(\max)$, effective correlation dimension, local flow, entropy, loss of recurrence LR as a measure of non-stationarity, mean phase coherence, conditional probability, brain dynamics (synchronization or desynchronization of neural activity, STL-max, T-index, angular frequency, and entropy), line length calculations, first, second and higher derivatives of amplitude or other features, integrals, and mathematical linear and non-linear operations including but not limited to addition, subtraction, division, multiplication and logarithmic operations. Of course, for other neurological conditions, additional or alternative characteristic extractors may be used with the systems described herein.

The extracted characteristics can be supplied to the one or more classifiers **166**, **167**. Like the feature extractors **164a**, **164b**, **165**, each classifier **166**, **167** may be, for example, a set of computer executable instructions stored on a computer readable medium or a corresponding instantiated object or process that executes on a computing device. Certain classifiers may also be implemented as programmable logic or as circuitry.

The classifiers **166**, **167** analyze one or more of the extracted characteristics, and either alone or in combination with each other (and possibly other subject dependent parameters), provide a result **168** that may characterize, for example, a subject's condition. The output from the classifiers may then be used to determine the subject's susceptibility for having a seizure, which can determine the output communication that is provided to the subject regarding their condition. As described above, the classifiers **166**, **167**

are trained by exposing them to training measurement vectors, typically using supervised methods for known classes, e.g. ictal, and unsupervised methods as described above for classes that can't be identified a priori, e.g. contra-ictal. Some examples of classifiers include k-nearest neighbor ("KNN"), linear or non-linear regression, Bayesian, mixture models based on Gaussians or other basis functions, neural networks, and support vector machines ("SVM"). Each classifier **166**, **167** may provide a variety of output results, such as a logical result or a weighted result. The classifiers **166**, **167** may be customized for the individual subject and may be adapted to use only a subset of the characteristics that are most useful for the specific subject. Additionally, over time, the classifiers **166**, **167** may be further adapted to the subject, based, for example, in part on the result of previous analyses and may reselect extracted characteristics that are used for the specific subject.

For the embodiment of FIG. **14**, the pro-ictal classifier **167** may classify the outputs from feature extractors **164a**, **164b** to detect characteristics that indicate that the subject is at an elevated susceptibility for a neurological event, while the contra-ictal classifier **166** may classify the outputs from feature extractors **164a**, **164b**, **165** to detect characteristics that occur when the subject is unlikely to transition into an ictal condition for a specified period of time. The combined output of the classifiers **166**, **167** may be used to determine the output communication provided to the subject. In embodiments which comprise only the contra-ictal algorithm, the output from the contra-ictal classifier **166** alone may be used to determine the output communication to the subject. Further details of exemplary algorithms that may be used to identify a subject's susceptibility to having a seizure may be found in co-pending U.S. patent application Ser. No. 12/020,450 (filed on Jan. 25, 2008 and published as U.S. Patent Publication No. 2008/0183096), the complete disclosure of which is incorporated herein by reference in its entirety.

Depending on the specific feature extractors and classifiers used, the computational demands of the analysis provided by feature extractors **164a**, **164b**, **165** and classification provided by classifiers **166**, **167** can be extensive. In the case of ambulatory systems supplied by portable power sources, such as batteries, supplying the power required to meet the computational demands can severely limit power source life. In preferred embodiments, both the seizure advisory algorithm are embodied in the external assembly **20**. Processing the EEG data with the algorithms in the external assembly **20** provides a number of advantages over having the algorithms in the implanted assembly. First, keeping the processing in the external assembly **20** will reduce the overall power consumption in the implanted assembly **14** and will prolong the battery life of the implanted assembly **14**. Second, charging of battery or replacing the battery of the external assembly **20** is much easier to accomplish. The battery of the external assembly may be charged by placing the external assembly **20** in a recharging cradle (e.g., inductive recharging) or simply by attaching the external assembly to an AC power source. Third, customizing, tuning and/or upgrading the algorithms will be easier to achieve in the external assembly **20**. Such changes may be carried out by simply connecting the external assembly to the physician's computer workstation **20** and downloading the changes. Alternatively, upgrading may be performed automatically over a wireless connection with the communication sub-assembly **64**.

While it is preferred to have the observer algorithms **160** in the external assembly **20**, in alternate embodiments, the

observer algorithms **160** may be wholly embodied in the implanted assembly **14** or a portion of one or more of the observer algorithms **160** may be embodied in the implanted assembly **14** and another portion of the one or more algorithms may be embodied in the external assembly **20**. In such embodiments, the processing sub-assembly **44** (or equivalent component) of the implanted assembly **14** may execute the analysis software, such as a seizure advisory algorithm(s) or portions of such algorithms. For example, in some configurations, one or more cores of the processing sub-assembly **44** may run one or more feature extractors that extract features from the EEG signal that are indicative of the subject's susceptibility to a seizure, while the classifier could run on a separate core of the processing sub-assembly **44**. Once the feature(s) are extracted, the extracted feature(s) may be sent to the communication sub-assembly **46** for the wireless transmission to the external assembly **20** and/or store the extracted feature(s) in memory sub-system **52** of the implanted assembly **14**. 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 wireless communication link **18** between the implantable assembly **14** and the external assembly **20**.

In other embodiments, the seizure advisory algorithms may be wholly embodied within the implanted assembly **14** and the data transmission to the external assembly **29** may include the data output from the classifier, a warning signal, recommendation, or the like. 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, and published as 2007/0149952) *al.*, and U.S. patent application Ser. No. 11/766,742 (filed Jun. 21, 2007, and published as 2008/0027515), the complete disclosures of which are incorporated herein by reference in their entireties.

FIG. **15** illustrates a method of using the systems described herein to collect data, tune the algorithms and use the tuned algorithms to estimate the subject's susceptibility to a seizure. At step **200**, the subject is implanted with the system **10** in which the seizure advisory algorithms are disabled or not yet present in the system. The user interface aspects that are related to the seizure advising may also be disabled.

At step **202**, the system is used to collect EEG data for a desired time period, as described in detail above. Generally, the desired time period will be a specified time period such as at least one week, between one week and two weeks, between two weeks and one month, between one month and two months, or two months or more. But the desired time period may simply be a minimum time period that provides a desired number of seizure events. At step **204**, the collected EEG data may be periodically downloaded to the physician's computer workstation or the entire EEG data may be brought into the physician's office in a single visit.

At step **206**, the physician may analyze the EEG data using the computer workstation that is running EEG analysis software, the EEG data may be transferred to a remote analyzing facility that comprises a multiplicity of computing nodes where the EEG data may be analyzed on an expedited basis, or it may even be possible to analyze the EEG analysis software in the external assembly **20**. Analysis of the EEG data may be performed in a piecewise fashion after the shorter epochs of EEG data is uploaded to the database, or the analysis of the EEG data may be started after the EEG data for the entire desired time period has been collected. Typically, "analysis of the EEG data" will include identify-

ing and annotating at least some of spike bursts, the earliest electrographic change (EEC), unequivocal electrical onset (UEO), unequivocal clinical onset (UCO), electrographic end of seizure (EES). Identification of such events may be performed automatically with a seizure detection algorithm, manually by board certified epileptologists, or a combination thereof. After the EEG data is annotated, the seizure advisory algorithm(s) may be trained on the annotated EEG data in order to tune the parameters of the algorithm(s) to the subject specific EEG data.

Once the algorithm(s) are tuned to meet minimum performance criteria, at step **208** the tuned algorithm(s) or the parameter changes to the base algorithm may be uploaded to the external assembly **20**. At step **210**, the tuned algorithm and the other user interface aspects of the present invention may be activated, and the observer algorithm may be used by the subject to monitor the subject's susceptibility to a seizure and/or detect seizures.

When the seizure advisory system **10** determines that the subject is at an increased susceptibility to a seizure (or otherwise detects a seizure), the external assembly may be configured to generate a seizure warning to the subject, as described above. For example, the external assembly may activate a red or yellow LED light, generate a visual warning on the LCD, provide an audio warning, deliver a tactile warning, or any combination thereof. If desired, the warning may be "graded" so as to indicate the confidence level of the seizure advisory, indicate the estimated time horizon until the seizure, or the like. "Grading" of the warning may be through generation of different lights, audio, or tactile warning or a different pattern of lights, audio or tactile warnings.

Additionally or alternatively, the external assembly may include an instruction to the subject regarding an appropriate therapy for preventing or reducing the susceptibility for the seizure. The instruction may instruct the subject to take a dosage of their prescribed AED, perform biofeedback to prevent/abort the seizure, manually activate an electrical stimulator (e.g., use a wand to activate an implanted VNS device) or merely to instruct the subject to make themselves safe. A more complete description of various instructions that may be output to the subject are described in U.S. patent application Ser. No. 11/321,897 (filed Dec. 28, 2005, and published as 2007/0150024) and Ser. No. 11/321,898 (filed Dec. 28, 2005, and published as 2007/0150025), both of which are incorporated by reference herein in their entireties.

The outputs provided to the subject via the external assembly may be a standardized warning or instruction, or it may be programmed by the physician to be customized specifically to the subject and their condition. For example, different subjects will be taking different AEDs, different dosages of the AEDs, and some may be implanted with manually actuatable stimulators (e.g., NeuroPace RNS, Cyberonics VNS, etc), and the physician will likely be desirous to customize the therapy to the subject. Thus, the physician will be able to program the warning and/or instruction to correspond to the level of susceptibility, estimated time horizon to seizure, or the like.

Embodiments may also be adapted to provide closed-loop therapy to the subject. FIG. **16** illustrates one embodiment of the system **10** that includes therapy delivery assembly in the implanted assembly **14**. The system **10** illustrated in FIG. **16** will generally have the same components as shown in FIGS. **1** and **13**, but will also include an implanted pulse generator (not shown) that is in communication with a vagus nerve cuff electrode **220** via a lead **222**. When the seizure advisory system determines that the subject is at an elevated suscep-

tibility to a seizure, the system may automatically initiate delivery of electrical stimulation to the vagus nerve cuff electrode. The parameters (e.g., burst/no burst mode, amplitude, pulse width, pulse frequency, etc.) of the electrical stimulation may be varied based on the subject's susceptibility, or the parameter may be constant.

While not shown in FIG. 16, other therapy outputs may be provided—such as electrical stimulation of the brain tissue (e.g., deep brain structures, cortical stimulation) using electrode array 12 or other electrode arrays (not shown), stimulation of cranial nerves (e.g., trigeminal stimulation), delivery of one or more drugs via implanted drug dispensers, cooling therapy to the brain tissue, cranial nerves, and/or peripheral nerves), or the like. Similar to vagus nerve stimulation, parameters of the therapy may be constant or the parameters of the therapy may be modified based on the subject's estimated susceptibility.

Such therapies may be used in addition to the vagus nerve stimulation or as an alternative to such therapy. If desired, the type of therapy delivered to the subject may be modified based on the subject's susceptibility. For example, if the elevated susceptibility estimates a long time horizon until seizure and/or a lower confidence level, a more benign type of therapy (e.g., electrical stimulation) may be employed. But if the elevated susceptibility estimates a shorter time horizon until seizure and/or has a higher confidence level, different type of therapy (e.g., pharmacotherapy) may be employed.

FIG. 17 illustrates an embodiment that is used with a vagus nerve stimulator 300, such as the Vagus Nerve Stimulation System by Cyberonics, Inc. of Houston, Tex. When the system 10 of the illustrated embodiment determines that the subject is at an elevated risk for a seizure, the system 10 may generate a communication to the subject via the external assembly 20, and the subject may use a wand associated with the vagus nerve stimulator 300 to manually active stimulation of the vagus nerve. Accordingly, it is not necessary that the implanted vagus nerve stimulator 300 be in communication with the other components in the system 10 in order for the patient to obtain the benefits of responsive stimulation based on the risk of seizure.

Some embodiments of the monitoring system may include an integral subject diary functionality. The subject diary may be a module in the external assembly and inputs by the subject 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 subject. Entries by the subject may be a voice recording, or through activation of user inputs on the external assembly. 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 subject'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 subject inputs recorded in the diary may also be used by the physician in assessing the subject'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 subject to the number of seizures detected by the seizure detection algorithm.

Caregiver Alert

In accordance with embodiments of the present invention, a system provides alerts of neurological events occurring in a human subject. This system includes a monitoring module adapted to detect and sample a neurological signal, an event detection module coupled to the monitoring module for detecting one or more types of predetermined reportable events based on the detected neurological signal, and an alert module coupled to the event detection module. Upon the detection of a reportable event by the event detection module, said alert module selects a first alert contact from a plurality of contacts contained in a contact list, and generates a first alert communication to the first alert contact.

FIG. 18 shows an embodiment of a system 1810 which provides alerts of neurological events. The system 1810 may include an implanted assembly 1814, and an external assembly 1820 which has a wireless communication module for transmitting alerts to other devices, such as a caregiver alert device 1821 or a remote computer system 1826 that can, in turn, relay alerts to other parties. Upon the occurrence of some predetermined reportable event, the system 1810 is configured to transmit an alert message to another person or device.

This wireless communication module may provide short range communication (using for example IEEE 802.11, WiFi, Bluetooth, Zigbee or any other short range communication protocol), long range communication (using for example cellular telephone capability, Short Message Service (SMS), Multimedia Messaging Service (MMS), or any other long range communication protocol). In some embodiments, the external device 1820 may be configured to utilize short range communication to communicate with a separate device having long-range communication capabilities. For example, the external device 1820 may communicate with a mobile telephone handset 1823 via Bluetooth or other short range protocol, and the mobile handset 1823 will communicate with a central call center or directly to a caregiver 1825 via long range cellular communication.

The system 1810 may be configured to transmit alerts based on any of a variety of predetermined events. These alerts may be customized for each individual subject based on that subject's previously monitored neurological or other physiological signals.

The reportable events can be any type of event that subject, the subject's caregiver, or health care provider believes is sufficiently significant that an alert should be issued. The reportable event can be any type of anomaly in the monitored physiological signal. The reportable event detection algorithm may be configured to detect a specific type of reportable event (e.g., a seizure), or to detect any of a variety of reportable events (e.g., a seizure continuing beyond a prescribed period of time or multiple seizures occurring within a prescribed period of time), and upon detection of a reportable event, the system 1810 will transmit an alert to a caregiver, the subject, or other device. Various types of alerts are described in more detail below.

In some embodiments, the subject may be monitored by the system 1810 for an extended period of time (e.g., one week, multiple weeks, one month, several months, or longer) so that the system 1810 has the opportunity to record and identify the characteristics of that subject's reportable events. For example, the system 1810 may be used to collect one or two months of EEG data from the subject so as to record a predetermined minimum number of seizures or other types of reportable events that are determined to be sufficiently significant that an alert should be issued any time they occur. Then, the system 1810 is configured to monitor

the subject's physiological signals and run a reportable event detection algorithm real time to continuously monitor the physiological signals for the presence of a reportable event. In some embodiments, after the reportable event detection algorithm has been implemented in the system **1810**, it may be desirable to cease recording physiological data in order to reduce power consumption. In other embodiments, it may be desirable to continue recording physiological data even after the reportable event detection algorithm has been implemented so that the algorithm may be improved to better detect the known reportable events or to detect new reportable events to add to a revised reportable event detection algorithm. In some embodiments, the reportable event detection algorithm may be adjusted over time to either increase or decrease sensitivity to the types of anomalies being detected, which would result in changes to the sensitivity and specificity of the alerts.

In some embodiments, the types of reportable events may be identified based on analysis of EEG data alone. In other embodiments, different types of inputs may be used alone or in combination by the reportable event detection algorithm to detect reportable events. These inputs may be, for example, ECG/EKG signals monitored by the system **1810** or accelerometer or other positioning or movement recordings by the system **1810**.

The reportable event detection algorithm may be configured to detect any of a variety of reportable events. For example, a reportable event may correspond to detection of a certain brain state (e.g., high seizure susceptibility brain state), detection of a suspected seizure, detection of a suspected seizure that continues beyond a predetermined period of time (e.g., more than anywhere from one to ten minutes, such as more than five minutes), or detection of a suspected seizure that has occurred within a certain period of time since the last suspected seizure (e.g., if more than one seizure is detected within an hour, or within anywhere from one to ten hours, or within anywhere from one to sixty minutes).

In other embodiments, the system **1810** may be configured to detect when a medication that the subject is taking is at a sub-therapeutic or suboptimal level in the subject's body. This detection may be performed based on analysis of the EEG signals, or may be performed using another sensor for monitoring other physiological signals or for performing a biochemical test, such as for the presence of drugs or metabolites in the subject's blood stream. This be performed using an implanted device or using an external device which receives biological specimens from the subject. Upon detection of sub-therapeutic or suboptimal levels in the subject, an alert may be issued to the subject and/or caregiver indicating this detection. This may serve as a reminder to the subject to take a forgotten dose of the medication or to the caregiver to provide closer monitoring of the subject's compliance.

The system **1810** may be configured to alert the subject of the detection of a suspected event, such as an elevated susceptibility brain state or a suspected seizure. In some cases, it may be desirable to alert the subject at the same time as the caregiver is alerted. In other cases such as when it is uncertain whether the detected event requires intervention or is a false positive detection of an event, it may be desirable to alert the subject prior to alerting a caregiver. If the subject is capable of acknowledging the alert (e.g., by pressing a button on the user interface of the external device **1820** in response to an audio or visual warning provided by the external device **1820**), then it can be assumed that the subject is not experiencing a seizure and no further alerts may be necessary. However, if the subject fails to acknowl-

edge the alert on the external device **1820**, then it may be deemed desirable to issue an alert to a caregiver to indicate that the subject was unresponsive.

In some embodiments, the system **1810** may be configured to transmit different alert messages upon detection of different types of events or to transmit a series of alerts depending on the circumstances. For example, if a subject transitioned out of a low susceptibility to seizure state, this situation may be deemed to be useful to know by the caregiver but not requiring urgent intervention. In this case, the system **1810** may transmit a low urgency alert type to a caregiver (e.g., a simple email or text message) to inform the caregiver of the transition. The caregiver may have been previously informed that such a message does not require any action because the subject is not at a high risk of injury, or the message may include express instructions to that effect. Because the risk of injury is low, it may not be necessary or desirable for the recipient of the alert to acknowledge receipt of the alert and it may be acceptable if the alert is not actually received by the caregiver. In one example, the external assembly **1820** is configured to transmit an SMS or email alert message to a previously-stored address corresponding to a family member, friend, caregiver, or healthcare provider.

If the system **1810** detects a type of reportable event that corresponds with a higher estimated risk of injury or other event that may require urgent intervention, it may be desirable to provide a more urgent warning alert type. This urgent warning may be transmitted using a communication channel that is more reliable, better able to attract the recipient's attention, or that provides the recipient the ability to acknowledge receipt of the alert.

In some embodiments, the system **1810** may be provided with an audio and/or video recording functionality. This functionality may be incorporated into the patient-carried external device **1820** or may be incorporated into a separate monitoring device **1827**. This monitoring device **1827** could be patient carried or may be installed in locations where the subject is frequently located, such as in various rooms within the subject's home (e.g., bedroom, bathroom, living room, kitchen). The monitoring device **1827** can in some embodiments continuously record audio and/or video of the patient and provide a live feed of the monitoring, similar to a webcam. In other embodiments, the system **1810** may be configured to transmit the audio and/or video monitoring from the monitoring device **1827** only when a certain reportable event is detected. For example, when a seizure is detected, the system **1810** may transmit an alert to a caregiver or emergency call center. That alert may contain an image of the subject, an audio recording of the subject, or a video recording of the subject at the time the event is occurring. In other embodiments, the alert may include a internet link to a recording or live feed of the subject. Therefore, the caregiver can see what is happening to the subject and get a better sense of whether the subject is in danger or needs assistance.

In some embodiments, the system **1810** may be provided with the ability to alert regarding communication errors between any of the various components and caregivers. As described above, the system **1810** may generate an alert when there is a communication error between the implanted assembly **1814** and the external device **1820**. The error may be detected using, e.g., a periodic heartbeat signal between the implanted assembly **1814** and the external device **1820**. This alert may be delivered to the subject via the user interfaced of the external device **1820**, or may be transmitted to one or more caregivers **1825** or a remote computer system

1826. In other embodiments, if there is a communication error anywhere between the implanted assembly **1814**, the external device **1820**, and the caregiver alert device **1821**, an alert is generated to both the external device **1820** and the caregiver alert device **1821**. With these automated alerts, both the subject and the caregiver can have comfort that the system **1810** is operating properly and the subject is being safely monitored. In other embodiments, the caregiver may be provided with the option to manually check the status of the communication channels. For example, the caregiver alert device **1821** may include a user interface including a status check button, which, when depressed, will generate a test signal through the system **1810** to ensure all components are operating properly and in communication with each other.

Contact Lists

In some embodiments, the system **1810** may be configured with a contact list having a list of caregivers to be contacted for alert messages. In some embodiments, a single contact list may be utilized for all alerts. In other embodiments, different contact lists containing different recipients and/or a different ordering of recipients may be used for different types of reportable events.

In some embodiments, urgent warnings may require that the recipient of the warning acknowledge receipt of that warning so as to be certain that any necessary action will be taken. If the first recipient in the contact list does not acknowledge receipt within a predetermined period of time, then an additional warning may be transmitted to the next recipient in the contact list, such as another preidentified caregiver, a physician, or emergency services provider.

For example, if the subject experiences a seizure having a duration of greater than five minutes, then the system **1810** may place a telephone call to a previously-stored mobile telephone number corresponding to the primary caregiver. In the telephone call, the system **1810** may require acknowledgement of receipt of the message by the caregiver, such as by requiring that the recipient of the call press a certain key or sequence of keys on the telephone. If no acknowledgement is received, the system **1810** may proceed to call the next contact in the contact list and continue until an acknowledgement is received. The next contact may be an alternate telephone number for that same primary caregiver, or may be a telephone number associated with a secondary caregiver. In some embodiments, the system **1810** may be configured to automatically call emergency services either if the previously identified caregivers could not be reached or if a certain high risk event is detected (e.g., if the system **1810** determines that the subject has been in a state of seizure for an extended period of time).

As described above, the system **1810** may be configured to contact each contact in the contact list in sequence until a contact confirms receipt of the alert. In other embodiments, alerts may be broadcast to multiple contacts simultaneously or in sequence without waiting to receive a confirmation of receipt. In yet other embodiments, the alerts may be first transmitted to a single contact and if no acknowledgement is received, then the alerts are broadcast to multiple contacts. Any combination of contact sequences may be used.

In yet other embodiments, the recipient of the alert may be provided with the option to instruct the system **1810** to contact other parties. For example, upon detection of a cluster of seizures, the system **1810** may be configured to place a call to the primary caregiver's mobile telephone. In that call, the system **1810** may provide an audio message indicating the type of alert being transmitted (e.g., a seizure cluster), and request input from the caregiver regarding the

next action for the system **1810** to take. This may be accomplished by prompting the caregiver to enter one or more keypress sequences to indicate the next action, which could be, for example, to immediately call an emergency services provider, call the subject's physician, or in systems **1810** that incorporate some form of therapy delivery mechanism, to deliver a therapy to the subject. This therapy could be, for example, electrical stimulation of the subject's brain or peripheral nervous system, or delivery of an AED to the subject.

In accordance with some embodiments, the system **1810** can be provided with location determining capability so as to be able to determine the location of the subject. Such location determining capability may utilize any of a variety of known technologies, such as, e.g., GPS, Wireless LAN location awareness, WiFi positioning, or other geolocation techniques. The external device **1820** may be provided with a location determining module, such as a GPS receiver chipset or the like, such that any communications or alerts issued by the external device **1820** may also include the location of the patient. This location may be provided in a variety of ways. For example, a specific geographic coordinate may be provided, or a general location may be provided instead. In some embodiments, the general location may be determined based on detected WiFi hotspots. In yet other embodiments, the subject's home or other frequently visited location (e.g., workplace) may be provided with hardware configured to precisely locate the system **1810** within that location. For example, the subject's home may include receivers in one or more rooms so that a caregiver can be informed which room the subject is located in at any moment or at the moment that an alert is issued. In yet other embodiments, the external device **1820** may be configured to receive positioning information from separate device, such as a mobile handset or GPS receiver, which is configured to communicate with the external device **1820** to provide positioning information.

FIG. **19** illustrates a system **1910** which incorporates a drug delivery device **1931** that can be triggered to deliver a rescue medication upon detection of a certain event or sequence of events. For example, some subjects are at risk of having seizures while asleep. If the subject experiences status epilepticus, during which the subject experiences a continuous unremitting seizure for an extended period of time or repetitive seizures for an extended period of time, the subject may be at high risk of suffering brain damage. It would be desirable for the system **1910** to alert a caregiver of such a nighttime seizure using any of the various technologies described herein. In addition, it may be desirable for the system **1910** to trigger the automatic delivery of a rescue drug for stopping the seizure, such as, e.g., benzodiazepine, phenytoin, fosphenytoin, carbamazepine, or valproate.

This drug delivery device may be an implanted drug delivery device or may be an external drug delivery device **1931** that is in wired or wireless communication with the external device **1920** or implanted assembly **1914**. This drug delivery device **1931** may be, e.g., incorporated into a mouthpiece, similar to a protective mouth-guard appliance, in a rectal device that may be temporarily inserted into the subject's rectum at night, or in a nasal device that may be temporarily inserted into the subject's nasal passages at night. This drug delivery device **1931** may include a drug reservoir that may be activated upon detection of a seizure, prolonged seizure, or series of seizures. The mouthpiece embodiment may spray or squirt a liquid rescue drug into the subject's mouth or throat upon detection of a seizure or

extended seizure. The rectal device may release a suppository rescue drug upon detection of the seizure or extended seizure.

FIG. 20 illustrates another embodiment in which the system 2010 includes an active transdermal drug delivery patch 2031 that may be activated by the system 2010 upon detection of a certain event or sequence of events. The drug delivery patch 2031 may be activated by, e.g., heat or an electrical field, and the system 2010 may be provided with a mechanism for generating heat or an electrical field upon detection of the event, such as a seizure, extended seizure, series of seizures within a certain time frame, or a certain brain state, such as a high susceptibility to seizure state.

In some embodiments, the heat or electrical field may be generated by the implanted assembly 2014, and the drug delivery patch may be placed on the subject's skin so as to overlay the implanted assembly 2014. In some embodiments, the implanted assembly 2014 may include an induction coil for recharging the battery that powers the implanted assembly 2014. This induction coil may also be used by the implanted assembly 2014 to create an electromagnetic field around the drug delivery patch. The drug delivery patch may be provided with an induction coil that can respond to this electromagnetic field to activate the transdermal drug delivery, e.g., by generating heat in the drug delivery patch.

In some embodiments, it may be desirable for the drug delivery patch 2031 to include more than one drug for treating the subject. For example, the drug delivery patch may include a chronic drug that is passively delivered to the subject from the patch, and may also include a rescue drug that is actively delivered by the patch upon detection of a triggering event, such as detection of a seizure, extended seizure, or other brain state.

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 subject's neurological system.

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 system for reporting physiological events occurring in a human subject, comprising:

a monitoring module adapted to receive a physiological signal from the subject, the physiological signal being a motion signal acquired from an accelerometer;

an event detection module configured to receive the physiological signal from the monitoring module, the event detection module further configured to generate outputs based on the physiological signal that distinguish between a first type of reportable event corresponding to a low urgency condition of the subject not requiring urgent intervention and a second type of reportable event corresponding to a high urgency neurological condition of the subject requiring urgent intervention;

a therapy delivery module configured to receive a therapy initiation signal from the event detection module, said therapy delivery module being configured to deliver a therapy to the subject; and

an alert module configured to receive at least one of the outputs from the event detection module, wherein upon receipt of an output corresponding to the second type of reportable event, said alert module generates an alert communication to each alert contact from a plurality of contacts contained in a contact list in sequence until receipt of at least one of the generated alert communications is acknowledged.

2. The system of claim 1, wherein the alert module generates an alert communication upon receipt of an output corresponding to the first type of reportable event.

3. The system of claim 2, wherein at least one of the generated alert communications provides a recipient information regarding the reportable event.

4. The system of claim 2, wherein the alert communication corresponding to the first type of reportable event does not prompt a recipient to acknowledge receipt of the alert communication.

5. The system of claim 2, wherein the alert communication corresponding to the first type of reportable event is transmitted via a first communication channel, and the alert communication corresponding to the second type of reportable event is transmitted via a second communication channel different than the first communication channel.

6. The system of claim 5, wherein the second communication channel differs from the first communication channel because the second communication channel is at least one of more reliable than the first communication channel and more noticeable to the alert contact than the first communication channel.

7. The system of claim 1, wherein at least one alert contact comprises an electronic message address or a telephone number.

8. The system of claim 1, wherein said at least one of the generated alert communications prompts a recipient to acknowledge receipt of the alert communication.

9. The system of claim 1, wherein said alert communication is selected from a plurality of predetermined alert types, each alert type being associated with a different type of reportable event.

10. The system of claim 1, wherein said alert module is configured to wirelessly transmit the alert communication to each alert contact from the plurality of contacts.

11. The system of claim 1, wherein said at least first and second types of reportable events comprise at least one of: detection of a suspected seizure, detection of a suspected seizure that continues beyond a predetermined period of time, and detection of a suspected seizure that has occurred within a certain period of time since a preceding suspected seizure.

12. The system of claim 1, wherein:

the monitoring module is further configured to receive one or more additional physiological signals; and the event detection module is further configured to generate additional outputs corresponding to additional reportable events based on the physiological signal and the one or more additional physiological signals.

13. The system of claim 12, wherein the monitoring module is configured to receive a cardiac signal.

14. The system of claim 12, wherein the one or more additional physiological signals correspond to at least one of subject heart rate, position, and movement.

15. The system of claim 1, wherein the monitoring module further comprises:

a housing;

one or more contacts for collecting a cardiac signal; and electronic components contained in the housing and configured for receiving the cardiac signal.

16. The system of claim 1, further comprising a third type of reportable event corresponding to an error in the physiological signal, wherein upon the detection of the third type of reportable event the alert module generates an error alert communication.

17. The system of claim 1, wherein the alert module is configured to receive a request for a manual status check, wherein upon the receipt of the request for the manual status check a test signal is provided to the system.

18. The system of claim 1, wherein the physiological signal corresponds to at least one of subject heart rate, position, and movement.

19. A method for reporting physiological events occurring in a human subject, comprising:

detecting a physiological signal from the subject, the physiological signal being a motion signal acquired from an accelerometer;

detecting one or more types of predetermined reportable events based on the detected physiological signal;

classifying each of the detected reportable events as a first type of reportable event corresponding to a low urgency condition of the subject or as a second type of reportable event corresponding to a high urgency neurological condition of the subject;

delivering a therapy to the subject upon detection of the one or more types of predetermined reportable events; generating a low-urgency alert communication in response to the first type of reportable event or a high-urgency alert communication in response to the second type of reportable event, the high-urgency alert communication including a request for acknowledgment of the alert communication;

transmitting the high-urgency alert communication to a first alert contact selected from a plurality of contacts contained in a contact list; and

transmitting the high-urgency alert communication to a second alert contact selected sequentially from the plurality of contacts when the first alert contact does not respond to the request for acknowledgement.

20. The method of claim 19, further comprising transmitting the low-urgency alert communication without the request for acknowledgement.

21. The method of claim 20, the transmitting of the low-urgency alert communication being via a first communication channel and the transmitting of the high-urgency alert communication being via a second communication channel different than the first communication channel.

22. The method of claim 21, wherein at least one of the first communication channel and the second communication channel is a wireless communication channel.

23. The method of claim 21, wherein the second communication channel differs from the first communication channel because the second communication channel is at least one of more reliable than the first communication channel and more noticeable to the alert contact than the first communication channel.

24. The method of claim 19, wherein said transmitting the high-urgency alert communication comprises calling a telephone number or transmitting an electronic message to an electronic message address.

25. The method of claim 19, wherein said high-urgency alert communication informs the selected alert contact of the detected reportable event.

26. The method of claim 19, wherein said one or more types of predetermined reportable events comprise at least one of: detection of a suspected seizure, detection of a suspected seizure that continues beyond a predetermined period of time, and detection of a suspected seizure that has occurred within a certain period of time since a preceding suspected seizure.

27. The method of claim 19, further comprising:

detecting one or more additional physiological signals;

wherein said detecting one or more types of predetermined reportable events based on the detected physiological signal comprises detecting one or more types of predetermined reportable events based on the detected physiological signal and the detected one or more additional physiological signals.

28. The method of claim 27, wherein the one or more additional physiological signals comprises a cardiac signal.

29. The method of claim 27, wherein the one or more additional physiological signals correspond to at least one of subject heart rate, position, and movement.

30. The method of claim 19, wherein the physiological signal corresponds to at least one of subject heart rate, position, and movement.

31. A system for providing alerts of physiological events occurring in a human subject, comprising:

a monitoring module adapted to detect a physiological signal, the physiological signal being a motion signal acquired from an accelerometer;

an event detection module for detecting one or more types of predetermined reportable events based on the detected physiological signal, the predetermined reportable events including a low-urgency type of reportable event corresponding to a low urgency condition of the subject and a high-urgency type of reportable event corresponding to a high urgency neurological condition of the subject;

a therapy delivery module configured to receive a therapy initiation signal from the event detection module, said therapy delivery module being configured to deliver a therapy to the subject; and

an alert module coupled to the event detection module, said alert module containing at least a low-urgency alert type associated with the low-urgency type of reportable event and a high-urgency alert type associated with the high-urgency type of reportable event;

wherein upon the detection of the high-urgency type of reportable event by the event detection module, said alert module selects the high-urgency alert type and generates an alert communication to each alert recipient from a plurality of alert recipients contained in a contact list in sequence until receipt of one of the alert communications is acknowledged, the plurality of alert recipients including a first recipient positioned in an initial position on the contact list, the first recipient being a first caregiver to the subject or a first electronic device.

32. The system of claim 31, wherein the plurality of alert recipients further including a second recipient positioned in a secondary position on the contact list, the second recipient being at least one of a second caregiver to the subject, the first electronic device, or a second electronic device.

33. The system of claim 31, wherein upon the detection of the low-urgency type of reportable event by the event detection module, said alert module selects the low-urgency

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alert type and generates an alert communication that does not require acknowledgement of receipt.

34. The system of claim 31, wherein the physiological signal corresponds to at least one of subject heart rate, position, and movement.

35. The system of claim 31, wherein:
the monitoring module is further configured to receive a cardiac signal; and
the event detection module is further configured to generate additional outputs corresponding to additional reportable events based on the motion signal and the cardiac signal.

36. A method for providing alerts of physiological events occurring in a human subject, comprising:

monitoring a physiological signal using a subject-contacting device, the physiological signal being a motion signal acquired from an accelerometer;

analyzing the physiological signal to detect one or more types of predetermined reportable events corresponding to a neurological condition of the subject;

delivering a therapy to the subject upon detection of the one or more types of predetermined reportable events; and

upon the detection of a reportable event, transmitting an alert communication to each alert contact from a plurality of contacts contained in a contact list sequentially until receipt of one of the alert communications is acknowledged, the plurality of contacts contained in

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the contact list including a first contact positioned in an initial position on the contact list, the first contact being a first caregiver to the subject or a first electronic device.

5 37. The method of claim 36, wherein the plurality of contacts contained in the contact list further including a second contact positioned in a secondary position on the contact list, the second contact being at least one of a second caregiver to the subject, the first electronic device, or a second electronic device.

10 38. The method of claim 36, wherein said transmitting the alert communication to each alert contact from the plurality of contacts comprises transmitting a high-urgency alert communication upon detection of a high urgency reportable event or transmitting a low-urgency alert communication upon detection of a low urgency reportable event.

15 39. The method of claim 36, wherein the physiological signal corresponds to at least one of subject heart rate, position, and movement.

20 40. The method of claim 36, further comprising:
monitoring a cardiac signal acquired from a sensor;
wherein the analyzing the physiological signal to detect one or more types of predetermined reportable events comprises analyzing the motion signal and cardiac signal to detect one or more types of predetermined reportable events.

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摘要(译)

提供了一种用于提供在人类受试者中发生的神经事件的警报的系统。该系统包括：监测模块，适于检测和采样神经信号；事件检测模块，耦合到监测模块，用于基于检测到的神经信号检测一种或多种类型的预定可报告事件；以及耦合到事件检测模块的警报模块，其中在事件检测模块检测到可报告事件时，所述警报模块从包含在联系人列表中的多个联系人中选择第一警报联系人，并生成第一警报通信到第一个警报联系人。

