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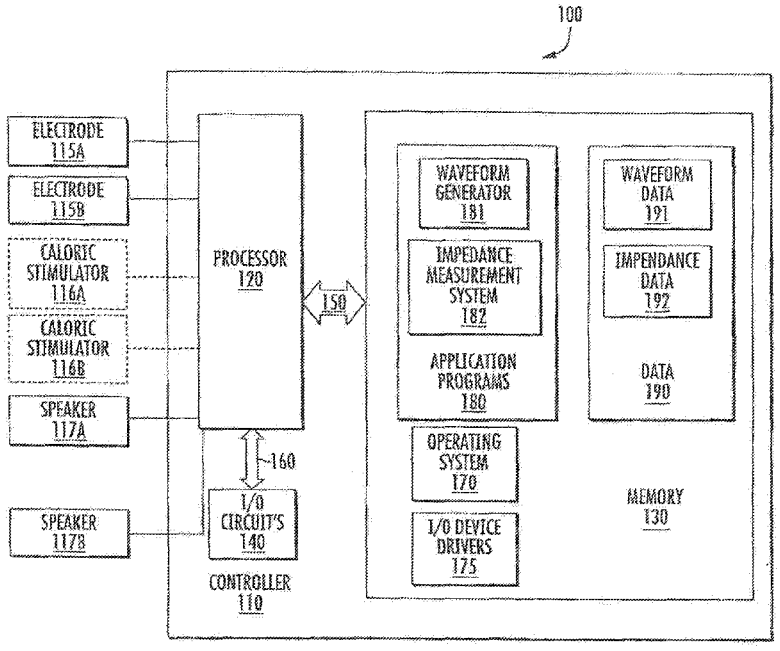


FIG. 1

(57) **Abstract:** Systems, devices, and methods for neurostimulation via vestibular stimulation are described. One example is a device for administering thermal stimulation to an ear canal of a subject. The device may include an earpiece configured to be at least partially insertable into the ear canal of the subject; a thermoelectric device thermally coupled to the earpiece and configured to heat and/or cool the earpiece to thereby heat and/or cool the ear canal of the subject; and a controller configured to administer a selected treatment plan including administering a caloric vestibular stimulation (CVS) stimulus to the ear canal of the subject in a condition-treatment effective amount during a first treatment interval. The treatment plan may be effective to produce a durable improvement in at least one symptom of the condition for a time of at least 1 week following cessation of the administering.

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SYSTEMS, DEVICES AND METHODS FOR NEUROSTIMULATION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims priority to U.S. Provisional Application No. 62/639,738, filed on March 7, 2018 in the United States Patent and Trademark Office, and entitled "SYSTEMS, DEVICES AND METHODS FOR NEUROSTIMULATION," the entire contents of which are hereby incorporated by reference for all purposes.

TECHNICAL FIELD

[0002] The present disclosure relates to neurostimulation, and in particular, to neurostimulation systems, devices, and methods.

BACKGROUND

[0003] Neurostimulation is the therapeutic and/or diagnostic activation of one or more parts of the nervous system. The nervous system may be electrically stimulated through invasive means, such as implantable electrodes, or though less invasive means, such as electrodes attached to the skin. Non-electrical forms of neurostimulation may employ electromagnetic waves, light, sound, or temperature to stimulate the nervous system. Neurostimulation has been used for the purpose of medical treatment and/or diagnosis of various disorders.

[0004] Vestibular stimulation is a form of neurostimulation that stimulates the vestibular branch of the vestibulocochlear nerve, the eighth cranial nerve. As used herein, "vestibular nerve" shall refer to the vestibular branch of the eighth cranial nerve. The vestibular nerve may be stimulated electrically, termed Galvanic Vestibular Stimulation ("GVS"), or may be stimulated using temperature, termed Caloric Vestibular Stimulation, or both.

SUMMARY

[0005] The present disclosure and aspects thereof provide systems, devices, and methods for neurostimulation that include vestibular stimulation. For example, one general aspect provides devices for administering thermal stimulation to an ear canal of a subject. Such devices may include: an earpiece configured to be at least partially insertable into the ear canal of the subject. The devices may also include a thermoelectric device thermally coupled to the earpiece and configured to heat and/or cool the earpiece to thereby heat and/or cool the ear canal of the subject. The devices may also include a controller associated with the thermoelectric device, and the controller may be configured to administer a selected treatment plan including administering

a caloric vestibular stimulation (CVS) stimulus to the ear canal of the subject in a condition-treatment effective amount during a first treatment interval, with the treatment plan effective to produce a durable improvement in at least one symptom of the condition for a time of at least 1 week following cessation of the administering. Other embodiments of this aspect include corresponding methods, systems (including computer systems), apparatuses, and computer programs recorded on one or more computer storage devices that control, facilitate, and/or supplement operation of such devices.

[0006] Another general aspect of the present disclosure provides one or more methods of treating a subject afflicted with a condition (e.g., a neurological disorder). Such methods may include: (a) administering, using a controlled vestibular stimulation device, vestibular stimulation to at least one ear of the subject in a condition-treatment effective amount during a first treatment interval. The vestibular stimulation may be effective to produce a durable improvement in at least one symptom of the condition for a time of at least 1 week following cessation of the administering. Various embodiments of this aspect include systems (including computer systems), apparatuses, and computer programs recorded on one or more computer storage devices, each configured to perform and/or cause performance of the operations of the methods.

[0007] Another general aspect of the present disclosure provides one or more methods. Such methods may include: (a) administering a first vestibular stimulation stimulus to a subject afflicted with a neurological disorder and determining a time to entrainment of at least one physiological oscillatory pattern to the stimulus in the subject. The methods may also include (b) ceasing administering of the vestibular stimulation and determining a time to relaxation of the at least one physiological oscillatory pattern from the entrainment subsequent to the ceasing, Various embodiments of this aspect include systems (including computer systems), apparatuses, and computer programs recorded on one or more computer storage devices, each configured to perform and/or cause performance of the operations of the methods.

[0008] Another general aspect of the present disclosure provides one or more methods for selecting a treatment for a subject afflicted with a neurological disorder, Such methods may include: (a) sequentially administering a plurality of different vestibular stimulation stimuli to the subject; (b) determining a time to entrainment and/or a time to relaxation of at least one physiological oscillatory pattern to each of the stimuli in the subject; (c) selecting, from among the plurality of different vestibular stimulation stimuli, a vestibular stimulation stimulus for administering to the subject based on the detected time to entrainment and/or time to relaxation of each vestibular stimulation stimulus of the plurality of different vestibular stimulation stimuli;

and (d) administering the selected vestibular stimulation stimulus to the subject at least once. Various embodiments of this aspect include systems (including computer systems), apparatuses, and computer programs recorded on one or more computer storage devices, each configured to perform and/or cause performance of the operations of the methods.

[0009] Another general aspect of the present disclosure provides methods. Such methods may include: (a') detecting a physiological oscillatory pattern in a subject during and/or after treatment(s) including administration of a vestibular stimulation stimulus; (b') optionally resetting the oscillatory pattern by administering an exogenous stimulus (e.g., transcranial magnetic stimulation) to the subject; and (c') repeating steps (a') through (b') for a plurality of different vestibular stimulation treatments to generate a database of vestibular stimulation treatment(s) correlated with different oscillatory patterns in a brain of the subject. The methods may also include (d') assigning efficacy scores to each different vestibular stimulation treatment in the database based on a durability of improvement of neurovascular coupling in the subject; (e') selecting from the database a vestibular stimulation treatment that provides a durable improvement in neurovascular coupling to the subject; and (f') administering the selected vestibular stimulation treatment to the subject in a subsequent treatment or treatment session. Various embodiments of this aspect include systems (including computer systems), apparatuses, and computer programs recorded on one or more computer storage devices, each configured to perform and/or cause performance of the operations of the methods.

[0010] Another general aspect of the present disclosure provides methods. Such methods may include: (a) administering a first vestibular stimulation stimulus to a subject afflicted with a neurological disorder to entrain at least one physiological oscillatory pattern to the stimulus in the subject, where the first vestibular stimulation stimulus includes a first waveform combination; (b) ceasing administering of the vestibular stimulation; (c) detecting, using a monitored proxy of the at least one physiological oscillatory pattern, a natural resonance of the at least one physiological oscillatory pattern; (d) modifying at least one characteristic of the first waveform combination of the first vestibular stimulation stimulus to target the natural resonance of the at least one physiological oscillatory pattern, resulting in a second waveform combination including the modified at least one characteristic; and (e) administering a second vestibular stimulation stimulus including the second waveform combination to the subject. Various embodiments of this aspect include systems (including computer systems), apparatuses, and computer programs recorded on one or more computer storage devices, each configured to perform and/or cause performance of the operations of the methods.

[0011] This summary provides only some examples of the aspects provided by the present disclosure. While illustrative of the inventive concepts provided in the present disclosure, this summary is not to be construed as limiting thereof. Although a few exemplary embodiments of the inventive concepts have been described herein, numerous additional and alternative embodiments are provided herein in the detailed description, and furthermore those skilled in the art will readily appreciate that many modifications to the exemplary embodiments are possible without materially departing from the novel teachings and advantages of the inventive concepts provided in the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate embodiments of the inventive concepts and, together with the description, serve to explain principles of the inventive concepts.

[0013] FIG. 1 is a schematic block diagram illustrating stimulation devices, methods, and systems according to some embodiments of the present inventive concepts;

[0014] FIG. 2 is a front view illustrating a stimulation device having in-ear electrodes according to some embodiments of the present inventive concepts;

[0015] FIG. 3 is a front and side view illustrating a user wearing a stimulation device according to some embodiments of the present inventive concepts;

[0016] FIG. 4 is a schematic block diagram illustrating a stimulation device according to some embodiments of the present inventive concepts;

[0017] FIGS. 5A and 5B are schematic block diagrams illustrating stimulation devices according to some embodiments of the present inventive concepts;

[0018] FIG. 6A is a front perspective view illustrating an earpiece of the stimulation device of **FIG. 5**;

[0019] FIG. 6B is a cross-sectional view schematically illustrating the earpiece of **FIG. 6A**;

[0020] FIG. 7 is a side view illustrating various alternative shapes and sizes of earpieces of stimulation devices according to some embodiments of the present inventive concepts;

[0021] FIG. 8 is a schematic diagram illustrating a path of a stimulation signal for an externally applied stimulation signal according to some embodiments of the present inventive concepts;

[0022] FIG. 9 is a cross-sectional view schematically illustrating an ear and surrounding

portions of a human body;

[0023] FIG. 10 is a cross-sectional view schematically illustrating relative placements of electrodes with respect to a computerized tomography scan of a human head;

[0024] FIG. 11 is a graph illustrating a relationship between an impedance of skin and a frequency of a stimulation waveform according to some embodiments of the present inventive concepts;

[0025] FIG. 12 is a graph illustrating modulated stimulation waveform according to some embodiments of the present inventive concepts;

[0026] FIG. 13 is a graph illustrating a modulated separation in time between adjacent ones of a plurality of packets of electrical pulses according to some embodiments of the present inventive concepts;

[0027] FIG. 14 is a graph illustrating a modulated separation in time between adjacent ones of a plurality of packets of electrical pulses and a corresponding modulated stimulation waveform according to some embodiments of the present inventive concepts;

[0028] FIGS. 15A, 15C, and 15E are graphs illustrating modulated target stimulus frequencies according to some embodiments of the present inventive concepts;

[0029] FIGS. 15B, 15D, and 15F are graphs illustrating modulated separations in time between adjacent ones of a plurality of packets of electrical pulses according to the modulated target stimulus frequencies of **FIGS. 15A, 15C, and 15E**, respectively.

[0030] FIGS. 16A-D are graphs illustrating a method for modulating an electrical signal according to some embodiments of the present inventive concepts.

[0031] FIG. 17 is a schematic block diagram illustrating portions of a controller according to some embodiments of the present inventive concepts.

[0032] FIG. 18 is a cross-sectional view schematically illustrating an effect of CVS on vestibular nerves according to some embodiments of the inventive concepts.

[0033] FIG. 19 is a cross-sectional view schematically illustrating an effect of GVS on vestibular nerves according to some embodiments of the inventive concepts.

[0034] FIG. 20 is a cross-sectional view schematically illustrating an effect of vestibular neurostimulation on a brain according to some embodiments of the inventive concepts.

[0035] FIG. 21 is a flowchart of operations in methods of administering vestibular stimulation, according to some embodiments of the present disclosure.

[0036] FIG. 22 is a flowchart of operations in methods of administering vestibular stimulation, according to some embodiments of the present disclosure.

[0037] FIG. 23 illustrates aspects of small-world coupling in a single ring oscillator model.

[0038] FIG. 24 illustrates phase amplitude cross-frequency-coupling (CFC) between beta and gamma bands.

[0039] FIG. 25 is a plot illustrating biomarker change scale over time, including during entrainment and relaxation.

[0040] FIG. 26 is a plot illustrating changes in pulsatility index over time, including during entrainment and relaxation.

[0041] FIG. 27 illustrates a difference between the habituation to repeated sensory stimulus for a migraneur as compared to a control subject.

[0042] FIG. 28 is a flowchart of operations in methods of administering vestibular stimulation and modifying characteristics of the administered vestibular stimulation, according to some embodiments of the present disclosure.

[0043] FIGS. 29A and **29B** illustrate example waveform combinations, according to some embodiments of the present disclosure.

[0044] FIGS. 30A and **30B** are plots demonstrating peripheral capillary oxygen saturation and heart rate, respectively, before, during, and after administration of vestibular stimulation, in accordance with some embodiments of the present disclosure.

DETAILED DESCRIPTION

[0045] As used herein, the term "vestibular system" has the meaning ascribed to it in the medical arts and includes but is not limited to those portions of the inner ear known as the vestibular apparatus and the vestibulocochlear nerve. The vestibular system, therefore, further includes, but is not limited to, those parts of the brain that process signals from the vestibulocochlear nerve.

[0046] "Treatment," "treat," and "treating" as used herein refer to reversing, alleviating, reducing the severity of, delaying the onset of, inhibiting the progress of, or preventing a disease or disorder as described herein, or at least one symptom of a disease or disorder as described herein (e.g., treating one or more of tremors, bradykinesia, rigidity or postural instability associated with Parkinson's disease; treating one or more of intrusive symptoms (e.g., dissociative states, flashbacks, intrusive emotions, intrusive memories, nightmares, and night terrors), avoidant symptoms (e.g., avoiding emotions, avoiding relationships, avoiding responsibility for others, avoiding situations reminiscent of the traumatic event), hyperarousal

symptoms (e.g., exaggerated startle reaction, explosive outbursts, extreme vigilance, irritability, panic symptoms, sleep disturbance) associated with post-traumatic stress disorder). In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved—for example, to prevent or delay their recurrence. Treatment may comprise providing neuroprotection, enhancing cognition and/or increasing cognitive reserve. Treatment may be as an adjuvant treatment as further described herein.

[0047] "Adjuvant treatment" as used herein refers to a treatment session in which the delivery of one or more galvanic and/or caloric waveforms to the vestibular system and/or the nervous system of a patient modifies the effect(s) of one or more active agents and/or therapies. For example, the delivery of one or more thermal waveforms to the vestibular system and/or the nervous system of a patient may enhance the effectiveness of a pharmaceutical agent (by restoring the therapeutic efficacy of a drug to which the patient had previously become habituated, for example). Likewise, the delivery of one or more galvanic and/or caloric waveforms to the vestibular system and/or the nervous system of a patient may enhance the effectiveness of counseling or psychotherapy. In some embodiments, delivery of one or more galvanic and/or caloric waveforms to the vestibular system and/or the nervous system of a patient may reduce or eliminate the need for one or more active agents and/or therapies. Adjuvant treatments may be effectuated by delivering one or more galvanic and/or caloric waveforms to the vestibular system and/or the nervous system of a patient prior to, currently with and/or after administration of one or more active agents and/or therapies.

[0048] "Chronic treatment," "Chronically treating," or the like as used herein refers to a therapeutic treatment carried out at least 2 to 3 times a week (or in some embodiments at least daily) over an extended period of time (typically at least one to two weeks, and in some embodiments at least one to two months), for as long as required to achieve and/or maintain therapeutic efficacy for the particular condition or disorder for which the treatment is carried out.

[0049] "Waveform" or "waveform stimulus" as used herein refers to the galvanic and/or caloric stimulus delivered to a subject through a suitable apparatus to carry out the methods described herein. "Waveform" is not to be confused with "frequency," the latter term concerning the rate of delivery of a particular waveform. The term "waveform" is used herein to refer to one

complete cycle thereof, unless additional cycles (of the same, or different, waveform) are indicated. As discussed further below, time-varying waveforms may be preferred over constant applications in carrying out the present inventive concepts.

[0050] "Actively controlled waveform" or "actively controlled time-varying waveform" as used herein refers to a waveform stimulus in which the intensity of the stimulus is repeatedly adjusted, or substantially continuously adjusted or driven, throughout the treatment session, typically by control circuitry or a controller in response to active feedback from a suitably situated sensor, so that drift of the stimulus from that which is intended for delivery which would otherwise occur due to patient contact is minimized.

[0051] "Packets of electrical pulses" as used herein refers to a series of at least two electrical pulses, wherein the pulses are separated apart from each other in time by a first time period and the last pulse of one packet is separated apart from the first pulse of the next packet by a second time period, the second time period being greater than the first time period. Although the electrical pulses are illustrated herein as a square wave, some embodiments of the inventive concept may include sinusoidal, sawtooth, or other suitable waveforms.

[0052] "Modulation," "modulated signal," or "modulated waveform" as used herein refers to varying one or more parameters of a signal or waveform over time. For example, in a modulated waveform comprising a plurality of packets of electrical pulses, one or more parameters may vary from one packet to another.

[0053] Subjects may be treated in accordance with the present disclosure for any reason. In some embodiments, disorders for which treatment may be carried out include, include, but are not limited to, migraine headaches (acute and chronic), depression, anxiety (e.g. as experienced in post-traumatic stress disorder ("PTSD") or other anxiety disorders), spatial neglect, Parkinson's disease, seizures (e.g., epileptic seizures), diabetes (e.g., type II diabetes), etc.

[0054] Headaches that may be treated by the methods and apparatuses of the present disclosure include, but are not limited to, primary headaches (e.g., migraine headaches, tension-type headaches, trigeminal autonomic cephalagias and other primary headaches, such as cough headaches and exertional headaches) and secondary headaches. See, e.g., International Headache Society Classification ICHD-II.

[0055] Migraine headaches that may be treated by the methods and systems of the present disclosure may be acute/chronic and unilateral/bilateral. The migraine headache may be of any type, including, but not limited to, migraine with aura, migraine without aura, hemiplegic migraine, opthalmoplegic migraine, retinal migraine, basilar artery migraine, abdominal

migraine, vestibular migraine and probable migraine. As used herein, the term "vestibular migraine" refers to migraine with associated vestibular symptoms, including, but not limited to, head motion intolerance, unsteadiness, dizziness and vertigo. Vestibular migraine includes, but is not limited to, those conditions sometimes referred to as vertigo with migraine, migraine-associated dizziness, migraine-related vestibulopathy, migrainous vertigo and migraine-related vertigo. See, e.g., Teggi, Roberto et al. "Migrainous vertigo: results of caloric testing and stabilometric findings" Headache vol. 49,3: 435-44. (2009).

[0056] Tension-type headaches that may be treated by methods and systems of the present disclosure, include, but are not limited to, infrequent episodic tension-type headaches, frequent episodic tension-type headaches, chronic tension-type headache and probable tension-type headache.

[0057] Trigeminal autonomic cephalagias that may be treated by methods and systems of the present disclosure, include, but are not limited to, cluster headaches, paroxysmal hemicranias, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and probable trigeminal autonomic cephalagias. Cluster headache, sometimes referred to as "suicide headache," is considered different from migraine headache. Cluster headache is a neurological disease that involves, as its most prominent feature, an immense degree of pain. "Cluster" refers to the tendency of these headaches to occur periodically, with active periods interrupted by spontaneous remissions. The cause of the disease is currently unknown. Cluster headaches affect approximately 0.1% of the population, and men are more commonly affected than women (in contrast to migraine headache, where women are more commonly affected than men).

[0058] Other primary headaches that may be treated by methods and systems of the present disclosure, include, but are not limited to, primary cough headache, primary exertional headache, primary headache associated with sexual activity, hypnic headache, primary thunderclap headache, hemicranias continua and new daily-persistent headache.

[0059] Additional disorders and conditions that can be treated by methods and systems of the present disclosure include, but are not limited to, neuropathic pain (e.g., migraine headaches), tinnitus, brain injury (acute brain injury, excitotoxic brain injury, traumatic brain injury, etc.), spinal cord injury, body image or integrity disorders (e.g., spatial neglect), visual intrusive imagery, neuropsychiatric disorders (e.g. depression), bipolar disorder, neurodegenerative disorders (e.g. Parkinson's disease), asthma, dementia, insomnia, stroke, cellular ischemia, metabolic disorders, (e.g., diabetes), post-traumatic stress disorder ("PTSD"), addictive

disorders, sensory disorders, motor disorders, and cognitive disorders.

[0060] Sensory disorders that may be treated by methods and systems of the present disclosure include, but are not limited to, vertigo, dizziness, seasickness, travel sickness cybersickness, sensory processing disorder, hyperacusis, fibromyalgia, neuropathic pain (including, but not limited to, complex regional pain syndrome, phantom limb pain, thalamic pain syndrome, craniofacial pain, cranial neuropathy, autonomic neuropathy, and peripheral neuropathy (including, but not limited to, entrapment-, heredity-, acute inflammatory-, diabetes-, alcoholism-, industrial toxin-, Leprosy-, Epstein Barr Virus-, liver disease-, ischemia-, and drug-induced neuropathy)), numbness, hemianesthesia, and nerve/root plexus disorders (including, but not limited to, traumatic radiculopathies, neoplastic radiculopathies, vaculitis, and radiation plexopathy).

[0061] Motor disorders that may be treated by methods and systems of the present disclosure include, but are not limited to, upper motor neuron disorders such as spastic paraplegia, lower motor neuron disorders such as spinal muscular atrophy and bulbar palsy, combined upper and lower motor neuron syndromes such as familial amyotrophic lateral sclerosis and primary lateral sclerosis, and movement disorders (including, but not limited to, Parkinson's disease, tremor, dystonia, Tourette Syndrome, myoclonus, chorea, nystagmus, spasticity, agraphia, dysgraphia, alien limb syndrome, and drug-induced movement disorders).

[0062] Cognitive disorders that may be treated by methods and systems of the present disclosure include, but are not limited to, schizophrenia, addiction, anxiety disorders, depression, bipolar disorder, dementia, insomnia, narcolepsy, autism, Alzheimer's disease, anomia, aphasia, dysphasia, parosmia, spatial neglect, attention deficit hyperactivity disorder, obsessive compulsive disorder, eating disorders, body image disorders, body integrity disorders, post-traumatic stress disorder, intrusive imagery disorders, and mutism.

[0063] Metabolic disorders that may be treated by the methods and systems present disclosure include diabetes (particularly type II diabetes), hypertension, obesity, etc.

[0064] Addiction, addictive disorders, or addictive behavior may be treated by methods and systems of the present disclosure. Such disorders include, but are not limited to, alcohol addiction, tobacco or nicotine addiction (e.g., using methods and systems in accordance with the present disclosure as a smoking cessation aid), drug addictions (e.g., opiates, oxycontin, amphetamines, etc.), food addictions (compulsive eating disorders), etc.

[0065] In some embodiments, the subject has two or more of the above conditions, and both conditions are treated concurrently with methods and systems of the present disclosure. For

example, a subject with both depression and anxiety (e.g., PTSD) can be treated for both, concurrently, with methods and systems of the present disclosure.

[0066] The methods and systems according to embodiments of the present inventive concepts utilize galvanic and/or caloric stimulation to induce physiological and/or psychological responses in a subject for medically diagnostic and/or therapeutic purposes. Subjects to be treated and/or stimulated with methods, devices and systems of the present disclosure include both human subjects and animal subjects. In particular, embodiments of the present disclosure may be used to diagnose and/or treat mammalian subjects such as cats, dogs, monkeys, etc. for medical research or veterinary purposes.

[0067] As noted above, some embodiments according to the present inventive concepts utilize galvanic and/or caloric stimulation to administer stimulation in the ear canal of the subject. The ear canal serves as a useful conduit to the subject's vestibular system and to the vestibulocochlear nerve. Without wishing to be bound by any particular theory, it is believed that galvanic and/or caloric stimulation of the vestibular system is translated into electrical stimulation within the central nervous system ("CNS") and propagated throughout the brain, including but not limited to the brain stem, resulting in certain physiological changes that may be useful in treating various disease states (increased blood flow, generation of neurotransmitters, etc). See, e.g., Zhang, et al. Chinese Medical J. 121:12:1120 (2008) (demonstrating increased ascorbic acid concentration in response to cold water CVS).

[0068] Some embodiments according to the present inventive concepts utilize the galvanic and/or caloric stimulation to entrain brain waves at a target frequency and/or within a target portion of the brain. Brainwave entrainment is any practice that aims to cause brainwave frequencies to fall into step with a periodic stimulus having a frequency corresponding to an intended brain-state or having a different frequency that induces entrainment by cross frequency coupling. Without wishing to be bound by any particular theory, it is believed that when the brain is presented with a rhythmic stimulus, the rhythm is reproduced in the brain in the form of electrical impulses. If the rhythm resembles the natural internal rhythms of the brain, brainwaves, the brain may respond by synchronizing its own electric cycles to the same rhythm. Examples of entrainment descriptors include: phase amplitude coupling, cross frequency coupling, and amplitude-amplitude coupling. The entrained brain waves may continue at the entrained frequency for some time after the stimulus is removed.

[0069] Without wishing to be bound by any particular theory, it is currently believed that various brain waves may be entrained by stimulation. For example, different subcortical

structures may be associated with different frequencies of brain wave modulations. *See, e.g.*, K Omata, T Hanakawa, M Morimoto, M Honda, "Spontaneous Slow Fluctuation of EEG Alpha Rhythm Reflects Activity in Deep-Brain Structures: A Simultaneous EEG-fMRI Study." *PLoS ONE*, vol 8, issue 6, e66869 (June 2013). Therefore, according to some embodiments of the present inventive concepts, stimulation frequencies and/or modulation frequencies may be selected corresponding to a region of the brain for which activation is desired. For example, the selected frequencies may correspond to the frequencies naturally associated with a region of the brain. Brain waves may be measured using electroencephalography (EEG). The realization that time-varying signals could be picked up on the scalp preceded any detailed understanding of what was being recorded. An EEG signal results from the collective action of a region of neurons that fire synchronously. That a voltage can be detected at all at the scalp is a result of the finite length over which voltage differences develop in the cortex (and EEG can only pick up signals from the cortex). Intraoperatively, there is a method called ECoG (electrocorticography) wherein an electrode array is placed directly on the surface of the cortex. This allows for finer scale measurements, but may be limited to patients undergoing brain surgery. ECoG generally confirms the findings of EEG in terms of larger-area synchronous firing. Historically, EEG signals were divided into non-overlapping frequency bands such that researchers had a common reference point for brain activity. This approach provided a gross map of important brain rhythms. For instance, the alpha band (8-13 Hz) may change a lot (increases power) when the eyes are closed and one focuses on internal thinking versus sensory perception. The gamma band (30-100+ Hz) may be associated with global "binding" and may be a marker of unitary thought processes. Brain waves in several bands may be entrained, for example, by listening to music. *See, e.g.*, Doelling, K.B., & Poeppel, D., "Cortical entrainment to music and its modulation by expertise." *Proceedings of the National Academy of Sciences*, vol 112, no. 45, E6233-E6242 (November 10, 2015).

[0070] Modulation of brain waves may be used for therapeutic effects. For example, non-invasive brain stimulation (NIBS) may improve behavioral performance in patients that have had a stroke or are suffering from neuropsychiatric disorders, such as Parkinson's disease (PD) or schizophrenia (SCZ). *See, e.g.*, Krawinkel LK, Engel AK, & Hummel FC, "Modulating pathological oscillations by rhythmic non-invasive brain stimulation – a therapeutic concept?," first published online at http://biorxiv.org/content/early/2015/01/29/014548 (January 29, 2015), also published in *Front. Syst. Neurosci.* (March 17, 2015). Some disorders, such as PD, may be associated with significant alterations in connectivity between brain regions. *See, e.g.*, Tropinic

G, Chiangb J, Wangb ZJ, Tya E, & McKeown MJ, "Altered directional connectivity in Parkinson's disease during performance of a visually guided task," *NeuroImage*, vol. 56, issue 4, 2144–2156 (June 15, 2011). PD patients have been found to have significantly lower interhemispheric EEG coherence in various frequencies than healthy control subjects, which may impair an ability of the PD patients with respect to cognitive and emotional functioning. *See, e.g.*, Yuvaraj R, Murugappan M, Ibrahim NM, Sundaraj K, Omar MI, Mohamad K, Palaniappan R, & Satiyan M, "Inter-hemispheric EEG coherence analysis in Parkinson's disease: Assessing brain activity during emotion processing," *J Neural Transm*, 122:237–252 (2015). Some of the effects of PD may be improved by the therapeutic use of neurostimulation. *See, e.g.*, Kim DJ, Yogendrakumar V, Chiang J, Ty E, Wang ZJ, & McKeown MJ, "Noisy Galvanic Vestibular Stimulation Modulates the Amplitude of EEG Synchrony Patterns," *PLoS ONE*, vol. 8, issue 7, e69055 (July 2013). Therapeutic neurostimulation may decouple inter-frequency activity to reduce or reverse abnormalities found in patients with neuropsychiatric disorders, such as PD. *See, e.g.*, de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, & Starr PA, "Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease," *Nature Neuroscience*, vol. 8, 779-786 (2015).

[0071] Aberrant EEG activity has been documented in patients with some neuropsychiatric disorders, such as PD. Non-invasive neuromodulation may be used to alter EEG. This can take the form of disrupting the dysfunctional rhythm or trying to entrain and thus guide the aberrant rhythm to a "proper" state. Success in achieving neuromodulation may be assessed by, for example, re-measuring EEG activity to see if the abnormal power levels and/or abnormal cross-frequency coupling has been addressed. Therefore, according to some embodiments, a therapeutic method may include identifying an EEG abnormality and prescribing an associated therapeutic rhythm. The method may include choosing a frequency range/ranges for neurostimulation, such as with GVS, that may couple to the abnormal oscillations. The chosen frequency range/ranges may not be exactly the same as frequencies of the EEG abnormality, because cross-frequency coupling can occur. The method may include administering the "corrective" GVS stimulation repeatedly over time. For example, the administration may continue until the desired change may be measured. The desired change may be measured, for example, using EEG or may be measured using other methods. In some embodiments, the effects may be measured by measuring a heart rate variability (HRV).

[0072] Some embodiments according to the present disclosure utilize a combination of galvanic and caloric stimulation. In such embodiments, the galvanic vestibular stimulation may

enhance a delivery of the caloric vestibular stimulation.

[0073] As noted above, some embodiments according to the present disclosure utilize galvanic stimulation to administer stimulation in the ear canal of the subject. A modulated electrical signal may be transmitted through the skin lining the ear canal, which may stimulate the vestibular system of the subject. The skin may provide an electrical resistance in the electrical path between the electrode and the vestibular system. The electrical resistance of the skin may be generally inversely proportional to the frequency of the electrical signal. Thus, in order to stimulate the vestibular system at lower frequencies, a waveform of larger amplitude may be required than a waveform at higher frequencies. The larger amplitude may not be desirable, as the subject may experience discomfort, pain, and/or physical damage based on the large voltage. However, the higher frequencies may not induce the desired diagnostic and/or therapeutic effects of galvanic vestibular stimulation. For example, some diagnostic and/or therapeutic uses of galvanic vestibular stimulation desire stimulation at lower frequencies. *See, e.g.*, G. C. Albert, C. M. Cook, F. S. Prato, A. W. Thomas, "Deep brain stimulation, vagal nerve stimulation and transcranial stimulation: An overview of stimulation parameters and neurotransmitter release." *Neurosci Biobehav Rev* 33, 1042-1060 (2009); published online EpubJul (10.1016/j.neubiorev.2009.04.006) (reviewing parameters of stimulation techniques that explore or treat neurological disorders). In some embodiments of the present disclosure, a modulation scheme may be provided that generates an electrical signal with a higher frequency to produce the lower impedance and that stimulates the vestibular system at a lower frequency.

[0074] For example, the modulation scheme may provide a repeating series of spaced-apart packets of electronic pulses. Each packet may comprise a plurality of electronic pulses. The electronic pulses within the packets may be closely separated in time (e.g., closely spaced in time) to provide the higher frequency and, thus, to produce the lower impedance that permits transmission through the skin. One or more parameters may be modulated according to a lower frequency. For example, one or more of the quantity of the plurality of pulses within ones of the plurality of packets of pulses, the width in time of the plurality of electrical pulses within ones of the plurality of packets of pulses, the amplitude of the plurality of pulses within ones of the plurality of packets of pulses, the separation in time between adjacent ones of the plurality of pulses within ones of the plurality of packets of pulses, and the separation in time between adjacent ones of the plurality of packets of pulses may be modulated. The vestibular system may be stimulated based on the lower frequency. For example, the lower frequency modulation may entrain brainwaves based on the low frequency of the modulation. Thus, the modulation scheme

may produce the lower impedance based on the higher frequency of the pulses within a packet and stimulate the vestibular system based on the lower frequency of the modulation.

[0075] In other embodiments, the modulation scheme may provide an electrical signal. The electrical signal may include a carrier function that includes an amplitude and a carrier frequency. For example, the carrier function may be a sine wave. However, in other embodiments the function may be another function such as a square wave, sawtooth wave, or another function. The frequency of the carrier function may be sufficiently high to produce the lower impedance that permits transmission through the skin. One or more parameters of the carrier function may be modulated according to modulation waveform. For example, one or more of the amplitude and frequency of the carrier function may be modulated to produce a modulated electrical signal. A frequency of the modulation waveform may be lower than the frequency of the carrier function. The vestibular system may be stimulated based on the lower frequency. For example, the lower frequency modulation may entrain brainwaves based on the low frequency of the modulation. Thus, the modulation scheme may produce the lower impedance based on the higher frequency of the pulses within a packet and stimulate the vestibular system based on the lower frequency of the modulation.

[0076] Some embodiments according to the present disclosure utilize sound-based stimulation and/or electronic stimulation based on sounds. Sounds may affect brain activity. For example, sounds containing significant quantities of non-stationary high-frequency components (HFCs) above the human audible range (approximately 20 kHz) may activate the midbrain and/or diencephalon, and may evoke various physiological, psychological and behavioral responses. *See, e.g.*, Fukushima A, Yagi R, Kawai N, Honda M, Nishina E, & Oohashi T, "Frequencies of Inaudible High-Frequency Sounds Differentially Affect Brain Activity: Positive and Negative Hypersonic Effects," *PLoS ONE*, vol. 9, issue 4, e95464 (April 2014). Sounds have been shown to activate vestibular responses at least up to 2000 Hz. *See, e.g.*, Welgampola MS, Rosengren SM, Halmagyi GM, & Colebatch JG, "Vestibular activation by bone conducted sound," *J Neurol Neurosurg Psychiatry*, 74:771–778 (2003).

[0077] Without wishing to be bound by any particular theory, it is believed that the vestibular response to sound may be a leftover trait from early evolution when the vestibular system was the organ of sound detection when animals lived in the water. The cochlea developed after animals lived on land and enabled better hearing in the air environment. Since the basic hair cell configuration is similar in the cochlea and vestibular organs, the basic ability to respond to a range of frequencies may be very similar, if not identical. Since hearing can

occur up to approximately 20 KHz in humans, the vestibular system may also respond likewise. Above approximately 1 KhZ, an A.C. component of cochlear response may be dominated by a D.C. response. *See, e.g.*, A.R. Palmer and I.J. Russell, "Phase-locking in the cochlear nerve of the guinea-pig and its relation to the receptor potential of inner hair-cells," *Hearing Research*, vol. 24, 1-15 at FIG. 9 (1986). Therefore, even at around 2000 Hz where a vestibular response has been shown, the nerve may not be able to follow the stimulus sound wave and instead a direct current, DC, offset may occur.

[0078] **System**

[0079] **FIG. 1** is a schematic block diagram illustrating a stimulation device according to some embodiments of the present inventive concepts. Referring to **FIG. 1**, a stimulation device **100** may include a controller **110** coupled to electrodes **115A**, **115B** and/or caloric stimulators **116A**, **116B**. Although the device is illustrated has having both electrodes **115A**, **115B** for providing galvanic vestibular stimulation and caloric stimulators **116A**, **116B** for providing caloric vestibular stimulation, it should be understood that in some embodiments, only caloric stimulators or only galvanic vestibular stimulation may be used. In some embodiments, the controller **110** may optionally be also coupled to speakers **117A**, **117B**. The controller **110** may include a processor **120**, I/O circuits **140**, and/or memory **130**. The memory may include an operating system **170**, I/O device drivers **175**, application programs **180** (which may be referred to herein as applications), and/or data **190**. The application programs **180** may include a waveform generator **181** and/or a measurement system **182**. The data **190** may include waveform data **191** and/or measurement data **192**. Although illustrated as software, one or more functions of the application programs **180** may be implemented in hardware or in any combination of hardware and/or software. Additionally, it should be understood that one or more of the functions of the stimulation device **100** may be provided by one or more separate devices. For example, one or more portions of the data **190** may be stored remote from the stimulation device **100**, and the stimulation device **100** may communicate with the remote storage, for example via I/O circuits **140**.

[0080] According to some embodiments of the present inventive concepts, the stimulation device **100** may stimulate a nervous system by providing first and second waveforms to a first electrode **115A** and a second electrode **115B**. In some embodiments, the first and second waveforms may be modulated electric signals. In some embodiments, the first and second waveforms may be a modulated voltage level between the electrodes **115A**, **115B**. In some embodiments, the first and second waveforms may be a modulated electrical current

between the electrodes **115A, 115B**. For example, the first and second waveforms may be asymmetric with respect to each other to provide the modulated voltage level and/or modulated electrical current between the electrodes **115A, 115B**. Other embodiments may include one or more neutral connections to the subject. For example, in some embodiments, the first waveform may be a modulated voltage level between the first electrode **115A** and at least one of the neutral connections and the second waveform may be a modulated voltage level between the second electrode **115B** and at least one of the neutral connections. In some embodiments, the first waveform may be a modulated electrical current between the first electrode **115A** and at least one of the neutral connections and the second waveform may be a modulated electrical current between the second electrode **115B** and at least one of the neutral connections. Thus the electrodes **115A, 115B** may be used together to provide one stimulus or may be used independently to provide more than one stimulus.

[0081] The controller **110** may generate the first and second waveforms. The controller **110** may include the memory **130**, the processor **120** and the I/O circuits **140** and may be operatively and communicatively coupled to the electrodes **115A, 115B**. The processor **120** may communicate with the memory **130** via an address/data bus **150** and with the I/O circuits **140** via an address/data bus **160**. As will be appreciated by one of skill in the art, the processor **120** may be any commercially available or custom microprocessor. The memory **130** may be representative of the overall hierarchy of memory devices containing software and data used to implement the functionality of the stimulation device **100**. Memory **130** may include, but is not limited to, the following types of devices: cache, ROM, PROM, EPROM, EEPROM, flash memory, SRAM and DRAM. Memory **130** may include non-volatile memory.

[0082] As shown in **FIG. 1**, the memory **130** may comprise several categories of software and data. For example, the memory may include one or more of: the operating system **170**, applications **180**, data **190**, and input/output (I/O) device drivers **175**.

[0083] The applications **180** may include one or more programs configured to implement one or more of the various operations and features according to embodiments of the present inventive concepts. For example, the applications **180** may include the waveform generator **181** configured to communicate a waveform control signal to one or both of the electrodes **115A, 115B**. The applications **180** may also include the measurement system **182** for measuring an impedance or other electrical characteristic (*e.g.*, capacitance) between the electrodes **115A, 115B**. In some embodiments, the memory **130** may include additional applications, such as a networking module for connecting to a network. In some embodiments, the waveform generator

181 may be configured to activate at least one electrode (*i.e.*, to control the magnitude, duration, waveform and other attributes of stimulation delivered by the at least one electrode). In some such embodiments, the waveform generator **181** may be configured to activate at least one electrode based upon a prescription from a prescription database, which may include one or more sets of instructions for delivering one or more time-varying waveforms to the vestibular system of a subject.

[0084] The data **190** may comprise static and/or dynamic data used by the operating system **170**, applications **180**, I/O device drivers **175** and/or other software components. The data **190** may include the waveform data **191** including one or more treatment protocols or prescriptions. In some embodiments, the data **190** may further include measurement data **192** including impedance measurements between the electrodes **115A**, **115B** and/or estimates of electrical contact based on electrical impedance measurements. Electrical impedance measurements may include resistive and capacitive components of the interface between the electrodes **115A**, **115B** and the ear canal. In some embodiments, the measurement data **192** may include measurements of electrical signals that are produced by the vestibular system. For example, the measurement data **192** may include electrovestibulography signals, or EVestG signals.

[0085] I/O device drivers **175** may include software routines accessed through the operating system **170** by the applications **180** to communicate with devices such as I/O circuits **140**, memory **130** components and/or the electrodes **115A**, **115B**.

[0086] In some embodiments, the waveform generator **181** may be configured to pass an electrical current through at least one of the electrodes **115A**, **115B** to stimulate the nervous system and/or the vestibular system of a subject. In particular embodiments, the waveform generator **181** may be configured to pass the electrical current through the at least one electrode **115A**, **115B** based upon a prescription comprising a set of instructions for delivering one or more time-varying waveforms to the vestibular system of a subject. In some embodiments, the electrical current may be produced in response to an electrical voltage differential provided between the two electrodes **115A**, **115B**. However, in some embodiments, the waveform generator **181** may be configured to pass two independent electrical currents through the two electrodes **115A**, **115B**, respectively. The two independent electrical currents may be produced in response to electrical voltage differentials provided between each of the two electrodes **115A**, **115B** and one or more additional points of electrical contact with the body of the subject.

[0087] In some embodiments, the stimulation device **100** may be communicatively

connected to at least one electrode **115A, 115B** via a conductive line. In some embodiments, the stimulation device **100** may be operatively connected to a plurality of electrodes, and the stimulation device **100** may be operatively connected to each electrode via a separate conductive line.

[0088] In some embodiments, the controller **110** may be operatively connected to at least one of the electrodes **115A, 115B** via a wireless connection, such as a Bluetooth connection. In some embodiments, the stimulation device **100** may be configured to activate the at least one of the electrodes **115A, 115B** to deliver one or more actively controlled, time-varying waveforms to the vestibular system and/or the nervous system of a patient. For example, one or more of the electrodes **115A, 115B** may be electrically connected to a wireless receiver and a power source independent of the controller **110**. The wireless receiver may receive the wireless signal corresponding to a modulated waveform and may activate the one or more of the electrodes **115A, 115B**.

[0089] In some embodiments, the stimulation device **100** may include one or more caloric stimulators, **116A, 116B**. The stimulation device **100** may stimulate a nervous system by providing third and fourth waveforms to the caloric stimulators, **116A, 116B**. The caloric stimulation from the caloric stimulators may be combined with the galvanic stimulation from the electrodes **115A, 115B**.

[0090] In some embodiments, the stimulation device **100** may include one or more speakers, **117A, 117B**. The stimulation device **100** may provide one or more audio waveforms to the speakers, **117A, 117B**. In some embodiments, the stimulation device **100** may include an input connector to receive one or more external audio waveforms that may be provided to the speakers **117A, 117B**.

[0091] FIG. 2 is a front view illustrating a stimulation device according to some embodiments of the present inventive concepts. Referring to **FIG. 2**, a stimulation device **200** may be an in-ear stimulation apparatus. The stimulation device **200** may be similar to the stimulation device **100** illustrated in **FIG. 1** except for the differences as noted. The stimulation device **200** may include a support or headband **230**, earphones **220**, a controller **210** and/or cables **240**. In some embodiments, the stimulation device may not include the cables **240** and the controller **210** may connect to the earphones **220** wirelessly. The earphones **220** may include respective electrodes **215A, 215B** that are configured to be positioned in the ear of a patient or subject. The electrodes **215A, 215B** may be configured to make electrical contact with an inner surface of the ear of the patient or subject such that, when activated, the electrode **215A, 215B**

may stimulate the vestibular system of the patient or subject.

[0092] The electrodes **215A, 215B** may be configured as respective earpieces **250A, 250B** or may be configured as parts of the respective earpieces **250A, 250B**. For example, in some embodiments, an earpiece may be formed primarily of a conductive metal and the entire earpiece **250A, 250B** may be an electrode **215A, 215B**. In other embodiments, a part of or all of an exterior surface of an earpiece **250A, 250B** may be coated with an electrically conductive metal to form the electrode **215A, 215B**. In some embodiments, a part of or all of an exterior surface of an earpiece **250A, 250B** may be coated with an thin layer of an electrically insulating material that covers the electrode **215A, 215B** and electrically insulates the electrode **215A, 215B** from the ear of the patient or subject at DC. However, the thin layer of the electrically insulating material may allow higher frequency waveforms to pass through the thin layer of the electrically insulating material from the electrode **215A, 215B** to the ear of the patient or subject. For example, in some embodiments, the thin layer of the electrically insulating material may be an anodized finish on an electrically conductive metal. However, in other embodiments, the electrically insulating material may be a thin layer of rubber, plastic, or another insulating material.

[0093] In some embodiments, the electrode **215A, 215B** may be in electrical contact with the ear canal without directly physically contacting the ear canal. An electrical conduit may be positioned and configured to provide or improve electrical contact between the ear canal and the electrode **215A, 215B**. The electrical conduit may be configured to conform to the ear canal, such as a flexible or conformable, electrically conductive material that is configured to increase contact and/or conductivity between the electrode **215A, 215B** and the ear canal. The electrically conductive material may be a liquid or solid material or a combination of liquid and solid materials. Moreover, the electrically conductive material may be affixed to the electrode **215A, 215B**. For example, in some embodiments, the electrode **215A, 215B** may be covered by a porous material that is permeated with an electrically conductive liquid. In some embodiments, the electrode **215A, 215B** may be covered with a layer of cotton to avoid direct physical contact with the ear canal. The layer of cotton may be soaked with an electrically conductive liquid, for example a saline solution, to provide the electrical connection between the electrode **215A, 215B** and the ear canal. In some embodiments, the electrically conductive liquid may be positioned in the ear canal. The ear canal may be sealed, for example, with an earplug or other sealing material to contain the electrically conductive liquid inside the ear canal. In some embodiments the electrode **215A, 215B** and/or an electrical attachment thereto may pass through or around the

earplug or other sealing material.

[0094] Although the electrodes **215A, 215B** are illustrated in **FIG. 2** as being integrated with the earpieces **250A, 250B**, In some embodiments, the electrodes **215A, 216B** may not be configured to fit within an ear cavity. For example, the electrodes **215A, 216B** may be configured to contact a portion of the skin next to the ear and over a mastoid part of a temporal bone.

[0095] It should be understood that other configurations for supporting the headphones and/or earpieces **250A, 250B** may be used, including support bands that are positioned under the chin or over the ear, for example, as may be used with audio earphones. For example, **FIG. 3** is a front and side view illustrating a user wearing a stimulation device according to some embodiments of the present inventive concepts. Referring to **FIG. 3**, a stimulation device **200'** may be similar to the stimulation devices **100, 200** illustrated in **FIGS. 1-2** except for the differences as noted. The stimulation device **200'** may include straps **260** and/or headbands **270**. In some embodiments, the headbands **270** may provide increased stability of the earphones **220** to provide potentially improved contact of the earpieces **250A, 250B** (not shown). In some embodiments, one or more of the straps **260** and/or headbands **270** may provide an additional point of electrical contact to the user, for example a neutral connection to the user.

[0096] Although embodiments according to the present inventive concepts are illustrated with respect to two ear stimulators in which an electric current is passed from electrode to another through the subject's tissue (e.g., the head), it should be understood that, in some embodiments, the stimulation device **200'** may only include one electrode **215**. In such embodiments, the stimulation device **200'** may provide an electrical stimulus as a voltage between the electrode **215A** and an additional point of electrical contact. For example, the additional point of electrical contact may be located on a strap **260** and/or headband **270**. In some embodiments, two electrodes **215A, 215B** in the ears or on the mastoids may be used with one or more additional points of electrical contact to pass separate electrical currents from each of the electrodes **215A, 215B** to the one or more additional points of electrical contact.

[0097] **FIG. 4** is a schematic block diagram illustrating a stimulation device according to some embodiments of the present inventive concepts. Referring to **FIG. 4**, a stimulation device may be similar to the stimulation devices **100, 200** illustrated in **FIGS. 1-2** except for the differences as noted. The controller **210** may include a waveform generator **281** and a measurement system **282** that may be similar to the waveform generator **181** and an measurement system **182** of **FIG. 1**, except for differences as noted. The waveform generator

281 may be configured to communicate first and second waveforms to the electrodes **215A, 215B**. It should be understood that the first and second waveforms may be the same, or in some embodiments, the first and second waveforms may be different such that the output delivered from the electrodes **215A, 215B** may be independently controlled and may be different from one another.

[0098] As illustrated in **FIG. 4**, in some embodiments, the measurement system **282** may deliver an electrical current to one or more of the electrodes **215A, 215B**. In this configuration, the impedance and/or capacitance value between the electrodes **215A, 215B** may be used to monitor the electrical contact between the electrodes **215A, 215B**. In some embodiments, impedance and/or capacitance values may be detected for a range of subjects to determine a range of impedance and/or capacitance values in which it may be assumed that the electrodes **215A, 215B** are in sufficient electrical contact with the subject's ear canal. When a headset is being fitted to a new patient, the impedance and/or capacitance between the electrodes **215A, 215B** may be detected, and if the impedance value is within the acceptable range, it may be assumed that there is good electrical contact between the electrodes **215A, 215B** and the subject's ear canal.

[0099] In some embodiments, when the headset is being fitted to a new patient, the impedance and/or capacitance value between electrodes **215A, 215B** may be detected and used as a patient specific baseline to determine if the patient is later using the headset and a proper configuration. For example, the patient may use a headset according to embodiments of the present inventive concepts in a setting that may or may not be supervised by a medical professional. In either environment, the measurement system **282** may record an impedance and/or capacitance value at a time that is close in time or overlapping with the time in which the treatment waveforms are delivered to the electrodes **215A, 215B**. The medical health professional or the measurement system **282** may analyze the impedance value to determine whether the electrodes **215A, 215B** were properly fitting during treatment. In some embodiments, the measurement system **282** may be configured to provide feedback to the user when impedance values detected that are inconsistent with properly fitting electrodes **215A, 215B** in good electrical contact with the ear canal. In this configuration, the measurement system **282** may provide a degree of electrical contact between the electrodes **215A, 215B** and the ear canal in real-time or in data recorded and analyzed at a later time. Accordingly, patient compliance with treatment protocols may be monitored based on the detected impedance during or close in time to treatment.

[0100] In some embodiments, the impedance may be calculated based separately for each of the electrodes **215A**, **215B**. For example, in some embodiments, an impedance may be measured between ones of the electrodes **215A**, **215B** and an additional point of connection located on a cable **240** and/or the headband **270**, as illustrated in **FIG. 3**.

[0101] In particular embodiments, the measurement system **282** may also provide feedback to the waveform generator **281**, for example, so that the waveform generator **281** may increase or decrease an amplitude of the waveform control signal responsive to the degree of electrical contact determined by the measurement system **282** based on the impedance and/or capacitance value. For example, if the measurement system **282** determines based on the impedance value that there is a poor fit and poor electrical contact with the ear canal, then the waveform generator **281** may increase an amplitude of the output to the electrodes **215A**, **215B** to compensate for the poor electrical contact. In some embodiments, the measurement system **282** may determine patient compliance, *e.g.*, whether the patient was actually using the device during administration of the waveforms.

[0102] Although embodiments of the present inventive concepts are illustrated with respect to two electrodes **215A**, **215B**, it should be understood that in some embodiments, a single electrode **215A** may be used, and an electrical contact may be affixed to another location on the user's head instead of the second earpiece **250B** to thereby provide an electrical circuit for determining impedance values and estimating thermal contact as described herein.

[0103] In some embodiments, the measurement system **282** may measure one or more impedance value based on the current and voltage levels of the first and second waveforms. In some embodiments, the measurement system **282** may include hardware to measure the current and/or voltage levels of the first and second waveforms. For example, the measurement system **282** may calculate an impedance by dividing a voltage level by a current level. In such embodiments, the measurement system **282** may calculate an impedance value while the waveform generator **281** generates the first and second waveforms.

[0104] In some embodiments, the measurement system **282** may measure one or more electrical signals that are produced by the vestibular system. For example, the measurement system **282** may measure electrovestibulography, or EVestG, signals. EVestG signals may be useful to determine an efficacy of a treatment. For example, EVestG signals may be useful in determining a presence and/or degree of one or more disorders. Accordingly, an efficacy of a treatment may be monitored based on feedback provided by the measured EVestG signals during or close in time to treatment. In some embodiments, a treatment may be revised and/or

discontinued based on measured EVestG signals.

[0105] FIG. 5A is a schematic block diagram illustrating a stimulation device according to some embodiments of the present inventive concepts. Referring to **FIG. 5A**, a stimulation device **500** may be similar to the stimulation device **100** illustrated in **FIGS. 1-4** except for the differences as noted. For example, the stimulation device may include a controller **510A** and electrodes **515A, 515B** that may be similar to the controller **210** and electrodes **215A, 215B** of **FIGS. 1-4**, except for differences as noted. The stimulation device may include earphones including earpieces **550A, 550B** including the electrodes **515A, 515B**. The earphones may further include thermal electric devices, "TEDs," attached to the earpieces **550A, 550B**. The controller **510A** may include a galvanic waveform generator **581A** that may be similar to the waveform generator **281** of **FIGS. 1-4**. The controller **510A** may also include a caloric waveform generator **581B**. The caloric waveform generator **518B** may be configured to activate the TEDs attached to the earpieces **550A, 550B**. In this configuration, caloric vestibular stimulation may be administered to a subject via the subject's ear canal. Administration of caloric vestibular stimulation using earpieces is discussed in U.S. Patent Application Serial No. 12/970,312, filed December 16, 2010, U.S. Patent Application Serial No. 12/970,347, filed December 16, 2010, U.S. Patent Application Serial No. 13/525,817, filed June 18, 2012, and U.S. Patent Application Serial No. 13/994,266, filed May 15, 2014, the disclosures of which are hereby incorporated by reference in their entirety.

[0106] In some embodiments, the galvanic waveform generator **581A** may deliver first and second waveforms to the electrodes **515A, 515B** and the caloric waveform generator may deliver third and fourth waveforms to the TEDs attached to the electrodes **515A, 515B**, respectively. In some embodiments, the galvanic waveform generator **581A** may deliver first and second waveforms and the caloric waveform generator may deliver third and fourth waveforms simultaneously. In such embodiments, the stimulation device may deliver galvanic vestibular stimulation and caloric vestibular stimulation. In some embodiments, the galvanic vestibular stimulation may enhance a delivery of the caloric vestibular stimulation.

[0107] FIG. 5B is a schematic block diagram illustrating a stimulation device according to some embodiments of the present inventive concepts. Referring to **FIG. 5B**, a stimulation device may be similar to the stimulation device **100** illustrated in **FIGS. 1-4** except for the differences as noted. For example, the stimulation device may include a controller **510B** and electrodes **515A, 515B** that may be similar to the controller **210** and electrodes **215A, 215B** of **FIGS. 1-4**, except for differences as noted. The stimulation device **500** may include earphones

including earpieces **550A, 550B** including the electrodes **515A, 515B**. The earphones may further include speakers attached to the earpieces **550A, 550B**. In some embodiments, the speakers may be included in the earpieces, **550A, 515B**. In other embodiments, the earpieces **550A, 550B** may include a tube or other channel of air that conducts sound from externally attached speakers to the inner ear. In yet other embodiments, the stimulation device **500** may include bone conduction speakers and the earpieces **550A, 550B** may conduct vibrations from the bone conduction speakers to bones that are adjacent to the ear canals.

[0108] In some embodiments, the galvanic waveform generator **581A** may deliver first and second waveforms to the electrodes **515A, 515B** and the audio waveform generator may deliver audio waveforms to the speakers attached to the electrodes **515A, 515B**, respectively. In some embodiments, the galvanic waveform generator **581A** may deliver first and second waveforms and the audio waveform generator may deliver audio waveforms simultaneously. In such embodiments, the stimulation device **500** may deliver galvanic vestibular stimulation and audio stimulation. As used herein, an audio waveform is a waveform that includes frequency components that are within a hearing range of the subject. For example, an audio waveform may include frequency components within a range of about 20 to 20,000 Hz. In some embodiments, the audio waveforms may be time-varying and/or may include one or more patterns. For example, the audio waveforms may include music and/or voice. In some embodiments, the waveforms of the galvanic vestibular stimulation may be modulated based on the audio waveforms.

[0109] For example, in some embodiments, the first and/or second waveforms of the galvanic vestibular stimulation may include a carrier function having a frequency that may be sufficiently high to produce the lower impedance that permits transmission through the skin. The audio waveforms may include one or more frequencies that are lower than the frequency of the carrier function. One or more parameters of the carrier function may be modulated according to the one or more lower frequencies of the audio waveforms. For example, one or more of the amplitude and frequency of the carrier function may be modulated to produce the first and/or second waveforms of the galvanic vestibular stimulation. In other embodiments, the first and/or second waveforms of the galvanic vestibular stimulation may be directly proportional to the audio waveforms.

[0110] **FIG. 6A** is a front perspective view illustrating an earpiece of the stimulation device of **FIG. 5A**. **FIG. 6B** is a cross-sectional view schematically illustrating the earpiece of **FIG. 6A**. Referring to **FIGS. 6A-6B** and **FIG. 5A**, an earpiece **550** may include an electrode

515. As noted above, the electrode **515** may form all, part of, or a coating on the surface of the earpiece **550**. A thermoelectric device **530** may be coupled between the earpiece **550** and a heatsink **540**.

[0111] The electrode **515** may receive a first or second electrical waveform from the galvanic waveform generator **581A** of the controller **510A**. The electrode **515** may be electrically conductive. For example, the electrode **515** may be formed of an electrically conductive metal. The electrode **515** may be formed to fit in an ear canal and provide an electrical interface to the ear canal. Thus, the galvanic waveform generator **581A** may provide a galvanic stimulus to stimulate the nervous system and/or vestibular system of the subject based on the first or second waveform delivered through the electrical connection between the electrode **515** and the ear canal.

[0112] In some embodiments, the electrode **515** may be in electrical contact with the ear canal without directly physically contacting the ear canal. An electrical conduit may be positioned and configured to provide or improve electrical contact between the ear canal and the electrode **515**. The electrical conduit may be configured to conform to the ear canal, such as a flexible or conformable, electrically conductive material that is configured to increase contact and/or conductivity between the electrode **515** and the ear canal. The electrically conductive material may be a liquid or solid material or a combination of liquid and solid materials. Moreover, the electrically conductive material may be affixed to the electrode **515**. For example, in some embodiments, the electrode **515** may be covered by a porous material that is permeated with an electrically conductive liquid. In some embodiments, the electrode **515** may be covered with a layer of cotton to avoid direct physical contact with the ear canal. The layer of cotton may be soaked with an electrically conductive liquid, for example a saline solution, to provide the electrical connection between the electrode **515** and the ear canal. In some embodiments, the electrically conductive liquid may be positioned in the ear canal. The ear canal may be sealed, for example, with an earplug or other sealing material to contain the electrically conductive liquid inside the ear canal. In some embodiments the electrode **515** and/or an electrical attachment thereto may pass through or around the earplug or other sealing material.

[0113] The thermoelectric device **530** may receive a third or fourth thermal waveform from the caloric waveform generator **581B**. The thermoelectric device **530** may provide a temperature differential between the earpiece **550** and the heatsink **540** based on the third or fourth waveform. The earpiece **550** and/or the electrode **515** of the earpiece **550** may provide a thermal interface between the thermoelectric device **530** and the ear canal. Thus, the caloric

waveform generator **581B** may provide a caloric stimulus to stimulate the nervous system and/or vestibular system of the subject based on the third or fourth waveform delivered through the thermal interface between the electrode **515** and the ear canal.

[0114] FIG. 7 is a side view illustrating various alternative shapes and sizes of earpieces of stimulation devices according to some embodiments of the present inventive concepts. Referring to **FIG. 7**, an earpiece **750** may be similar to the earpieces illustrated in **FIGS. 2-6** except for the differences as noted. A shape and/or size of the earpiece **750** may be selected to optimize the electrical and/or thermal connection. The shape and/or size of the earpiece **750** may be selected for optimal comfort of the subject. In some embodiments, the earpiece **750** may be user replaceable, however embodiments of the present inventive concepts are not limited thereto. For example, in some embodiments, the earpiece **750** may be permanently attached to a TED and/or earphone. In some embodiments, a size of the earpiece **750** may be selected according to a size of the ear canal of the subject. For example, the earpiece **750** may be small, medium, large, or extra large. In some embodiments, a shape of the earpiece **750** may be selected based upon a shape of the ear canal of the subject. For example, the earpiece **750** may be angled and/or tortuous (twisted or curved) with respect to a base of the earpiece **750**. However, the present disclosure is not limited to the illustrated shapes and sizes.

[0115] FIG. 8 is a schematic diagram illustrating a path of a stimulation signal according to some embodiments of the present inventive concepts. Referring to **FIG. 8**, a path of a stimulation signal according to some embodiments of the present inventive concepts may include the controller **210**, an electrode **215**, skin, and the vestibular system. The controller **210** may be the controller **210** as described above with reference to **FIGS. 2-4**. The electrode **215** may be one or more of the electrodes **215A**, **215B**, as described above with reference to **FIGS. 2-4**. The electrode **215** may be in physical and electrical contact with the skin of a subject. For example, the electrode **215** may be inserted into an ear canal of the subject and may be in physical and electrical contact with a portion of the skin lining the ear canal of the subject.

[0116] FIG. 9 is a cross-sectional view schematically illustrating an ear and surrounding portions of a human body. Referring to **FIG. 9**, a vestibular nerve **910** of the vestibular system may be in proximity to an ear canal **920**. **FIG. 10** is a cross-sectional view schematically illustrating relative placements of electrodes with respect to a computerized tomography scan of a human head. Referring to **FIG. 10**, an electrode **1010** contacting a portion of the skin lining the ear canal may be in closer proximity to a vestibular nerve **1030** (approximate location shown) than an electrode **1020** contacting the skin next to the ear and over a mastoid part of a temporal

bone. Referring to **FIGS. 8-10**, an electrode **215** inserted into an ear canal of the subject may be in close proximity to a vestibular nerve.

[0117] Referring again to **FIGS. 8** and **2-4**, the waveform generator **281** of the controller **210** may electrically stimulate the vestibular system based on a waveform. The waveform may be an electrical signal. The electrical signal may be modulated. The waveform generator **281** may provide the modulated electrical signal to the electrode **215**. In some embodiments, the waveform generator **281** may be electrically connected the electrode **215**, although the embodiments of the present inventive concepts are not limited thereto. For example, in some embodiments, the waveform generator **281** may be wirelessly in communication with an earpiece **250A**, **250B** that may generate and provide the electrical signal to the electrode **215**.

[0118] The electrode **215** may provide the electrical signal to the vestibular system. For example, the electrode **215** may provide the electrical signal to the vestibular system via an electrical connection through the skin. The skin may provide an electrical resistance in the electrical path between the electrode and the vestibular system. Thus, the waveform generator **281** may control an amplitude of the waveform such that an amplitude of the electrical signal is sufficient to traverse the skin and stimulate the vestibular system. In some embodiments, the waveform may be modulated based on a frequency.

[0119] FIG. 11 is a graph illustrating a relationship between an impedance of skin and a frequency of a stimulation waveform according to some embodiments of the present inventive concepts. Referring to **FIGS. 8** and **11**, an impedance of the skin may decrease as a frequency of the waveform increases. *See*, e.g., J. Rosell, J. Colominas, P. Riu, R. Pallas-Areny, J. G. Webster, Skin impedance from 1 Hz to 1 MHz, *IEEE Trans Biomed Eng* 35, 649-651 (1988); published online EpubAug (10.1109/10.4599).

[0120] For example, at a frequency of zero Hertz (0 Hz), in other words a direct current of a fixed amplitude, the skin may provide a large impedance in the electrical path between the electrode and the vestibular system. Thus, in order to stimulate the vestibular system at a frequency of zero Hertz (0 Hz), the waveform generator **281** may provide a waveform of large amplitude and, accordingly, the electrode may provide an electrical signal with a large voltage. This may not be desired as the subject may experience discomfort, pain, and/or physical damage based on the large voltage.

[0121] At higher frequencies, the skin may provide a lower impedance in the electrical path between the electrode and the vestibular system. Thus, in order to stimulate the vestibular system at higher frequencies, the waveform generator **281** may provide a waveform of smaller

amplitude and, accordingly, the electrode may provide an electrical signal with a smaller voltage. At the lower voltage, the subject may not experience the discomfort, pain, and/or physical damage. However, the higher frequency may not induce the desired diagnostic and/or therapeutic effects of galvanic vestibular stimulation. For example, some diagnostic and/or therapeutic uses of galvanic vestibular stimulation desire stimulation at a lower frequency. In some embodiments of the present inventive concepts, a modulation scheme is provided that generates an electrical signal with a higher frequency to produce the lower impedance and that stimulates the vestibular system at a lower frequency.

[0122] FIG. 17 is a schematic block diagram illustrating portions of a controller according to some embodiments of the present inventive concepts. Referring to **FIG. 17**, a controller **1710** may be similar to the one or more of the controllers **210**, **510A**, **510B** of **FIGS. 4-5B** except for the differences as noted. The controller **1710** may include a waveform generator **1720** that may generate the modulated electrical signal based on a time-varying modulation waveform. The waveform generator may receive the modulation waveform from a first function generator **1730**. The first function generator **1730** may define the modulation waveform and provide the modulation waveform as a modulated voltage to the waveform generator **1720**. The waveform generator **1720** may include a second function generator **1740**. The second function generator **1740** may receive a carrier function and the modulation waveform. The second function generator **1740** may modulate the carrier function based on the modulation waveform. For example, the second function generator **1740** may perform frequency modulation or amplitude modulation to generate a voltage-based modulated electrical signal. In some embodiments, the voltage-based modulated electrical signal may be received by a current supply **1750** that produces a clamped current output that may be provided to the first and second electrodes as the modulated electrical signal.

[0123] Packet-Based Modulation

[0124] FIG. 12 is a graph illustrating modulated stimulation waveform according to some embodiments of the present inventive concepts. Referring to **FIG. 12**, a waveform may include a plurality of spaced-apart packets of pulses. The pulses may correspond to electrical pulses produced based on the waveform.

[0125] Ones of the plurality of packets may include a quantity, N, of pulses and a separation in time, S, between adjacent ones of the plurality of packets of pulses. For example, as illustrated in **FIG. 12**, the packets may each include a quantity, N, of 3 pulses, although the present inventive concepts is not limited thereto. For example, the quantity, N, of pulses may be

more or less than three but, in some embodiments, may be at least 2. The separation in time, S, between adjacent ones of the plurality of packets may be defined as a quantity of time between an end of a last pulse of one packet and a beginning of the first pulse of the next adjacent packet.

[0126] Ones of the pulses may include a width in time, W, an amplitude, A, and a separation in time, X, between adjacent ones of the pulses within a packet. The width in time, W, of a pulse may be defined as a quantity of time between a rising edge and a falling edge of a single pulse, although the present inventive concepts is not limited thereto. The amplitude, A, of the waveform may correspond to the amplitude of the voltage of the electrical signal provided by the electrode **215** of **FIG. 8**. The separation in time, X, between adjacent ones of the pulses within a packet may be defined as a quantity of time between an end of one pulse within a packet and a beginning of the next pulse within the same packet.

[0127] An impedance provided by the skin of **FIG. 8** in response to an electrical signal corresponding to the stimulation waveform may be based on the width in time, W, of the pulses and the separation in time, X, between adjacent ones of the pulses within a packet. For example, the width, W, and separation, X, may define a time period of a pulse. A frequency of the pulses may be the inverse of the time period. The impedance may be inversely proportional to the frequency of the pulses, as illustrated in **FIG. 11**. Thus, the width, W, and separation, X, may be selected to be smaller to provide a higher frequency and, thus, a lower impedance.

[0128] At least one of the quantity, N, of the plurality of pulses within ones of the plurality of packets of pulses, the width in time, W, of the plurality of electrical pulses within ones of the plurality of packets of pulses, the amplitude, A, of the plurality of pulses within ones of the plurality of packets of pulses, the separation in time, X, between adjacent ones of the plurality of pulses within ones of the plurality of packets of pulses, and the separation in time, S, between adjacent ones of the plurality of packets of pulses may be modulated to modulate the stimulation waveform. The at least one modulated parameter may be modulated based on a target stimulus frequency. Referring to **FIGS. 8** and **10**, the vestibular system may be stimulated based on the target stimulus frequency. Thus, the target stimulus frequency may be selected to be low based on the desired diagnostic and/or therapeutic uses of the galvanic vestibular stimulation.

[0129] In some embodiments, the separation in time, S, between adjacent ones of the plurality of packets of pulses may be modulated to modulate the stimulation waveform. In other words, the separation in time, S, may not be constant and may be varied based on the target stimulus frequency. For example, the separation in time, S_1 between the first packet and the

second packet illustrated in **FIG. 12** may be different from the separation in time, S_2 between the second packet and the third packet illustrated in **FIG. 12**.

[0130] FIG. 13 is a graph illustrating a modulated separation in time between adjacent ones of a plurality of packets of electrical pulses according to some embodiments of the present inventive concepts. Referring to **FIGS. 12** and **13**, the separation in time, S, between adjacent ones of the plurality of packets of pulses may be varied in a sinusoidal modulation. The separation in time, S, may vary between a minimum separation value and a maximum separation value. A period of the sinusoidal modulation may define the stimulation frequency. For example, a duration in time between minimum values or between maximum values may define the period. The stimulation frequency may be defined as the inverse of the period. Thus, the separation in time, S, may be varied in a sinusoidal modulation to stimulate the vestibular system based on the target stimulation frequency.

[0131] Target neurons of the vestibular system may require a minimum amount of time after stimulation to recover. The target neurons may be stimulated by each pulse. Because the separation in time, X, between pulses within a packet may be selected to be small to provide decreased impedance, the target neurons may not recover between pulses within a packet. Thus, the target neurons may be constantly stimulated within a duration of a packet of pulses. However, the minimum value of the separation in time, S, between packets may be selected to be sufficiently large to allow target neurons to recover before being activated by the next packet of pulses. Thus, by modulating the separation in time, S, the stimulation of the target neurons may be modulated based on the target stimulus frequency. *See*, e.g., M. W. Bagnall, L. E. McElvain, M. Faulstich, S. du Lac, Frequency-independent synaptic transmission supports a linear vestibular behavior. *Neuron* 60, 343-352 (2008); published online EpubOct 23 (S0896-6273(08)00845-3 [pii]10.1016/j.neuron.2008.10.002) (discussing recovery of vestibular afferent synapse after stimulus trains).

[0132] The galvanic vestibular stimulation may have downstream effects in other portions of the brain of the subject based on the target stimulus frequency. In some embodiments, a frequency of the modulated signal may be selected to induce brain rhythms in a target portion of the brain. In some embodiments, the galvanic vestibular stimulation may entrain endogenous brain rhythms in a target portion of the brain based on the modulated signal.

[0133] In some embodiments, the separation in time, S, may be varied according to the formula $S(t) = S_{min} + S_c*\sin(\omega t)$, wherein S(t) is the separation in time, S, between adjacent ones of the plurality of packets of electrical pulses, S_{min} and S_c are time constants, and ω is

proportional to the target stimulus frequency. However, embodiments of the present inventive concepts are not limited thereto. For example, in some embodiments, the separation in time, S, may be varied according to other formulas, such as $S(t) = S_{min} + S_c*\cos(\omega t)$. Without wishing to be bound by any particular theory, it is believed that an amplitude of the separation in time, S, may be inversely proportional to an amplitude of an induced stimulus. For example, with a reduced separation in time, S, a vestibular system will receive more packets of electrical pulses within a given time. Conversely, with an increased separation in time, S, the vestibular system will receive fewer packets of electrical pulses within the given time. By modulating the separation in time, S, an amplitude of the induced stimulus may therefore be modulated. Thus, by modulating the separation in time, S, according to a target frequency, the induced stimulus may therefore be modulated according to the target frequency. Accordingly, brainwaves may be entrained according to the stimulus frequency.

[0134] FIG. 14 is a graph illustrating a modulated separation in time between adjacent ones of a plurality of packets of electrical pulses and a corresponding modulated stimulation waveform according to some embodiments of the present inventive concepts. Referring to **FIG. 14**, a separation of time, S, between adjacent ones of a plurality of packets of pulses is illustrated as varied in a sinusoidal modulation. An amplitude of a waveform is illustrated corresponding to the modulation of S. For example, a longer separation in time is illustrated between adjacent packets when S is higher and a shorter separation in time is illustrated when S is lower. In the illustrated example, each of the packets includes three pulses of equal amplitude, width, and separation, however embodiments are not limited thereto.

[0135] FIGS. 15A, **15C**, and **15E** are graphs illustrating modulated target stimulus frequencies according to some embodiments of the present inventive concepts. **FIGS. 15B**, **15D**, and **15F** are graphs illustrating modulated separations in time between adjacent ones of a plurality of packets of electrical pulses according to the modulated target stimulus frequencies of **FIGS. 15A**, **15C**, and **15E**, respectively. Referring to **FIGS. 12-13** and **15A-15F**, in some embodiments, the formula may include more than one target stimulus frequency. For example, in some embodiments, the formula may include a range of frequencies. In some embodiments, the modulating may include modulating the target stimulus frequency between a lower target frequency and a higher target frequency.

[0136] Referring to **FIGS. 15A-15B**, in some embodiments, the modulating may include repeatedly decreasing the target stimulus frequency in a pattern between the higher target frequency and the lower target frequency. A period of the sinusoidal modulation of the

separation in time, S, may increase over time as the target frequency decreases. The patterns illustrated in **FIGS. 15A-15B** may be consecutively repeated for a duration of the galvanic vestibular stimulation.

[0137] Referring to **FIGS. 15C-15D**, in some embodiments, the modulating may include repeatedly increasing the target stimulus frequency in a pattern between the lower target frequency and the higher target frequency. A period of the sinusoidal modulation of the separation in time, S, may decrease over time as the target frequency increases. The patterns illustrated in **FIGS. 15C-15D** may be consecutively repeated for a duration of the galvanic vestibular stimulation.

[0138] Referring to **FIGS. 15E-15F**, in some embodiments, the modulating may include repeatedly cycling the target stimulus frequency in a pattern of increasing from the lower target frequency to the higher target frequency and then decreasing back to the lower target frequency. A period of the sinusoidal modulation of the separation in time, S, may decrease over time as the target frequency increases and may increase as the target frequency decreases. The patterns illustrated in **FIGS. 15E-15F** may be consecutively repeated for a duration of the galvanic vestibular stimulation.

[0139] **Carrier-Based Modulation**

[0140] **FIGS. 16A-D** are graphs illustrating a method for modulating an electrical signal according to some embodiments of the present inventive concepts. For example, **FIG. 16A** is a graph illustrating a carrier waveform function according to some embodiments of the present inventive concepts, **FIG. 16B** is a graph illustrating a modulation waveform according to some embodiments of the present inventive concepts, **FIG. 16C** is a graph illustrating an amplitude modulated electrical signal according to some embodiments of the present inventive concepts, and **FIG. 16D** is a graph illustrating a frequency modulated electrical signal according to some embodiments of the present inventive concepts. Referring to **FIG. 16A**, a carrier waveform function may be a continuous cyclical function. For example, in some embodiments, the carrier waveform function may be a sine wave. In some embodiments, the carrier waveform function may be a square wave, a sawtooth wave, or another waveform function. The carrier waveform function may include an amplitude and a carrier frequency. The carrier waveform function may include a sequence of pulses that may correspond to electrical pulses produced based on the function.

[0141] Ones of the pulses may include a width in time, W and an amplitude, A. The width in time, W, of a pulse may be defined as a quantity of time between corresponding phases

of adjacent pulses. The amplitude, A, of the waveform may correspond to the amplitude of the voltage and/or current of the electrical signal provided by the electrode **215** of **FIG. 8**.

[0142] An impedance provided by the skin as shown in **FIG. 8** in response to an electrical signal corresponding to the carrier waveform function may be based on the width in time, W, of the pulses. For example, the width, W, may define a time period of a pulse. A carrier frequency of the carrier waveform function may be the inverse of the time period. The impedance may be inversely proportional to the frequency of the pulses, as illustrated in **FIG. 11**. Thus, the width, W, may be selected to be smaller to provide a higher frequency and, thus, a lower impedance. For example, in some embodiments, the carrier frequency may be greater than or equal to about 3 kHz. In some embodiments, the carrier frequency may be about 10 kHz.

[0143] Referring to **FIGS. 16A-16D**, at least one of the amplitude, A, and the carrier frequency may be modulated to modulate a stimulation waveform. The at least one modulated parameter may be modulated based on a time-varying modulation waveform. For example, referring to **FIGS. 16A-16C**, the amplitude of the carrier waveform function may be modulated based on the modulation waveform to produce an amplitude modulated electrical signal. Referring to **FIGS. 16A-16B** and **FIG. 16D**, the frequency of the carrier waveform function may be modulated based on the modulation waveform to produce a frequency modulated electrical signal. In some embodiments, the modulation waveform may be a sinusoidal function. In such embodiments, the amplitude and/or frequency of the carrier waveform function may be varied in a sinusoidal modulation. However, in other embodiments, the modulation waveform may not be sinusoidal and may be another waveform. Referring to **FIGS. 8** and **10**, the vestibular system may be stimulated based on the modulation frequency. Thus, the modulation frequency may be selected to be low based on the desired diagnostic and/or therapeutic uses of the galvanic vestibular stimulation. In some embodiments, the modulation frequency may be less than about 1 kHz. For example, in some embodiments, the modulation frequency may be between about 0.005 Hz and about 200 Hz. However, in some embodiments, a modulation frequency that is greater than 1kHz may be selected based on another desired diagnostic and/or therapeutic use of the galvanic vestibular stimulation.

[0144] The galvanic vestibular stimulation may have downstream effects in other portions of the brain of the subject based on the modulation frequency. In some embodiments, a frequency of the modulated signal may be selected to induce brain rhythms in a target portion of the brain. In some embodiments, the galvanic vestibular stimulation may entrain endogenous brain rhythms in a target portion of the brain based on the modulated signal.

[0145] In some embodiments, the modulation waveform may include more than one modulation frequency. For example, in some embodiments, the modulation waveform may include a range of frequencies. In some embodiments, the modulating may include modulating the modulation waveform between a lower target frequency and a higher target frequency. In some embodiments, the modulating may include repeatedly decreasing the modulation frequency in a pattern between the higher target frequency and the lower target frequency. In some embodiments, the modulating may include repeatedly increasing the modulation frequency in a pattern between the lower target frequency and the higher target frequency. In some embodiments, the modulating may include repeatedly cycling the modulation frequency in a pattern of increasing from the lower target frequency to the higher target frequency and then decreasing back to the lower target frequency.

[0146] **Applications**

[0147] Embodiments according to the present inventive concepts will now be described with respect to the following non-limiting examples

[0148] ALTERATION OF CROSS-FREQUENCY COUPLING

[0149] The oscillatory activity in multiple frequency bands may be observed in different levels of organization from micro-scale to meso-scale and macro-scale. Studies have been shown that some brain functions are achieved with simultaneous oscillations in different frequency bands. The relation and interaction between oscillations in different bands can be informative in understanding brain function. This interaction between several oscillations is also known as cross-frequency coupling (CFC).

[0150] Two forms of recognized CFC in brain rhythms are: phase amplitude coupling (PAC), and phase-phase coupling (PPC). In phase amplitude coupling, the phase of the lower frequency oscillation may drive the power of the coupled higher frequency oscillation, which may result in synchronization of amplitude envelope of faster rhythms with the phase of slower rhythms. Phase-phase coupling is amplitude independent phase locking between high and low frequency oscillation.

[0151] It is believed that phase-amplitude coupling may be a mechanism for communication within and between distinct regions of the brain by coordinating the timing of neuronal activity in brain networks. That brain rhythms modulate the excitability of neuronal ensembles through fluctuations in membrane potentials, biasing the probability of neuronal spiking at a specific phase of the slower rhythm. PAC is thought to dynamically link functionally related cortical areas that are essential for task performance.

[0152] Parkinson's disease (PD) has been shown to be associated with exaggerated coupling between the phase of beta oscillations and the amplitude of broadband activity in the primary motor cortex, likely constraining cortical neuronal activity in an inflexible pattern whose consequence is bradykinesia and rigidity. *See*, e.g., C. de Hemptinne, N. C. Swann, J. L. Ostrem, E. S. Ryapolova-Webb, M. San Luciano, N. B. Galifianakis, P. A. Starr, Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease, *Nat Neurosci* 18, 779-786 (2015); published online EpubApr 13 (10.1038/nn.3997). Parkinson's disease may be associated with a range of symptoms that originate, or are centered, in different brain regions. It is believed that aberrant cross-frequency coupling between two different EEG bands may be present when a patient experiences tremor. It is believed that CVS and/or GVS may be used to alter the cross-frequency coupling so as to renormalize function and re-establish proper balance.

[0153] Stimulation of a region in the brain stem called the PPN has been shown to improve, for example, the normalization of gait in PD patients. *See*, e.g., H. Morita, C. J. Hass, E. Moro, A. Sudhyadhom, R. Kumar, M. S. Okun, Pedunculopontine Nucleus Stimulation: Where are We Now and What Needs to be Done to Move the Field Forward? *Front Neurol* 5, 243 (2014); published online (10.3389/fneur.2014.00243). With respect to the present inventive concepts, without wishing to be bound by theory, it is believed that vestibular stimulation may modulate activity of the PPN. For example, CVS may be used to stimulate the PPN. In some embodiments, GVS may be used to break up the aberrant cross frequency coupling associated with tremor simultaneous with the use of CVS to stimulate the PPN. Thus, the two modalities may modulate different brain regions to improve the efficacy of the treatment.

[0154] More generally, GVS may be used to sensitize or give preference to a subset of neural pathways that respond to a specific excitation frequency (for example, within the EEG bands), making them more responsive to CVS neuromodulation. These selected pathways would then be subject to differential modulation in the background of other, non-selected pathways. An illustrative example would be the use of GVS in the theta band frequency range, associated with hippocampal activity, to sensitize pathways associated with memory encoding. GVS at a sub-threshold intensity may be used, or the intensity may be above the activation threshold of the afferent vestibular nerves. The CVS waveform would be chosen so as to overlap and enhance the neuromodulatory effects of the targeted GVS modulation.

[0155] CONTROLLING IGF-1 ACCRETION

[0156] Insulin-like growth factor 1 (IGF-1) is a hormone that is similar in molecular structure to insulin that is believed to play an important role in childhood growth and to have

anabolic effects in adults. The protein is encoded in humans by the IGF1 gene. It is believed that IGF-1 may also provide mitochondrial protection

[0157] Insulin-like growth factor number one (IGF-1) is a hormone (MW: 7649 daltons) similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. Its production is encoded by the IGF1 gene and it is produced primarily in the liver as an endocrine hormone, though production in the central nervous system has also been observed. In circulation, IGF-1 is bound to one of six proteins, the most common being IGFBP-3. These chaperone proteins increase the half life of IGF-1 in circulation from around 15 minutes (unbound) to 15 hours (bound). IGF-1 production is associated with growth hormone (GH) and blood tests for GH use IGF-1 as a surrogate, since the concentration of the latter tends not to vary as much over a daily cycle as that of GH does. IGF-1 is one of the most potent natural activators of the AKT signaling pathway, a stimulator of cell growth and proliferation, and a potent inhibitor of programmed cell death. It protects and strengthens cells at one of their most vulnerable moments, when they are in the process of and immediately after dividing. It is believed that IGF-1 may provide mitochondrial protection from mitochondrial stress.

[0158] Electrical stimulation of the fastigial nucleus (FN) for a sufficient time and at the right frequency has been shown to lead to neuroprotection via reduction of apoptosis in mitochondria in the ischemic area. *See*, e.g., P. Zhou, L. Qian, T. Zhou, C. Iadecola, Mitochondria are involved in the neurogenic neuroprotection conferred by stimulation of cerebellar fastigial nucleus, *J Neurochem* 95, 221-229 (2005). It is believed that IGF-1 may be a factor in such neuroprotection. Electrical stimulation has been shown to result in the recruitment of IGF-1 from systemic circulation, through the blood-brain-barrier (BBB), and to very localized usage by or around the point of the stimulated nerves. Effectively, the nerve activity signaled for and recruited IGF-1. *See*, e.g., T. Nishijima, J. Piriz, S. Duflot, A. M. Fernandez, G. Gaitan, U. Gomez-Pinedo, J. M. Verdugo, F. Leroy, H. Soya, A. Nunez, I. Torres-Aleman, Neuronal activity drives localized blood-brain-barrier transport of serum insulin-like growth factor-I into the CNS, *Neuron* 67, 834-846 (2010). It is believed that vestibular stimulation may similarly accomplish the recruitment of and/or enhance the efficiency of IGF-1, either directly affecting nerves active during vestibular stimulation or possibly nearby nerves receive IGF-1 in a bystander effect. For migraine headache in particular, increased rCBF may be a key factor enabling increased IGF-1 uptake through the BBB. Mechanisms for altering blood flow mesh nicely with existing observations/beliefs around the etiology of migraines. That IGF-1 also

facilitates synaptic plasticity could mean it has a role in mitigating central pain associated with chronic migraines.

[0159] With respect to the present inventive concepts, without wishing to be bound by theory, it is believed that vestibular stimulation, or in particular CVS and/or GVS, may be used to increase IGF-1 transport across the blood-brain-barrier, and therefore increase mitochondrial protection, in frequency-dependent targeted regions of the central nervous system. In some embodiments, CVS and GVS may be combined. For example, CVS may be used to provide stimulation of frequency-dependent regions of the brain and GVS may be used to provide neuroprotection to the stimulated regions and/or surrounding regions.

[0160] Although embodiments have been described with reference to galvanic vestibular stimulation through an ear canal, the present inventive concepts are not limited thereto. For example, in some embodiments, the vestibular system may be stimulated through at least one electrode in contact with a portion of the skin behind the ear in proximity to a mastoid part of a temporal bone. In some embodiments, delivering the electrical signal may include transdermal electrical stimulation of other portions of a nervous system of the subject. In some embodiments, the described modulation scheme may be used with implantable electrodes or other devices that do not stimulate through the skin.

[0161] AUDIO WAVEFORMS

[0162] In some embodiments, neurostimulation may be performed based on an audio waveform. For example, a time-varying modulation waveform used for modulating an electrical signal that is delivered to a patient may be an audio waveform. As used herein, an audio waveform is a waveform that includes frequency components that are within a hearing range of the subject. For example, an audio waveform may include frequency components within a range of about 20 to 20,000 Hz. In some embodiments, the audio waveform may be time-varying and/or may include one or more patterns. For example, the audio waveforms may include music and/or voice. In some embodiments the audio waveforms may include sounds of an environment, such as the sounds of rain, birds, moving water, cars, etc. In some embodiments, the audio waveforms may be based on audio recordings. In some embodiments, the waveforms of the galvanic vestibular stimulation may be modulated based on the audio waveforms.

[0163] As used herein, modulation of an electrical signal based on an audio waveform means that the frequency components of the audio waveform within a hearing range of the subject are encoded into the electrical signal. For example, notes or sounds that are in the audio waveform may be encoded into the electrical signal. In some embodiments, the electrical signal

may include a carrier waveform at a frequency that is at least twice a highest frequency of the frequency components of the audio waveform encoded into the electrical signal. The audio waveform may be encoded into the carrier waveform via, for example, frequency or amplitude modulation. In some embodiments, an electrical signal may not be referred to as being modulated based on the audio waveform if the electrical signal is modulated based on beats or other features of the audio waveform in the absence of the frequency components of the audio waveform that are within the hearing range of the subject.

[0164] COMBINATION OF CVS AND GVS TO ENHANCE IGF-1 DELIVERY

[0165] As discussed in more detail below, in some embodiments, a combination of CVS and GVS may be used to activate a neuroprotective function. For example, without wishing to be bound by any particular theory, apoptosis in mitochondria may be reduced through neurostimulation by increasing IGF-1 uptake through a blood-brain-barrier by inducing oscillations in cerebral blood flow.

[0166] FIG. 18 is a cross-sectional view schematically illustrating an effect of CVS on vestibular nerves according to some embodiments of the inventive concepts. Referring to **FIG. 18**, administration of CVS may include raising and/or lowering temperatures of the earpieces **550A, 550B**. For example, in some embodiments, as illustrated in **FIG. 18**, the temperature of earpiece **550A** may be controlled to a higher temperature while the earpiece **550B** may be controlled to a lower temperature. Regular neurons have an equilibrium firing rate of about 100 Hz. Lowering the temperature of the regular neurons may lower the firing rate of the neurons and increasing the temperature of the neurons may increase the firing rate of the neurons. Accordingly, the temperatures of the earpieces **550A, 550B** may be controlled to alter the firing rate of neurons in the respective ears corresponding to a CVS waveform. The period of a CVS waveform may be limited by the thermal conduction time of the temporal bone. However, the actual firing pattern created by time-varying CVS in the vestibular nuclei may be complex. A temperature ramp may create an increasing or decreasing frequency signal, often termed a "chirp." Thus, even though the frequency of a CVS thermal waveform is significantly less than 1 Hz, the induced firing rate may extend for many 10's of Hz above and/or below the equilibrium firing rate. Furthermore, each ear may be stimulated independently, leading to a highly complex frequency modulation space in the brainstem.

[0167] FIG. 19 is a cross-sectional view schematically illustrating an effect of GVS on vestibular nerves according to some embodiments of the inventive concepts. Referring to **FIG. 19**, administration of GVS may include providing modulated voltage and/or current to the

electrodes **515A, 515B**. For example, in some embodiments, as illustrated in **FIG. 19**, a negative voltage/current may be applied to the electrode **515A** and a positive voltage/current may be applied to the electrode **515B**. The negative voltage/current may increase the firing rate of the neurons and the positive voltage/current may lower the firing rate of the neurons. Accordingly, the modulated voltage and/or current applied to the electrodes **515A, 515B** may be controlled to alter the firing rate of neurons in the respective ears corresponding to a modulated GVS waveform.

[0168] FIG. 20 is a cross-sectional view schematically illustrating an effect of vestibular neurostimulation on a brain according to some embodiments of the inventive concepts. **FIG. 20** illustrates a map of some brain regions (particularly relevant to migraine headache) that may be innervated by the vestibular system. Via thalamic relays, the vestibular system may exert control on other sensory cortices. For example, information en route to the cerebral cortex may first pass through the thalamus. However, a long-held view that the thalamus serves as a simple high fidelity relay station for sensory information to the cortex has over recent years been dispelled. There are multiple projections from the vestibular nuclei to thalamic nuclei, including the ventrobasal nuclei, and the geniculate bodies, regions typically associated with other modalities. Further, some thalamic neurons have been shown to respond to stimuli presented from across sensory modalities. For example, neurons in the anterodorsal and laterodorsal nuclei of the thalamus may respond to visual, vestibular, proprioceptive and somatosensory stimuli and integrate this information to compute heading within the environment. Therefore, the thalamus may serve crucial integrative functions, at least in regard to vestibular processing, beyond that imparted by a "simple" relay. Accordingly, a vestibular neuromodulation waveform may be relayed to target portions of the brain and may entrain brain waves at a target frequency.

[0169] In mammals there are generally two types of vestibular hair cells, Type I hair cells and Type II hair cells. Each of these classes of hair cells has a distinctive pattern of afferent ending onto the hair cell. One important factor that varies between the different afferents is the regularity of the afferent's resting discharge rate. Afferents that are innervated only by type I hair cells have action potentials that generally fire at very irregular rates when firing spontaneously. Afferents that are innervated only by type II hair cells generally have very regular static discharge rates.

[0170] GVS may preferentially affect irregularly firing hair cells within the vestibular receptor organs. Further, GVS may affect hair cells in all of the semicircular canals and otoliths (not a subset). Cathodal (DC) GVS may increase afferent firing rate whereas anodal GVS may

decrease the firing rate. This is analogous to an increase in firing rate associated with warm CVS (that is, above body temperature) and a decrease with cold CVS. Irregularly firing hair cells comprise roughly 25% of the afferent output of the vestibular organs.

[0171] CVS may be capable of activating both regularly and irregularly firing hair cells. Regular hair cells fire at approximately100 Hz in equilibrium and CVS may alter firing rate around this value. A rapid temperature change may engage irregularly firing hair cells as well. Whereas the horizontal semicircular canal is generally described as the principal target of CVS, the other canals and otoliths may also respond.

[0172] Therefore, CVS may affect regularly and irregularly firing hair cells in all of the vestibular sensing organs, whereas GVS primarily affects the irregularly firing hair cells in all of the vestibular sensing organs. Accordingly, CVS and GVS activation patterns may not be identical.

[0173] Irregularly firing hair cells may have evolved with amniotes in order to facilitate vestibular tracking of higher frequency movements. For example, land animals developed necks and this new degree of freedom may have necessitated a faster-responding hair cell type (irregular). So-called head direction cells have been identified in the hippocampal complex and this type of sensory cell may rely on irregularly firing vestibular hair cells to properly provide feedback on the position of the body in space. Across different species of mammals, there is a substantial constancy of the linear dimensions of the respective vestibular organs. Across seven orders of magnitude in size, the physical dimensions of the semicircular canals may vary by less than one order of magnitude. This level of evolutionary conservancy in vestibular organs attributes may be evidence of a high significance of a change in basic vestibular function, such as the emergence of irregularly firing hair cells.

[0174] Borrowing from a development in optics and visual processing, spatial frequency analysis, it may be possible to characterize an image by separating high and low spatial frequencies. High spatial frequencies are necessary to encode edges and sharp changes in contrast. Low spatial frequencies capture general shape and general contrast. The visual system in mammals may segregate raw input from the retina, with some cortical regions responding to edges, contrast changes, etc. In other words, the visual cortex may perform operations analogous to a spatial frequency decomposition on raw sensory flow from the retina. The processing of visual images has been studied in terms of areas in the visual cortex that respond to rapid or less rapid changes in image contrast over a given length scale, so-called high and low spatial frequencies respectively. The brain may unit the different spatial frequency regimes into a

coherent whole, but may also utilize the two domains individually for some processing tasks.

[0175] This result may be generalized to other sensory modalities, like the vestibular system. The vestibular system has fast-responding (irregular) and more slowly responding (regular) hair cells that may characterize movement. The brain's overall perception of movement may be informed by the integration of both movement categories. The output of the irregularly firing hair cells may contribute to excitation at high frequencies and, therefore, GVS stimulation may primarily contribute to excitation at high frequencies. Slowly changing temperatures delivered by CVS may primarily affect regularly firing hair cells and may provide higher information density in the lower spatial frequencies. Therefore, it may be possible to utilize CVS and GVS in combination to affect different ends of the frequency spectrum of vestibular sensory flow. Regular and irregular vestibular outputs may innervate the same brain regions (that is, the two components don't have divergent pathways), but the information content may be different and may enable different outcomes in terms of cognitive or behavioral states. As a specific example, the irregularly firing hair cells may have evolved specifically because new behavioral abilities of land animals were not being well-encoded by regular hair cells alone.

[0176] As discussed above, electrical stimulation of the fastigial nucleus (FN) for a sufficient time and at the right frequency has been shown to lead to neuroprotection via reduction of apoptosis in mitochondria in the ischemic area. More specifically, electrical stimulation of the FN may reduce the release of cytochrome-c from mitochondria. Cytochrome-c release is part of the apoptotic chain. The neuroprotective effect may be frequency dependent and a minimum duration of stimulation may be needed to provide neuroprotection.

[0177] IGF-1 may inhibit cytochrome-c release from mitochondria. Passage of IGF-1 through the blood-brain-barrier may occur in response to specific signaling in the brain and may be facilitated by enhancement of neurovascular coupling by increase blood flow. This effect may also be frequency dependent.

[0178] Stimulation of the FN may lead to changes in cerebral blood flow (CBF). This may be important in facilitating the signaling in the brain to activate passage of IGF-1 though the blood-brain-barrier. Time-varying CVS may induce oscillations in CBF. Therefore, vestibular stimulation may be used to activate the FN, which may induce oscillations in CBF, which may activate passage of IGF-1 through the blood-brain-barrier, which may protect mitochondria against apoptotic death, promote synaptogenesis, and/or improve neurovascular coupling, thus providing neuroprotective effects. For example, IGF-1 may inhibit cytochrome-c release from mitochondria, which may reduce apoptosis in mitochondria. This may be an innate response that

protects neurons in the brain. Accordingly, time-varying CVS and/or GVS may be used to activate this innate protective mode.

[0179] The impact of vestibular stimulation on IGF-1 movement may be dependent on a time-varying aspect of the CVS and/or GVS. For example, time-varying CVS may leads to oscillations in CBF. In some embodiments, stimulation waveforms may be selected that facilitate the production of CBF oscillations. For example, the CBF oscillations may be measured using, for example, transcranial Doppler sonography. Accordingly, a plurality of stimulation waveforms may be sequentially tried while measuring for CBF oscillations. One or more waveforms that produce desired CBF oscillations may be selected. This may be done with a patient at a start of a therapy to optimize the waveform choice that provides the most effective amount of CBF oscillations.

[0180] In some embodiments, time-varying CVS may be used to excite CBF oscillations while using a narrow frequency GVS to select a subset of brain regions to activate, thus facilitating the movement of IGF-1 across the BBB. The time-varying CVS and the narrow-frequency GVS may both work to increase IGF-1 uptake through the blood-brain-barrier.

[0181] In some embodiments, a positron-emitting radionuclide may be used as a Positron Emission Tomography (PET) label on IGF-1. The PET label may be introduced systemically while measuring uptake in the brain via PET imaging. Accordingly, it may be seen where IGF-1 uptake increases based on the type of vestibular neurostimulation applied. In some embodiments, the positron-emitting radionuclide may be a PET label on glucose or oxygen to detect blood flow. For example, some embodiments may use fluorine-18 labeled fluorodeoxyglucose or oxygen-15. In some embodiments, transcranial Doppler sonography to measure the induction of cerebral blood flow oscillations. In some embodiments, CBF oscillations may be measured via transcranial Doppler sonography while sequentially trying a plurality of stimulation waveforms to select one or more waveforms that produce desired CBF oscillations, as described above, at a start of a therapy to optimize the waveform choice that provides the most effective amount of CBF oscillations. In some embodiments, the transcranial Doppler sonography may be used to compare before and during vestibular neuromodulation to identify differences in PET uptake to hone in on regions where additional IGF-1 has entered the central nervous system due to the vestibular neuromodulation.

[0182] As an example, cerebral blood flow oscillations may include B waves. B waves are spontaneous oscillations in cerebral blood flow velocity (CBFv) that may have a frequency of about 0.5 to about 3 cycles per minute, thus a period of about 20 seconds to about 2 minutes.

There is experimental evidence that B waves may be due to fluctuations in vessel diameters triggered by monoaminergic and serotonergic centers in the midbrain and pons. B waves may be part of an autoregulatory response and their average period may to correspond to a complete cycle time for blood moving from the heart to the brain and back. Some studies have shown a correlation between abnormal B wave activity and migraine headaches, that period leg movements (also called restless leg syndrome) may be part of a common endogenous rhythm matching the B wave period, and that B waves may be more prominent in NREM sleep. B waves may be a significant predictor of survival after traumatic brain injury.

[0183] The B wave period may fall in a range found in functional connectivity studies of the sensory cortices. Functional connectivity in the auditory, visual, and sensorimotor cortices may be significantly characterized by frequencies slower than those in the cardiac and respiratory cycles. In functionally connected regions, these low frequencies may be characterized by a high degree of temporal coherence. This functional connectivity may have the same pacing nexus that gives rise to B waves, which may indicate neurovascular coupling. Thus, the entrainment of B waves may also entrain the above describe sensory functional connectivity.

[0184] For example, time-varying CVS may induce significant oscillations in the Gosling Pulsatility Index (PI), which is a measure of cerebrovascular resistance defined as [(peak systolic velocity - end diastolic velocity)/ mean cerebral blood flow velocity], a primary measure of

[0185] cerebrovascular dynamics. A time-varying CVS treatment may induce PI spectral peaks at intervals that may fall within the periodicity range of B waves and may not match periods of the warm and cold waveforms. Studies have provided evidence for a monoaminergic B-wave pacing center in the pons, an area that receives direct innervation from the vestibular nuclei in the brainstem, which may be how the time-varying CVS treatment may induce oscillations.

[0186] In other words, the time-varying CVS may entrain the pontine structures responsible for B-wave pacing, as evidenced by a significant increase of spectral power at spectral frequencies within the range of B-waves in a post-CVS period.

[0187] <u>CVS AND GVS CO-NEUROMODULATION</u>

[0188] As used herein, the terms "vestibular neuromodulation" and "vestibular neurostimulation" may each refer to the stimulation of the vestibular nerve, which may include CVS and/or GVS.

[0189] Methods of treating a patient using neuromodulation may include a combination

of CVS and GVS that are applied together. For example, in some embodiments, the CVS and GVS may be applied simultaneously. The CVS and GVS may each include a time-varying stimulation waveform. As used herein, stimulations may be considered to be applied simultaneously when applied as part of a single treatment. For example, in some embodiments, the CVS and GVS may be applied simultaneously when applied within an hour of each other as measured from the end of the first to the beginning of the second. In some embodiments, the CVS and GVS may be applied simultaneously when applied within an thirty minutes of each other, or fifteen minutes, or five minutes. In some embodiments, the CVS and GVS may be applied simultaneously when there is an overlap in time between the application of the CVS and the application of the GVS.

[0190] In some embodiments, the CVS and GVS may excite different frequencies in the brain. For example, the CVS may be used to excite frequencies less than 1 Hz. The GVS may be used to excite frequencies greater than 1 Hz. In some embodiments, the GVS may be used to excite frequencies between about 0.005 Hz and about 200 Hz and may be different than a frequency of the CVS. In some embodiments, frequencies of the GVS may be at least a multiple of a maximum frequency of the CVS. For example, the frequencies of the GVS may be at least 10 times a maximum frequency of the CVS.

[0191] In some embodiments, there may be a defined phase difference between the stimulation waveform of the CVS and the stimulation waveform of the GVS. For example, the stimulation waveform of the CVS and the stimulation waveform of the GVS may be controlled to maintain a 180° phase difference. Accordingly, the GVS may suppress an irregular hair cell contribution of the net applied vestibular neuromodulation. Therefore, a net applied vestibular neuromodulation may be controlled to affect mainly regular firing hair cells, mainly irregular firing hair cells, or a mixture of regular and irregular firing hair cells.

[0192] In some embodiments, a small relative frequency difference between the stimulation waveform of the CVS and the stimulation waveform of the GVS may result in a net effect at a beat frequency. The beat frequency may be equal to the difference between the stimulation waveform of the CVS and the stimulation waveform of the GVS. For example, a target frequency may be selected for a desired effect in a treatment. The stimulation frequency of the CVS and the stimulation frequency of the GVS may each be controlled to have a difference equal to the desired target frequency. One or more of the stimulation waveform of the CVS and the stimulation waveform of the GVS may be modulated to vary the target frequency.

[0193] DURABLE GAINS

[0194] Conditions such as neurological disorders, may be treated by administering stimulation, for example vestibular stimulation, for example CVS, to at least one ear of a subject in a condition-treatment effective amount during a treatment interval. The stimulation may be effective to produce a durable improvement in at least one symptom of the condition. For example, the durable improvement may remain for a time of at least 1 or 2 weeks, or 1, 2, or 3 months, or more, following cessation of the stimulation. Examples of such conditions may include, but may not be limited to, neurodegenerative diseases, such as Parkinson's disease, and other neurological conditions, such as headache, for example migraine headache. In some examples, the symptom may be a non-motor symptom of the condition.

[0195] Examples of non-motor symptoms of a condition as described herein (including but not limited to Parkinson's disease) may include, but are not limited to: cardiovascular symptoms (for example, light-headedness, dizziness, weakness on standing from a sitting or lying position; fall because of fainting or blacking out), sleepiness and fatigue (for example, doze off or fall asleep unintentionally during daytime activities; fatigue (tiredness) or lack of energy (not slowness) limiting daytime activities; difficulties falling or staying asleep; urge to move the legs or restlessness in legs that improves with movement when sitting or lying down inactive); mood and cognitive symptoms (for example, loss of interest in surroundings; loss of interest in doing things or lack of motivation to start new activities; nervous, worried or frightened for no apparent reason; sad or depressed; flat moods without normal "highs" and "lows"; difficulty experiencing pleasure from their usual activities); perceptual problems and hallucinations (for example, seeing things that are not there; having beliefs that are known to be untrue; double vision); attention and memory symptoms (for example, problems sustaining concentration during activities; forget things told a short time ago or events that happened in the last few days; forget to do things); gastrointestinal tract symptoms (dribble saliva during the day; difficulty swallowing; suffer from constipation, etc.), urinary tract symptoms (incontinence/urgency; frequent urination; nocturia (get up at night to urinate), etc.); sexual dysfunction (for example, altered interest in sex; problems having sex, etc.); and other miscellaneous symptoms (for example, pain not explained by other known conditions; change in ability to taste or small; change in weight not related to dieting; excessive sweating).

[0196] In some embodiments, the stimulation may be administered to both ears of the subject. In some embodiments, the stimulation to each ear may be different. In some embodiments, the stimulation may be administered as a time-varying waveform. The stimulation may be carried out in a plurality of sessions. For example, the sessions may be administered 2,

3, or 4 times per week over a time of from 1 week to 1, 2 or 3 months, or more. For example, the sessions may include stimulation 1-2 times per day, 7 days per week, over a time from 1 week to 1, 2 or 3 months, or more.

[0197] In some embodiments, some or all of the sessions may be separated in time by rest intervals. For example, the treatment may include ceasing the administering of the stimulation for a rest interval having a duration of at least 1 or 2 weeks, or at least 1, 2, or 3 months, and then cyclically repeating the treatment sessions and the rest intervals at least once, or for a plurality of cycles. For example, the cycles may be repeated over a time of at least six months, or at least one or two years, or more.

[0198] In some embodiments, the at least one symptom of the condition may be measured during the rest interval. For example, the at least one symptom may be measured after ceasing the stimulation for a time of at least 1 or 2 weeks, or at least 1, 2, or 3 months. The stimulation may be modified in response to the measured at least one symptom. For example, a waveform may be selected based on the measurement. In some embodiments, an amplitude, duration, or other characteristic of the waveform may be altered. In some embodiments, a frequency of the waveform may be altered. In some embodiments, a type of waveform may be altered. In some embodiments, other characteristics of the stimulation may be altered.

[0199] Some example flowcharts of the treatments described herein are illustrated in **FIGS. 21** and **22**. For example, in **FIG. 21**, a method **2100** may include sequentially administering at least one CVS stimulus to a subject. For each administered CVS stimulus, a time to entrainment (T_E) and/or a time to relaxation (T_R) of at least one physiological oscillatory pattern may be determined, such as cross-functional coupling. If the time to entrainment and the time to relaxation of the at least one physiological oscillatory pattern are within target ranges (e.g., exceed a threshold) for one of the at least one CVS stimulus, then that at least one CVS stimulus may be an optimized CVS stimulus, which may be administered to the subject (e.g., once, or on multiple occasions during a first or an initial or subsequent treatment interval) as treatment. Periodic measurements of the at least one physiological oscillatory pattern may be performed to gauge when durable gains have been achieved. Upon achieving durable gains, administering of the optimized CVS stimulus may be paused, for example during a rest interval. Therapy may be repeated or restarted if continued measurements of the at least one physiological oscillatory pattern diverge from target values.

[0200] As another example, in **FIG. 22**, a method **2200** may include sequentially administering at least one CVS stimulus to a subject. For each administered CVS stimulus,

dynamic changes in sensory habituation resulting from the administered CVS stimulus may be measured. If the measured dynamic changes in sensory habituation are within a target range (e.g., exceed a threshold) for one of the at least one CVS stimulus, then that at least one CVS stimulus may be an optimized CVS stimulus, which may be administered to the subject (e.g., once, or on multiple occasions during a first or an initial or subsequent treatment interval) as treatment. Periodic measurements of sensory habituation may be performed to gauge when durable gains have been achieved. Upon achieving durable gains, administering of the optimized CVS stimulus may be paused, for example during a rest interval. Therapy may be repeated or restarted if continued measurements of the sensory habituation or parameters thereof diverge from target values.

[0201] MODELING NEUROLOGICAL DISEASE AS DYSFUNCTION OF INTERCONNECTED BRAIN OSCILLATORS

[0202] Brain dynamics may include collective oscillatory states. Accordingly, neurological disease may be modeled as dysfunctional brain oscillators. This model may be used as a platform for vestibular sensory neuromodulation as a treatment for, for example, episodic migraine (EM) headache and other neurological disorders. Other forms of clinical neuromodulation may work by applying (with implanted or externally placed electrodes) an empirically derived stimulation waveform. The applied stimulus for these other forms may affect nerves in proximity to the electrodes and may not reflect the endogenous activity patterns of those nerves. This can lead to unintended side effects, since empirical optimization for one outcome, say the reduction of tremor, may worsen other functions. It may be challenging to match an exogenously generated stimulus to a target as there may not be a clear preferred resonance or peak frequency. Neuromodulation of a sensory network may address this matching challenge. Using neuromodulation of a sensory network, the brain target may be accessed by endogenous neural pathways and the modulation signal applied to the sensory organ may be transformed in a way that it is matched to the native dynamics of the target region. *See* Black et al., "Sensory Neuromodulation" (publication forthcoming), incorporated by reference herein in its entirety.

[0203] In the modeling of biological oscillators, in order to make the mathematics tractable, simplifying assumptions, which may or may not be physically realistic, may be made. Common assumptions may include a narrow range of independent oscillator frequencies and extensive, but weak, coupling between component oscillators. Even with these simplifications, some oscillator models may coincide with current models of brain function. For example, a

"small-world" coupling in a simple ring oscillator model, as seen in **FIG. 23**. may enable synchronization without the need for all-to-all coupling of the individual nodes. This result is congruent with real cortical networks that have predominantly local modularity with sparse long-range connections. Specifically, the observation of excessive phase amplitude cross-frequency-coupling (CFC) in the motor cortex between beta and gamma bands in PD, as seen between bands **2400** and **2450** in **FIG. 24**, may be viewed as a breakdown in optimal small-world architecture. Aberrant CFC may be used as a viable biomarker of disease.

[0204] Time-varying vestibular neuromodulation (VNM) may stimulate entrainment of a pontine pacing center, which may engender oscillations in cerebral blood flow velocity. Oscillations may sharpen to a natural resonance when VNM is stopped, which may indicate entrainment. Functional brain oscillators may not remain isolated (uncoupled) from other oscillators (this is the essence of the small-world network concept) and sensory neuromodulation may present a powerful method for exciting complete networks, innervated by the vestibular system. Accordingly, measuring the onset and strength of entrainment of targeted brain oscillators may be used for the titration of VNM. For example, VNM may be used to reduce the pernicious effects of beta-gamma CFC in PD, moving the pathways closer to a pre-disease (reduced CFC) status. Without wishing to be bound by theory, VNM may be used to activate an innate neuroprotective system. An innate neuroprotective system may be responsive to abnormalities in brain oscillations which may trigger a systemic response. That is, the response pathway may work to maintain normal oscillatory dynamics. For example, an IGF-1 response may provide a mechanism to protect mitochondria against apoptotic death, improve neurovascular coupling and aid synaptogenesis, all crucial to maintaining baseline oscillator function. Viewing neurological disease in terms of dysfunctional oscillators enforces a systemic viewpoint since all brain oscillators are ultimately connected to each other. Neuromodulation via a sensory organ may be categorically different from some other clinical approaches in that the modulation signal can be carried via endogenous neural pathways. The vestibular system may enable broad access to distributed brain regions.

[0205] The idea that neurological disease may be viewed as a change in oscillatory brain dynamics may build upon models proposed previously. In a "communication through coherence" model, neuronal communication is mechanistically subserved by neuronal coherence. *See* Fries, "A mechanism for cognitive dynamics: neuronal communication through neuronal coherence," *Trends Cogn Sci*, vol 9, pg 474-80 (2005). Neuronal damage may change the baseline nature of neuronal oscillators. For example, tremor in a Parkinson's disease patient may

correlate with excessive phase-amplitude coupling between beta rhythms and broadband gamma. This coupling may dissipate during stimulation with a DBS implant. The DBS signal may disrupt an aberrant mode of oscillation, one that should not have naturally existed. Oscillatory activities in neural systems may play a role in orchestrating brain functions and dysfunctions, in particular those of neurological disorders. On the other hand, NIBS [non-invasive brain stimulation] techniques may be used to interact with these brain oscillations in a controlled way. Therefore, modulating brain oscillations may be an effective strategy for clinical NIBS interventions.

[0206] Hypothetically, viewing neurological disease through the lens of the collective dynamics of oscillators may explain why VNM may provide efficacy across a wide range of disease symptoms while manifesting a very low side effect profile. Brain oscillators develop during ontogeny and it may be possible to view many brain functions as being enabled by interactions of these oscillators. Neuronal damage, then, will obviously alter the oscillators that rely on those neurons. This may result in aberrant cross-frequency coupling, a reduced ability of the oscillator to resonate and therefore transfer information, etc. Time-varying VNM may entrain pathways innervated by the vestibular system and may thereby provide a forcing function that can rehabilitate oscillatory networks, returning them to baseline function. If a network is performing properly, this "stress test" may not alter it. VNM may modify, neuroplastically, brain oscillators and drive them towards developmentally established, normative function.

[0207] OPTIMIZING TREATMENTS BY IDENTIFYING OSCILLATORY PATTERNS

[0208] In some embodiments, an optimization protocol for selecting characteristics of the stimulation to be administered to the subject may be performed prior to a first treatment interval, or during a rest interval. An optimization protocol for selecting a treatment for the subject may include administering a stimulus, such as GVS or CVS, to the subject while determining a time to entrainment (T_E) of at least one physiological oscillatory pattern to the stimulus in the subject, and then ceasing the stimulus and then determining a time to relaxation (T_R) of the oscillatory pattern from the entrainment. The oscillatory pattern may optionally be reset by administering an exogenous stimulus to the subject. The optimization protocol may include repeatedly administering stimuli and measuring T_E and/or T_R for a plurality of different stimuli. The optimization protocol may include selecting a stimulus for administering to the subject during treatment based on the detected T_E and/or T_R, wherein a longer T_E and/or a shorter T_R (as compared to predetermined standard value for T_E or T_R, or as compared to those values for other

CVS and/or GVS stimuli administered to that subject) indicates greater efficacy of the stimulus for the at least one symptom. The selected stimulus may be administered to the subject, for example, once, or on multiple occasions during a first or an initial or subsequent treatment interval.

[0209] In some embodiments, an optimization protocol may include repeating cycles of detecting a physiological oscillatory pattern in the subject during and/or after the stimulation treatment(s) and, optionally, resetting the oscillatory pattern by administering an exogenous stimulus to the subject, for a plurality of different stimulation treatments to generate a database of CVS and/or GVS treatment(s) correlated with different oscillatory patterns in the brain of the subject. Efficacy scores may be assigned to each different stimulation treatment in the database based on the durability of improvement of the at least one symptom. A treatment may be selected from the database that provides a durable improvement in the symptom to the subject. The selected treatment may be administered to the subject in a subsequent treatment or treatment session.

[0210] In some embodiments, at least one physiological oscillatory pattern may be measured in the subject during the stimulation. The rest interval may be initiated when the oscillatory pattern is detected. For example, a rest interval may be initiated when a sufficient degree of entrainment in the oscillatory pattern, as compared to a predetermined target value, is measured. Examples of oscillatory patterns may include, but are not limited to, cross-frequency coupling (CFC) and cerebrovascular blood flow velocity (CBF_v) oscillations. CFC may be detected, for example, by electroencephalography (EEG). CBF_v oscillations may be detected, for example, by transcranial Doppler sonography. In some embodiments, the exogenous stimulus may include transcranial magnetic stimulation (TMS), such as repetitive TMS (rTMS), which may be used as a means to "reset" acute changes created by VNM. In that way, different VNM treatment parameters can be evaluated in one session, using rTMS to perturb the target cortical oscillators, preparing them for serial VNM applications.

[0211] A calibration phase may include cycles of delivering a stimulation to the subject, measuring an onset and/or a recovery time resulting from the stimulation, and determining if the onset and/or recovery time are within a target range. For example, the onset time may be T_E and the recovery time may be T_R of changes in cross-frequency coupling. After the calibration phase, an optimized stimulation that is determined to produce the onset and/or recovery time within the target range may be delivered to the subject in a treatment phase. During the treatment phase, periodic measurements may be performed to gauge when durable gains have

been achieved. These measurements may include, for example, the onset and/or recovery times for changes in CFC and/or the overall magnitude of the CFC for comparison with a normative range. In some embodiments, these measurements may include, for example, a measure of dynamic changes in sensory habituation to sensory stimuli. The therapy may be paused or completed when the target gains are achieved. Optionally, the therapy may be repeated or resumed if the measured parameters start to diverge from the target values.

[0212] In some embodiments, cross-frequency coupling EEG (CFC) may be used as a specific biomarker to gauge progress towards the neuroplastic changes that can underpin durable gains. **FIG, 25** illustrates an example of measuring of onset and recovery as entrainment and relaxation of cross frequency coupling in plot **2500**.

[0213] The center portions of the sine waves illustrate a slower wave, such as a beta brain wave being affected by a faster wave, such as a gamma brain wave. The gamma wave may be amplitude modulated at the frequency of the beta. The center portion **2520** illustrates a phenomenon of phase-amplitude coupling that may be absent from first portion **2510** (from a time $\mathbf{T_0}$ to entrainment at time $\mathbf{T_E}$) and from last portion **2530** (after relaxation time $\mathbf{T_R}$). This phase-amplitude coupling may be induced by VNM stimulation. The two times show how long it took the VNM stimulus to create phase-amplitude CFC and how long that coupling lasted when VNM was stopped. These times may be used to adjust the VNM stimulus parameters to achieve "target" values. For example, it may be desired for T_E to be short and T_R to be long. That is, fast coupling to the target oscillator system and robust duration of the oscillations when the VNM stimulus is stopped may be desirable. For example, if T_E were to be very long (on the time scale of or longer than a duration of the VNM therapy), then the VNM treatment may not be effective at inducing CFC. It may be desirable for T_R to be long to maximize the duration of the gains. For example, it may be desired to permanently create CFC. It may therefore be desirable to progress to the point where the baseline signal looks like the center part of the diagram, which may indicate that VNM has created a neuroplastic change that enabled baseline CFC. In some embodiments, such as in the case of beta and gamma waves for symptoms of PD, it may be desired to reduce CFC, and the opposite of the above may apply.

[0214] Thus the characteristic times may be measured, acutely and dynamically, and used to guide changes to the VNM stimulus parameters. The aim may be to move the system to a durable change. Then, as therapy progresses, the measurements may be repeated to gauge how rapidly a desired end goal is approached, for example a persistent change in the baseline CFC characteristics. In some embodiments, VNM stimulus parameters may be adjusted on a per

patient basis to hit those target times. Accordingly, CFC may be used to titrate a VNM therapy.

[0215] In some embodiments, cerebral blood flow velocity (CBFv) may be used as a specific biomarker to gauge progress towards the neuroplastic changes that can underpin durable gains. **FIG. 26** illustrates a recording of CBFv changes in plot **2600**, showing a portion 2610 prior to administering of the vestibular stimulation. The plot **2600** also shows the entrainment time during portion **2620**, where a pulsatility index may be between approximately 0.68 and 0.78 during entrainment, and having a comparatively larger range of between approximately 0.6 and 0.99 once entrainment has been achieved, and the relaxation time during portion **2630**, where the pulsatility index may be between approximately 0.6 and 0.99 during relaxation, and having a comparatively smaller range of between approximately 0.68 and 0.83 after T_R .

[0216] Other biomarkers that may be used to gauge progress towards the neuroplastic changes that can underpin durable gains may include heart-rate-variability (HRV), eye tracking, functional imaging, and/or measurement of sensory habituation. HRV may be measured in the dynamic way presented herein, measuring these characteristic times, and thus provide a metric for titrating VNM. Eye tracking may be observed with video or electrical oculography. In addition to nystagmus, eye movements including micro-saccadic bursts may be induced during VNM. The onset and relaxation times for these target eye movements may be used to titrate VNM treatments. With functional imaging, one specific measure may include coupling between B waves (CBFv oscillations) and sensory functional connectivity oscillations. The two may be part of a common pacing system. The onset and relaxation of oscillations in functional connectivity, induced by VNM, may provide valuable information about the degree to which sensory processing is balanced in the two hemispheres.

[0217] With respect to measurement of sensory habituation, for example in migraineurs, there may be a reduction in ability to habituate to sensory stimuli. For example, **FIG. 27** illustrates a difference between the habituation to repeated sensory stimulus for a migraneur as compared to a control subject.

[0218] Measurements that assess sensory habituation may include evoked response potentials in the motor, visual, auditory and somatosensory cortices. Measurements of habituation may be facilitated by repetitive sensory stimuli or indirectly by using repetitive transcranial magnetic stimulation (rTMS) to fatigue a target cortical region. Measurements, during the application of VNM, can be made to see the onset and relaxation times associated with changes in acute habituation to sensory stimuli. Migraineurs may show less of a decrement to TMS fatigue than controls. A VNM therapy may be titrated to most rapidly converge on

normal levels of habituation by creating neuroplastic modification of the relevant sensory response.

[0219] Other potential biomarkers that can be measured dynamically in the way described above may include, as examples, pulse rate variability (PRV) measured using a pulse oximeter, electrogastography (EGG), functional Transcranial Doppler sonography (fTCD), photoplethysmography (PPG), pupillometry, breathing rate, heart rate, and/or biochemical measurements with kinetics that are comparable to the typical VNM treatment time (~15-30 minutes). Examples of such biochemicals may include histamine, vasopressin, catecholomines, serotonin, insulin, serum glucose, CGRP, orexin, IGF-1, growth hormone, BDNF, alpha amylase, and/or cytochrome c. Generally, an applicable biomarker may be measured acutely in time, in association with the application of VNM, so that onset and relaxation time measurements can be acquired in order to assess the level of entrainment of the underlying brain oscillators for the applied VNM treatment parameters. An overall goal of titration may be to choose the VNM parameters that reduce the onset time of entrainment and lengthen the relaxation time after VNM stops.

[0220] In some embodiments, the stimulation may include concurrently administering CVS and GVS to at least one ear of the subject. The GVS may be effective to enhance an efficacy of the CVS. In some embodiments, the GVS may be administered to both ears of the subject and, optionally, the GVS to each ear may be different. The GVS may be delivered between electrodes in each of the ears and a counter electrode that may be attached to the forehead, chest, etc., thus enabling two sides to operate independently. Optionally, one ear may be grounded while the other ear goes to a higher or lower voltage. The GVS may include modulating a waveform to vary a target stimulus frequency. The GVS may have an average waveform frequency at least 10 or 20 times greater than the CVS average waveform frequency. For example, the GVS may have a high frequency, for example about 5-10 KHz, that may traverse the skin with a lower impedance without rubbing the outer layer of skin off and/or applying an electrically conductive gel. The higher frequency "carrier" signal may be modulated at a desired GVS frequency, which may be very low, for example 0.01 Hz up to 100 Hz or more, corresponding to the target stimulus frequency. Thus, in some embodiments the frequency of GVS may be matched to a frequency of the CVS and in some embodiments the frequency of the GVS may be higher than the frequency of the CVS. For example the frequency of the GVS may be selected to match a range of EEG bands.

[0221] Embodiments of the inventive concepts may provide chronic treatment in order to

prevent return of the one or more symptoms. In other words, treatment may be halted for some period of time without the return of the one or more symptoms, thus improving patient experience and compliance.

[0222] Repeated caloric vestibular stimulation (CVS), a non-invasive form of neuro-modulation, has been shown to induce a lasting and clinically-relevant reduction in Parkinson's disease (PD) symptoms. *See* D. Wilkinson et al., A durable gain in motor and non-motor symptoms of Parkinson's Disease following repeated caloric vestibular stimulation: A single-case study. Neurorehabilitation 38(2) (Feb. 2016). Wilkinson describes a patient diagnosed with PD 7 years prior to study enrolment, who self-administered CVS at home 2×20 minutes per day for three months using a solid-state portable device. The patient in Wilkinson showed behavioral improvements that exceeded the minimal detectable change on the EQ5D, Unified Parkinson's Disease Rating Scale, Schwab and England scale, 2 minute walk, Timed up and go, Non-motor symptom assessment scale for PD, Montreal cognitive assessment, Hospital depression scale and Epworth sleepiness scale. The level of change exceeded the threshold for a minimal clinically important difference on all scales that were known to have a published threshold. By contrast, Wilkinson described little improvement seen during the sham (i.e. placebo) phase.

[0223] The device used by the patient in Wilkinson for vestibular stimulation included a headset fashioned like music headphones with aluminum earpieces that contained a solid-state heater/cooler element which warmed and cooled the external ear canals via controlled, time-varying thermal waveforms. One earpiece delivered a cold sawtooth waveform (ear canal temperature to 17 °C every 2mins) and the other delivered a warm sawtooth (ear canal temperature to 42 °C every 1 minute). To ensure balanced hemispheric activation over the course of the study (warm currents primarily activate ipsilateral cortex while cold currents primarily activate contralateral cortex) we switched the waveform assigned to each ear every 2 days. Each stimulation session lasted 20mins during which time the patient lay passively supine with his head resting on a wedge shaped pillow angled at 30°. Two sessions, spaced at least 4hrs apart, were administered by the patient (with the help of his wife) twice per day, 5 days per week for 3 months. Sham stimulation was delivered in the first month, followed by 2 months of active stimulation.

[0224] **FIG. 28** illustrates operations of methods of improving or enhancing entrainment and may improve a rate at which induction of beneficial effects using time-varying CVS (tvCVS) may be achieved. The methods and operations of **FIG. 28** may be used in conjunction with other described methods and systems herein.

[0225] In **FIG. 28**, in operation **2801**, a generic waveform combination may be applied to a subject to entrain an oscillator in the brain of the subject. The generic waveform combination may include a first waveform (e.g., a "cold" CVS waveform) and a second waveform (e.g., a "warm" CVS waveform), which may have different frequencies. In operation **2802**, application of the generic waveform may be ceased or halted after the generic waveform has been applied for a duration of time (e.g., a predetermined period of time). In operation **2803**, data values of a monitored brain oscillator biomarker proxy (e.g., heart rate) may be examined, and based on the data values of the monitored proxy, a natural resonance or frequency of the entrained brain oscillator may be determined or identified. In operation **2804**, based on the determined natural resonance of the entrained brain oscillator (determined from the monitored oscillator proxy values), one or more characteristics of at least one waveform may be modified to target the natural resonance of the brain oscillator entrained in operation **2801**. For example, a frequency of either the first or second waveform may be modified, the temperature range of the CVS waveform may be modified, a number and time duration of each administering session may be modified, or so on. Targeting the natural resonance of the entrained brain oscillator may include modifying characteristics of the first or second waveform to increase a strength, amplitude, or power of the brain oscillator by a desired amount. The modification of the characteristics of the at least one waveform may result in a modified waveform combination. In operation **2805**, the modified waveform combination may be applied to the subject.

[0226] In some embodiments, the method of improving or enhancing entrainment described with respect to **FIG. 28** may be repeated over a time period. For example, a heart-rate-variability of a subject may improve over time, and an entrainment frequency could shift over time. It may therefore be desirable to re-acquire a drifting entrainment frequency over a course of longitudinal therapy.

[0227] To further illustrate the method of **FIG. 28**, **FIGS. 29A** and **29B** illustrate example waveform combinations **2900** and **2950**, each including a cold waveform **2910/2960** and a warm waveform **2920/2970**. In some embodiments, the cold waveform **2910/2960** may be administered to a first external ear canal of a subject via a first heating/cooling element while the warm waveform **2920/2970** is applied to a second external ear canal of the subject via a second heating/cooling element. In **FIG. 29A**, the waveform combination **2900** may include a cold waveform **2910** that has a period twice as long as the warm waveform **2920**. The cold waveform **2910** and the warm waveform **2920** may each begin at a start time (e.g., a time T0) at a first temperature. For example, the temperature may be approximately 37 °C. Over a first time period

from T0 to T1, the warm waveform **2920** may increase in temperature while the cold waveform **2910** may decrease in temperature. During a second time period from T1 to T2, the warm waveform **2920** and the cold waveform **2910** may both decrease in temperature. During a third time period from T2 to T3, the warm waveform **2920** and the cold waveform **2910** may both increase in temperature. During a fourth time period from T3 to T4, the warm waveform **2920** may decrease in temperature, and the cold waveform **2910** may increase in temperature. At approximately the time T4, both the warm waveform **2920** and the cold waveform **2910** may be at the first temperature. Application of the waveform combination **2900** shown in **FIG. 29A** may result in entrainment of one or more brain oscillators. Without being bound by any particular theory, it is suggested that each time period of the cold waveform **2910** and/or the warm waveform **2920** leads to a change in a collective firing rate of the vestibular nerves, with a periodicity of the changes acting as a driver to entrain a brain oscillator. Additionally, other physiological indicators, such as heart rate and heart rate variability, may also be entrained or exhibit oscillatory behavior as a result of the administering of the waveform combination **2900**. *See* Black et al., 2016, "Non-Invasive Neuromodulation Using Time-Varying Caloric Vestibular Stimulation," IEEE J Transl Eng Health Med, vol 4, 2000310.

[0228] With reference to **FIG. 28**, the waveform combination **2900** of **FIG. 29A** may be a default or first waveform combination applied in, e.g., operation **2801**. After application of the waveform combination is ceased in operation **2802**, one or more of the proxies of brain oscillatory behavior (e.g., heart rate) may be examined and a natural resonance of the entrained brain oscillator may be determined. For example, it may be determined that the natural resonance of the entrained brain oscillator is proximate to each half-wave of the warm waveform **2920** (e.g., having a cyclical frequency that is based on the time periods of **FIG. 29A**). To further target this natural resonance in operation **2804**, characteristics of the cold waveform **2910** or the warm waveform **2920** may be modified. For example, with reference to **FIG. 29B**, the waveform combination **2950** may be selected or generated. Comparison of **FIG. 29A** and **FIG. 29B** shows that the cold waveform **2960** has an equal period to the warm waveform **2970**, and has a higher minimum temperature than cold waveform **2910**. The waveform combination **2950** of **FIG. 29B** may be selected or generated based on a recognition that the natural resonance of the entrained brain oscillator may be driven by the warm waveform **2920/2970**, in that that the natural resonance of the entrained brain oscillator is proximate to each half-wave of the warm waveform **2920**. Selection of a different cold waveform **2960** may be predicated on improving the strength of the entrainment. The waveform combination **2950** may be applied in operation **2805**.

[0229] NEURO-VASCULAR COUPLING

[0230] As discussed above, the central nervous system may be segregated from the systemic blood supply by the blood-brain-barrier. (BBB). The BBB may be comprised of endothelial cells in capillary walls, the "feet" of astrocytes, and pericytes. One way to negotiate the BBB may be a signaling system called neurovascular coupling (NVC). NVC may reflect the dynamic relationship between active neurons and the cerebral blood supply that enables that activity. Historically, a neuro-centric bias has existed, with the vasculature component of NVC being minimized or ignored. The present disclosure recognizes that the two halves of the term "neurovascular" are equally relevant when considering both normal brain function and neurological disease.

[0231] With recognition of the discussion above with respect to oscillator-centric models of brain function, the coupling between cerebrovascular dynamics and the activity of neuronal networks may be bilateral, with neither capable of existing without the other. Diminished coupling may occur through damage to neurons, or through damage to the capillary network suppling a region of brain tissue, but in both cases the effects of the damage will be felt by all elements of the neurovascular unit, not just neurons. See, e.g., Cauli, B. and E. Hamel, "Revisiting the role of neurons in neurovascular coupling." *Front Neuro*, 2010. 2: p. 9.

[0232] Without wishing to be bound to any one particular theory, it is thought that NVC may be an efficient control mechanism, in that it supplies additional blood to brain parenchyma that requires increased blood flow. Cerebral autoregulation may have both global and regional control features. For example, globally, autoregulation implies the maintenance of consistent, continuous blood flow to the brain, irrespective of the other demands of the body. Heart rate, blood pressure, and cerebrovascular compliance may all work to maintain steady cerebral blood flow (CBF). As an example of regional control features, active neuronal tissue may be able to initiate enhanced blood flow so as to accommodate enhanced metabolic demand. As an evolutionary adaptation, NVC may be particularly relevant in humans, given the significant metabolic demands placed on the body by the brain. This complex system is not without the potential to fail, however, and consequential neurological dysfunction may result.

[0233] NVC may act across a range of time scales. BOLD imaging has yielded snap shots of neurovascular contrast on the ~1 second scale. NVC effects on longer time scales, called ultralow frequency or infra-slow, < 0.10 Hz, have been studied separately both to better understand slow cortical modulations of functional connectivity and slow oscillations in CBF velocity.

[0234] The present disclosure considers whether there is more than a coincidental overlap between B waves (discussed above, or more generally slow hemodynamic cycles) and infra-slow functional connectivity fluctuations. Without wishing to be bound by any one particular theory, it is thought that these phenomena may be coupled, as the oscillators supporting them may support entrainment. It may be that there is a more fundamental relationship between infra-slow fluctuations in autoregulation and those seen in functional connectivity.

[0235] It is thought that NVC dysfunction may play a role in neurological, physiological and/or psychiatric diseases and conditions, such as those discussed herein, including cognitive impairment, dementia, neuroinflammation, PD, Alzheimer's disease, migraine and other cephalalgias, symptoms resultant from traumatic brain injuries (such as headache, dizziness, fatigue, irritability, and/or insomnia), epilepsy, depression, and cognitive decline resultant from, for example, aging.

[0236] Some literature has reviewed the effects of exercise on the vasculature, including brain-related vasculature. For example, vascular aging has been evaluated with a focus on arterial elasticity and the vascular endothelium, and a conclusion that aerobic exercise modulates structural proteins, reduces oxidative stress and inflammation, and improves nitric oxide (NO) availability. Santos-Parker, J.R., et al., "Aerobic exercise and other healthy lifestyle factors that influence vascular aging." *Adv Physiol Educ*, 2014. 38(4): p. 296-307. It is noted that NO has a potential vasodilatory effect on blood vessels, and also may have a role as a neurotransmitter. It has also been demonstrated that exercise may create an increase in total and regional CBF, though such increases seem to abate during heavier, sustained exercise. Some aspects of the interplay between aging and exercise may include that exercise may promote neuronal plasticity and cerebrovascular plasticity, while aging is antagonistic to both neuronal plasticity and cerebrovascular plasticity. Nishijima, T., I. Torres-Aleman, and H. Soya, "*Exercise and cerebrovascular plasticity.*" Prog Brain Res, 2016. **225**: p. 243-68. Nishijima et al. provide a specific example of how the increased access to IGF-1 by the NVU may lead to improved cerebrovascular patency, with one expectation being that exercise may strengthen NVC and thereby improve baseline brain function in a broad fashion.

[0237] The present disclosure considers the action of time-varying CVS (tvCVS) on cerebrovascular dynamics. In an NVC context, tvCVS may induce neuronal activity so as to engage vascular coupling. tvCVS may entrain CBFv oscillations, and this action suggests a mechanism for improving the health and functioning of the neurovascular unit (NVU). *See* Black

et al. "Does Time-Varying CVS Improve Neurovascular Coupling," (publication forthcoming), which is incorporated by reference herein in its entirety.

[0238] Without wishing to be bound to any one particular theory, it is thought that the modulatory effects of vestibular stimulation on CBFv, if applied longitudinally, may lead to plastic cerebrovascular change of the sort that has been attributed to exercise. Exercise produces CBFv changes in a dynamic fashion. Black et al., 2016, "Non-Invasive Neuromodulation Using Time-Varying Caloric Vestibular Stimulation," IEEE J Transl Eng Health Med, vol 4, 2000310. The application of tvCVS, and the ability to induce entrainment of CBFv, that results in the continuation of CBFv oscillations after the cessation of applied neuromoduation is a mechanism of action that may also lead to plastic cerebrovascular change. As described herein, monitoring CBFv may also provide a capability to titrate tvCVS therapy for a given individual.

[0239] To restate a fundamental linkage again, cerebrovascular plasticity may promote neuronal plasticity and neuronal plasticity may depend on adaptation of the vascular supply. tvCVS may act to both enhance cerebrovascular plasticity and neuronal plasticity through the vestibular sensory network, for example by delivering sensory neuromodulation as discussed above.

[0240] In some embodiments, one or more biomarkers may be used to gauge progress towards changes in cerebral blood flow velocity (CBFv) caused by vestibular stimulation. For example, heart-rate-variability (HRV) may be used as a specific biomarker to gauge progress. HRV may be measured in the dynamic way presented herein, measuring these characteristic times, and thus provide a metric for titrating vestibular stimulation. In some embodiments, HRV may serve as a proxy measurement. Other biomarkers may be used as proxies to gauge progress towards changes in CBFv, including those discussed elsewhere herein.

[0241] As another example, blood oxygen level, measured as peripheral capillary oxygen saturation (SpO2), and/or variability in blood oxygen level/SpO2, may be used as a biomarker proxy. Normal values for SpO2 may fall within a range of 95%-100% with minimal variation. However, as seen in **FIG. 30A**, and in chart **3000** thereof, SpO2 may exhibit oscillations or variations during administration of vestibular stimulation, which may be used to gauge progress towards changes in CBFv and/or brain oscillators. CVS was administered to a subject during a period **3020**, and as seen, the subject's peripheral capillary oxygen saturation demonstrates a greater variability than before CVS was administered (period **3010**). Interestingly, during a post-administration period (period **3030**), the SpO2 of the individual achieved a higher value (99%) at sub-period **3031** and remained relatively constant for a number of minutes over sub-period **3032**.

Chart **3050** of **FIG. 30B** shows a heart rate of the subject during the same periods of before (**3010**), during (**3020**), and after (**3030**) administration of the CVS.

[0242] The inventive concepts provided by the present disclosure have been be described above with reference to the accompanying drawings and examples, in which examples of embodiments of the inventive concepts are shown. The inventive concepts provided herein may be embodied in many different forms than those explicitly disclosed herein, and the present disclosure should not be construed as limited to the embodiments set forth herein. Rather, the examples of embodiments disclosed herein are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the inventive concepts to those skilled in the art.

[0243] Like numbers refer to like elements throughout. In the figures, the thickness of certain lines, layers, components, elements or features may be exaggerated for clarity.

[0244] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the inventive concepts. As used herein, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, steps, operations, elements, components, and/or groups thereof. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. As used herein, phrases such as "between X and Y" and "between about X and Y" should be interpreted to include X and Y. As used herein, phrases such as "between about X and Y" mean "between about X and about Y." As used herein, phrases such as "from about X to Y" mean "from about X to about Y."

[0245] Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the specification and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. Well-known functions or constructions may not be described in detail for brevity and/or clarity.

[0246] It will be understood that when an element is referred to as being "on," "attached" to, "connected" to, "coupled" with, "contacting," etc., another element, it can be directly on,

attached to, connected to, coupled with or contacting the other element or intervening elements may also be present. In contrast, when an element is referred to as being, for example, "directly on," "directly attached" to, "directly connected" to, "directly coupled" with or "directly contacting" another element, there are no intervening elements present. It will also be appreciated by those of skill in the art that references to a structure or feature that is disposed "adjacent" another feature may have portions that overlap or underlie the adjacent feature.

[0247] Spatially relative terms, such as "under," "below," "lower," "over," "upper" and the like, may be used herein for ease of description to describe one element or feature's relationship to another element(s) or feature(s) as illustrated in the figures. It will be understood that the spatially relative terms are intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if the device in the figures is inverted, elements described as "under" or "beneath" other elements or features would then be oriented "over" the other elements or features. Thus, the exemplary term "under" can encompass both an orientation of "over" and "under." The device may be otherwise oriented (rotated 90 degrees or at other orientations) and the spatially relative descriptors used herein interpreted accordingly. Similarly, the terms "upwardly," "downwardly," "vertical," "horizontal" and the like are used herein for the purpose of explanation only unless specifically indicated otherwise.

[0248] It will be understood that, although the terms "first," "second," etc. may be used herein to describe various elements, these elements should not be limited by these terms. These terms are only used to distinguish one element from another. Thus, a "first" element discussed below could also be termed a "second" element without departing from the teachings of the present inventive concepts. The sequence of operations (or steps) is not limited to the order presented in the claims or figures unless specifically indicated otherwise.

[0249] Some of the inventive concepts are described herein with reference to block diagrams and/or flowchart illustrations of methods, apparatus (systems) and/or computer program products, according to embodiments of the inventive concepts. It is understood that one or more blocks of the block diagrams and/or flowchart illustrations, and combinations of blocks in the block diagrams and/or flowchart illustrations, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, and/or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer and/or other programmable data processing apparatus, create means for implementing

the functions/acts specified in the block diagrams and/or flowchart block or blocks.

[0250] These computer program instructions may also be stored in a computer-readable memory that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable memory produce an article of manufacture including instructions which implement the function/act specified in the block diagrams and/or flowchart block or blocks.

[0251] The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce a computer-implemented process such that the instructions which execute on the computer or other programmable apparatus provide steps for implementing the functions/acts specified in the block diagrams and/or flowchart block or blocks.

[0252] Accordingly, the inventive concepts may be embodied in hardware and/or in software (including firmware, resident software, micro-code, etc.). Furthermore, embodiments of the present inventive concepts may take the form of a computer program product on a computer-usable or computer-readable non-transient storage medium having computer-usable or computer-readable program code embodied in the medium for use by or in connection with an instruction execution system.

[0253] The computer-usable or computer-readable medium may be, for example but not limited to, an electronic, optical, electromagnetic, infrared, or semiconductor system, apparatus, or device. More specific examples (a non-exhaustive list) of the computer-readable medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory such as an SD card), an optical fiber, and a portable compact disc read-only memory (CD-ROM).

[0254] The foregoing is illustrative of the present inventive concepts and is not to be construed as limiting thereof. Although a few exemplary embodiments of the inventive concepts have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of the inventive concepts provided herein. Accordingly, all such modifications are intended to be included within the scope of the present application as defined in the claims. Therefore, it is to be understood that the foregoing is illustrative of the present inventive concepts and the present disclosure is not to be construed as limited to the specific embodiments

disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims.

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THAT WHICH IS CLAIMED IS:

1. A device for administering thermal stimulation to an ear canal of a subject, comprising:

an earpiece configured to be at least partially insertable into the ear canal of the subject;

a thermoelectric device thermally coupled to the earpiece and configured to heat and/or cool the earpiece to thereby heat and/or cool the ear canal of the subject; and

a controller associated with the thermoelectric device, the controller comprising a processor and memory storing non-transitory computer-readable instructions that, when executed by the processor, cause the processor to administer a selected treatment plan comprising administering a caloric vestibular stimulation (CVS) stimulus to the ear canal of the subject during a first treatment interval; and

a monitoring device configured to monitor a physiological oscillatory pattern and/or a proxy of the physiological oscillatory pattern for a duration of time after administering the CVS stimulus during the first treatment interval, wherein the controller is configured to commence a second treatment interval of the selected treatment plan based on parameters of the physiological oscillatory pattern or the proxy of the physiological oscillatory pattern diverging from target values,

wherein the controller is configured to cease administration of the selected treatment plan for a rest interval in response to the controller detecting that a degree of entrainment in the physiological oscillatory pattern exceeds a predetermined target value.

2. The device of claim 1, wherein the monitoring device is configured to monitor a biomarker as a proxy for the physiological oscillatory pattern for a duration of time after administering the CVS stimulus during the first treatment interval.

3. The device of claim 2, wherein the monitoring device comprises a pulse rate monitor, wherein the biomarker is heart rate variability (HRV), and wherein the physiological oscillatory pattern comprises cerebrovascular blood flow velocity (CBF_V) oscillations.

4. The device of claim 1, wherein the subject is afflicted with a neurodegenerative disease.

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5. The device of claim 1, wherein the CVS stimulus comprises a time-varying waveform.

6. The device of claim 1, wherein the controller is further configured to cease administration of the CVS stimulus at an end of the first treatment interval for a rest interval.

7. The device of claim 6, wherein the controller is further configured to receive a measurement of at least one symptom of a condition during the rest interval; and to modify the selected treatment plan in response to the measurement of the at least one symptom.

8. A device for administering thermal stimulation to an ear canal of a subject, comprising:

an earpiece configured to be at least partially insertable into the ear canal of the subject;

a thermoelectric device thermally coupled to the earpiece and configured to heat and/or cool the earpiece to thereby heat and/or cool the ear canal of the subject; and

a controller associated with the thermoelectric device, the controller comprising a processor and memory storing non-transitory computer-readable instructions that, when executed by the processor, cause the processor to administer a selected treatment plan comprising administering a caloric vestibular stimulation (CVS) stimulus to the ear canal of the subject during a first treatment interval; and

a monitoring device configured to monitor a physiological oscillatory pattern and/or a proxy of the physiological oscillatory pattern for a duration of time after administering the CVS stimulus during the first treatment interval,

wherein the controller is configured to cease administration of the CVS stimulus at an end of the first treatment interval for a rest interval, and then commence a second treatment interval of the selected treatment plan based on parameters of the physiological oscillatory pattern or the proxy of the physiological oscillatory pattern diverging from target values,

wherein the controller is configured to cease administration of the selected treatment plan for the rest interval in response to the controller detecting that a degree of entrainment in the physiological oscillatory pattern exceeds a predetermined target value.

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9. The device of claim 8, wherein the monitoring device is configured to monitor a biomarker as the proxy for the physiological oscillatory pattern for a duration of time after administering the CVS stimulus during the first treatment interval.

10. The device of claim 9, wherein the monitoring device comprises a pulse rate monitor, wherein the biomarker is heart rate variability (HRV), and wherein the physiological oscillatory pattern comprises cerebrovascular blood flow velocity (CBF_V) oscillations.

11. The device of claim 1 or claim 8, wherein the device further comprises one or more electrodes configured to administer galvanic vestibular stimulation (GVS) to at least one ear of the subject, and wherein the selected treatment plan comprises administering a GVS stimulus having characteristics selected to enhance an efficacy of the administered CVS.

12. The device of claim 11, wherein the controller is further configured to perform operations comprising modulating the GVS stimulus to vary a target stimulus frequency.

13. The device of claim 11, wherein the one or more electrodes comprises first and second electrodes, wherein the controller is configured to deliver the GVS stimulus to both the first and second electrodes, and wherein delivering the GVS stimulus to the first and second electrode comprises maintaining the first electrode at a reference voltage level while the GVS stimulus is applied the second electrode as a time-varying voltage level corresponding to a stimulation waveform.

14. The device of claim 1 or claim 8, wherein the thermoelectric device is configured to heat and/or cool the earpiece with a temperature that changes at a predetermined rate.

15. The device of claim 14, wherein the predetermined rate is 15° C. per minute or greater.

16. The device of claim 15, wherein caloric vestibular stimulation (CVS) comprises thermal waveform having a starting temperature at a range of either 34 to 38° C. or at 23 to 26° C. and an amplitude of at least 5° C.

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17. The device of claim 16, wherein the thermal waveform is a sawtooth waveform having a temperature range above and/or below the starting temperature.

18. The device of claim 8, wherein said controller is configured to utilize an optimization protocol for selecting CVS and/or GVS to be administered to said subject, said optimization protocol administered prior to the first treatment interval, or during the rest interval, the optimization protocol comprising:

(a′) detecting a physiological oscillatory pattern in said subject during and/or after said CVS and/or GVS treatment(s);

(b′) optionally resetting said oscillatory pattern by administering an exogenous stimulus (e.g., transcranial magnetic stimulation) to said subject; then

(c′) repeating steps (a′) through (b′) for a plurality of different CVS and/or GVS treatments to generate a database of CVS and/or GVS treatment(s) correlated with different oscillatory patterns in the brain of said subject; then

(d′) assigning efficacy scores or to each said different CVS and/or GVS treatment in said database based on the durability of improvement of at least one symptom in said subject;

(e′) selecting from said database a CVS and/or GVS treatment that provides a durable improvement in said symptom to said subject; and then

(f′) administering said selected CVS and/or GVS treatment to said subject in a subsequent treatment or treatment session.

19. The device of claim 8, wherein the rest interval has a duration of at least one week.

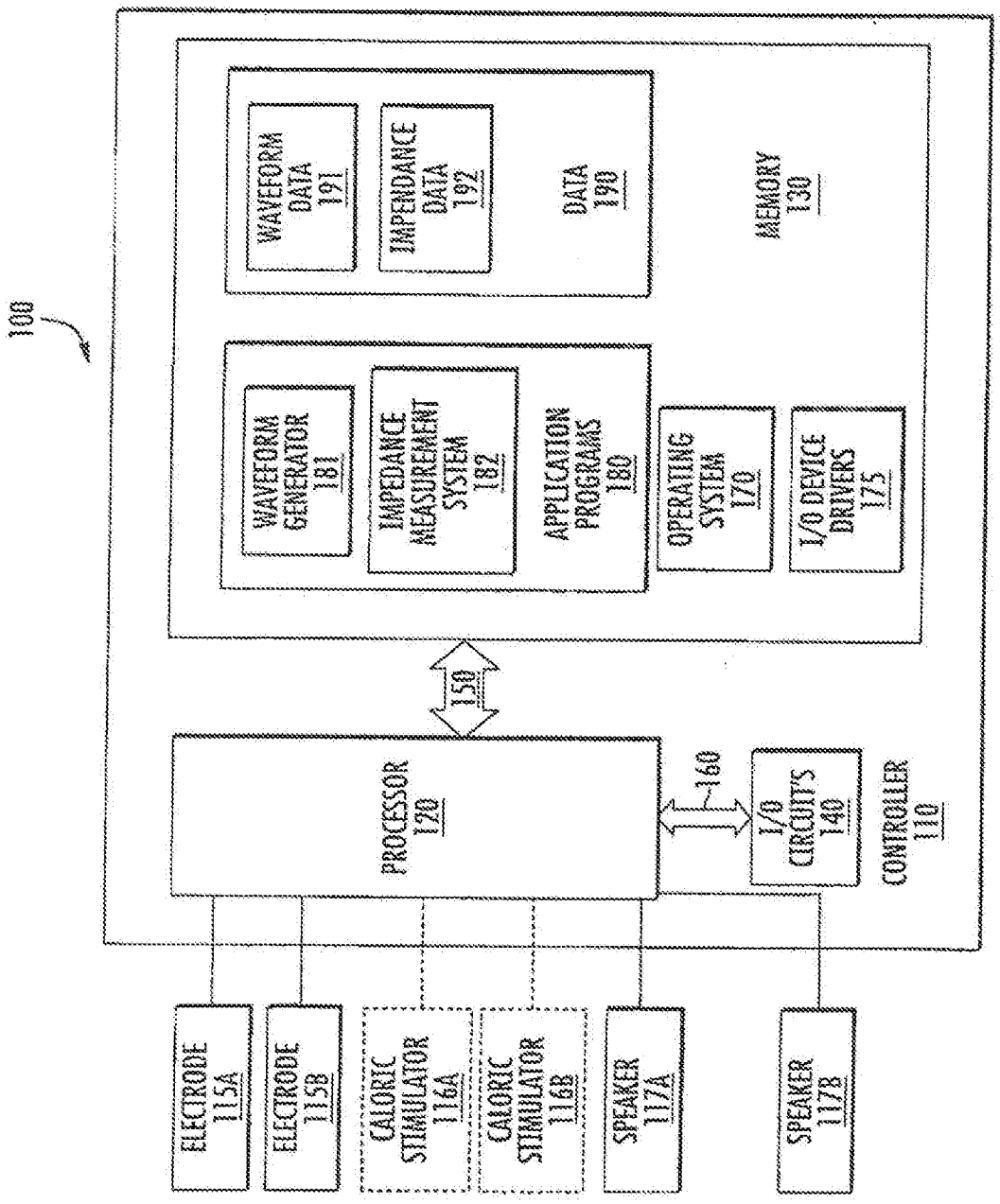

108
MEMORY 130
DATA 190
WAVEFORM DATA 191
IMPENDANCE DATA 192
APPLICATION PROGRAMS 180
WAVEFORM GENERATOR 181
IMPEDANCE MEASUREMENT SYSTEM 182
OPERATING SYSTEM 170
I/O DEVICE DRIVERS 175
150
PROCESSOR 120
160
I/O CIRCUITS 140
CONTROLLER 110
ELECTRODE 115A
ELECTRODE 115B
CALORIC STIMULATOR 116A
CALORIC STIMULATOR 116B
SPEAKER 117A
SPEAKER 117B

FIG. 1

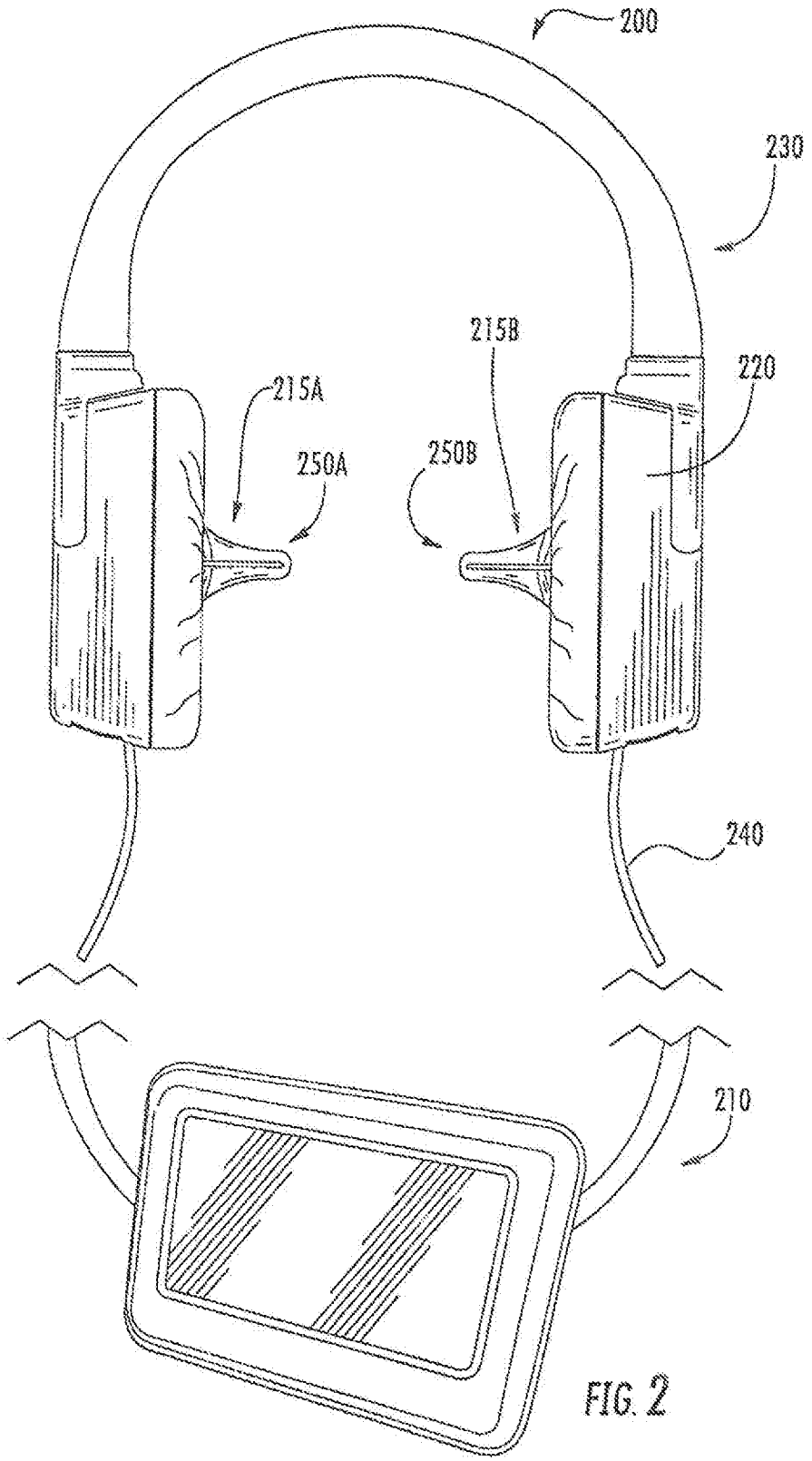


FIG. 2

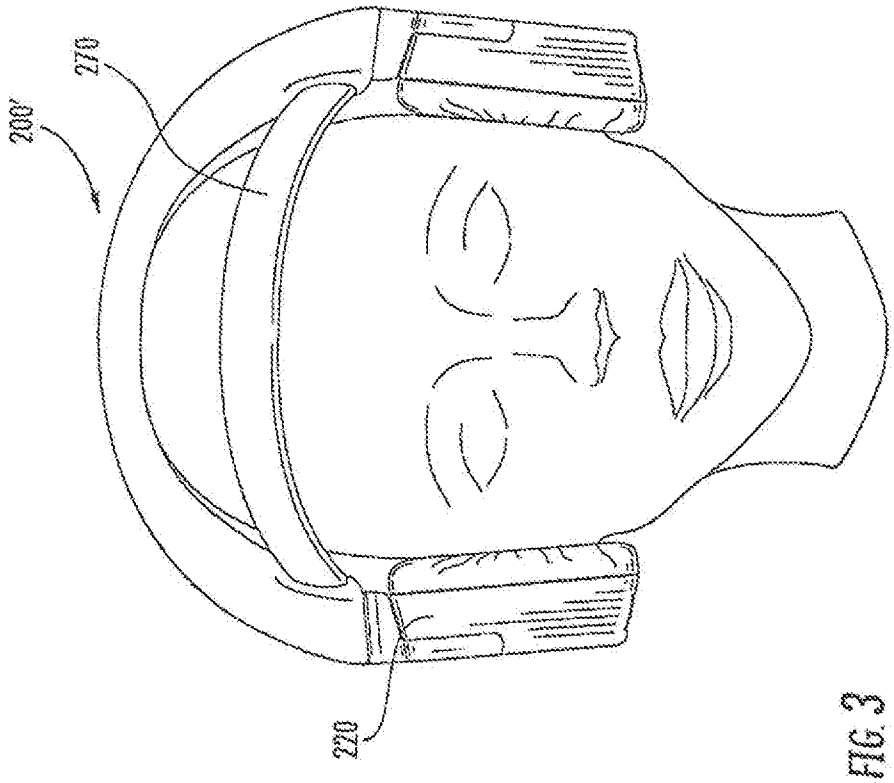
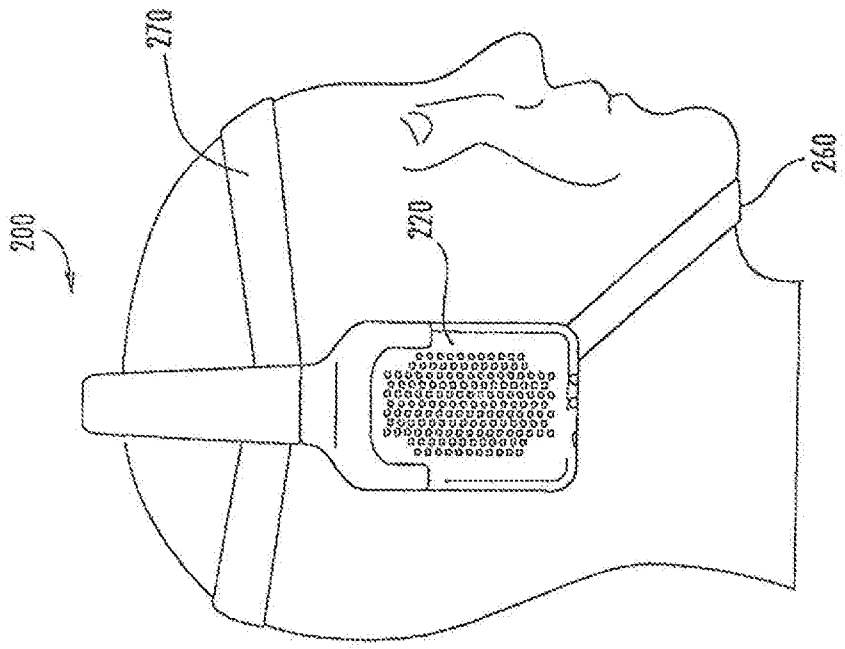


FIG. 3



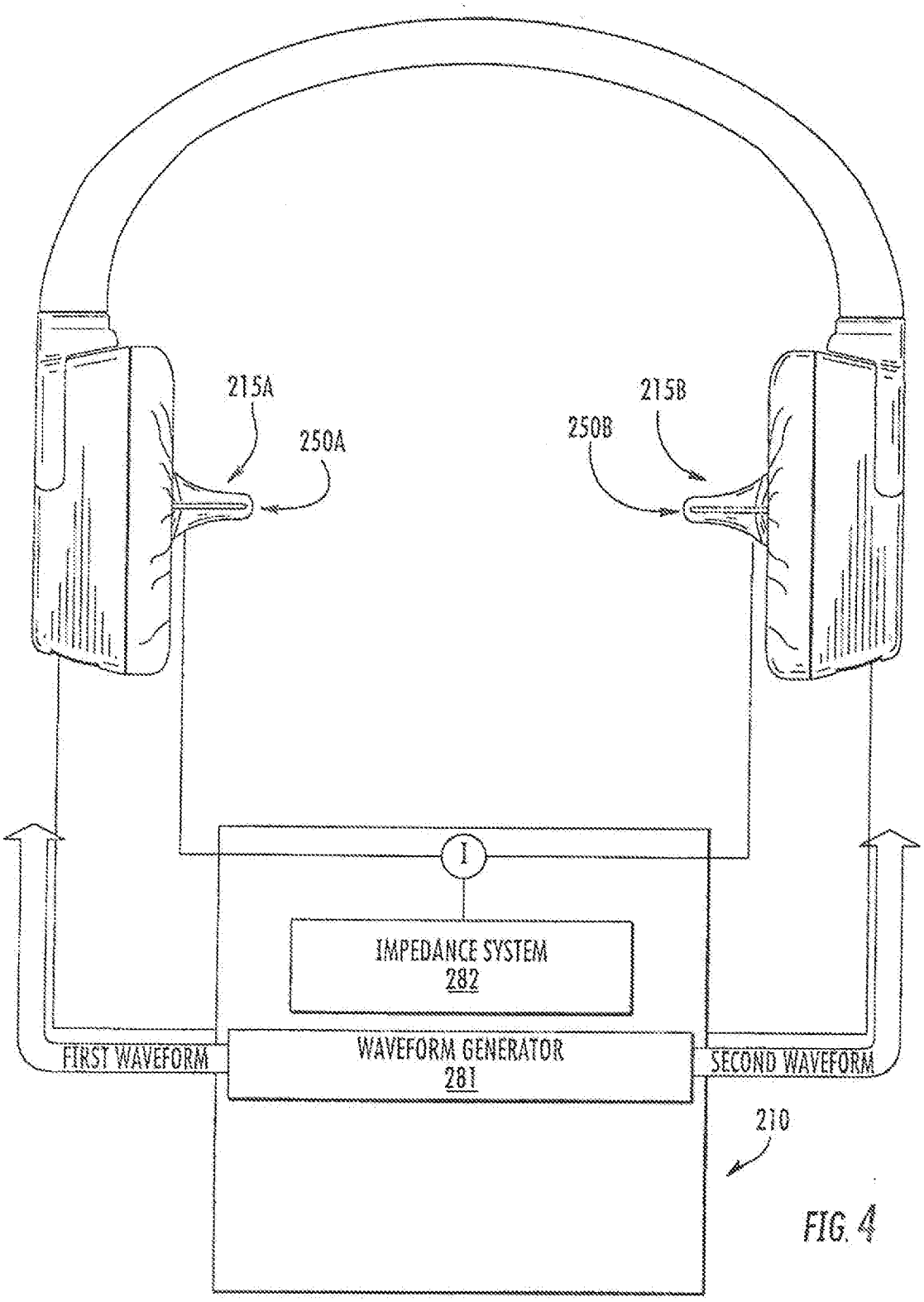

215A
250A
215B
250B
I
IMPEDANCE SYSTEM
282
FIRST WAVEFORM
WAVEFORM GENERATOR
281
SECOND WAVEFORM
210

FIG. 4

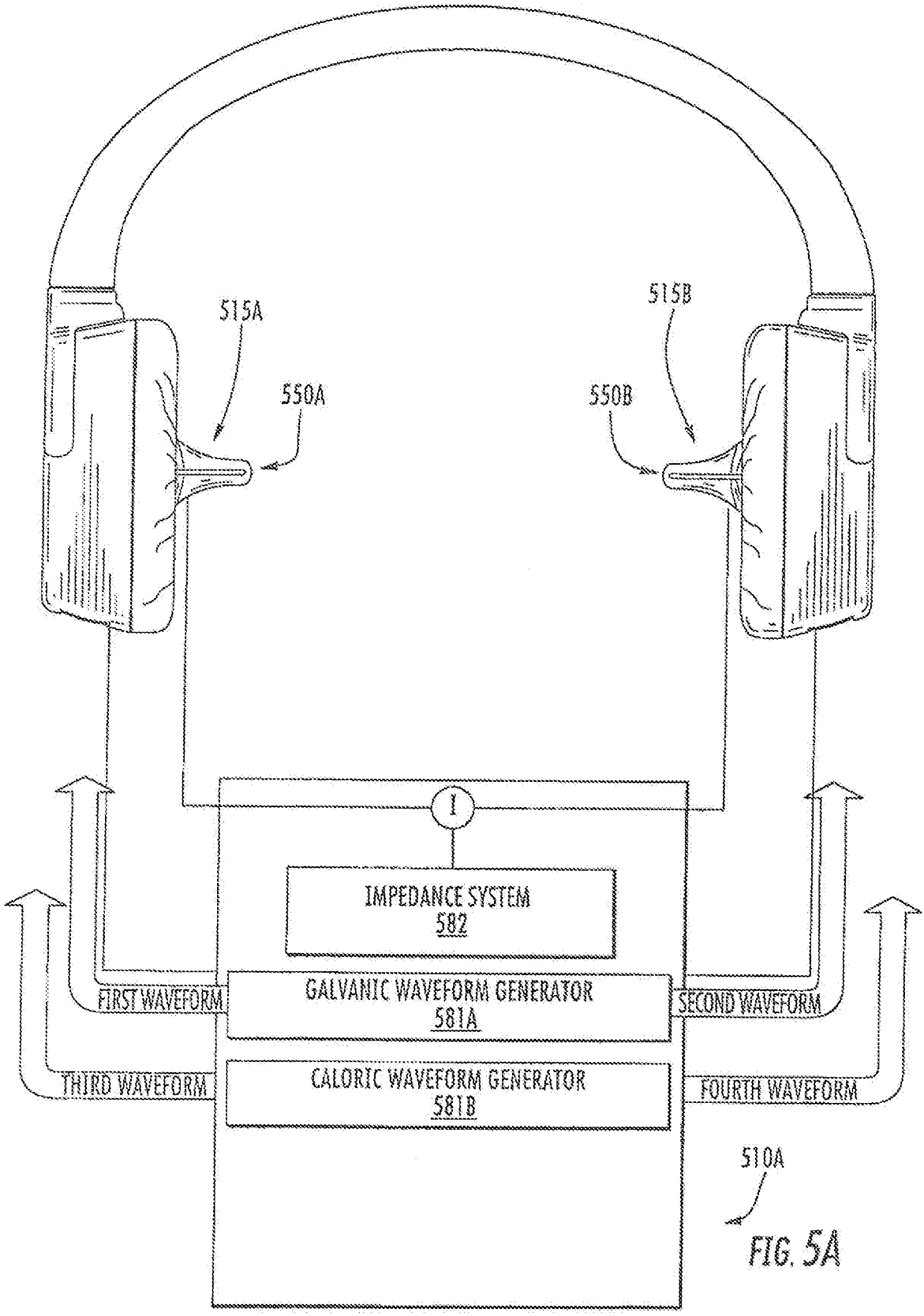

515A
550A
515B
550B
I
IMPEDANCE SYSTEM
582
FIRST WAVEFORM
GALVANIC WAVEFORM GENERATOR
581A
SECOND WAVEFORM
THIRD WAVEFORM
CALORIC WAVEFORM GENERATOR
581B
FOURTH WAVEFORM
510A

FIG. 5A

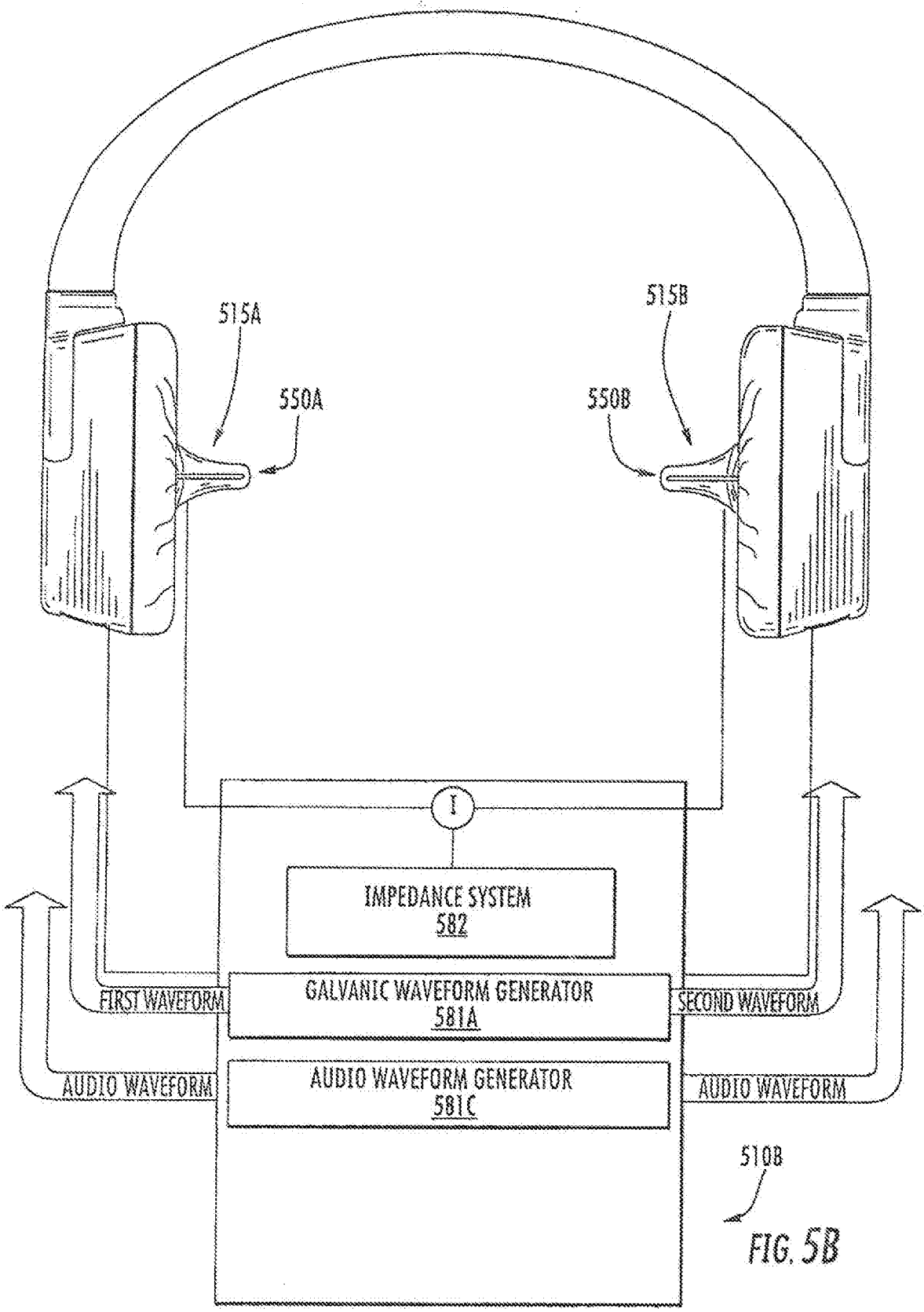

515A
550A
515B
550B
I
IMPEDANCE SYSTEM
582
FIRST WAVEFORM
GALVANIC WAVEFORM GENERATOR
581A
SECOND WAVEFORM
AUDIO WAVEFORM
AUDIO WAVEFORM GENERATOR
581C
AUDIO WAVEFORM
510B

FIG. 5B

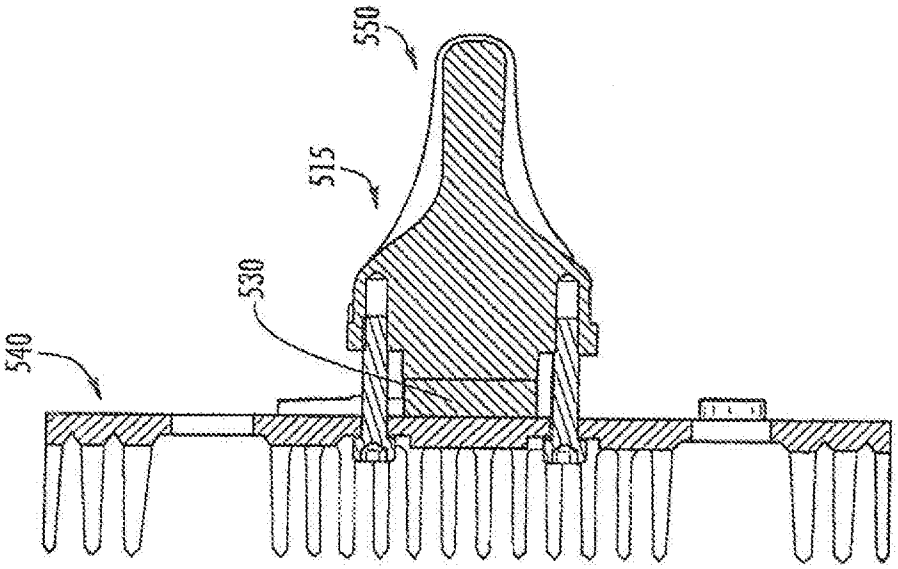


FIG. 6B

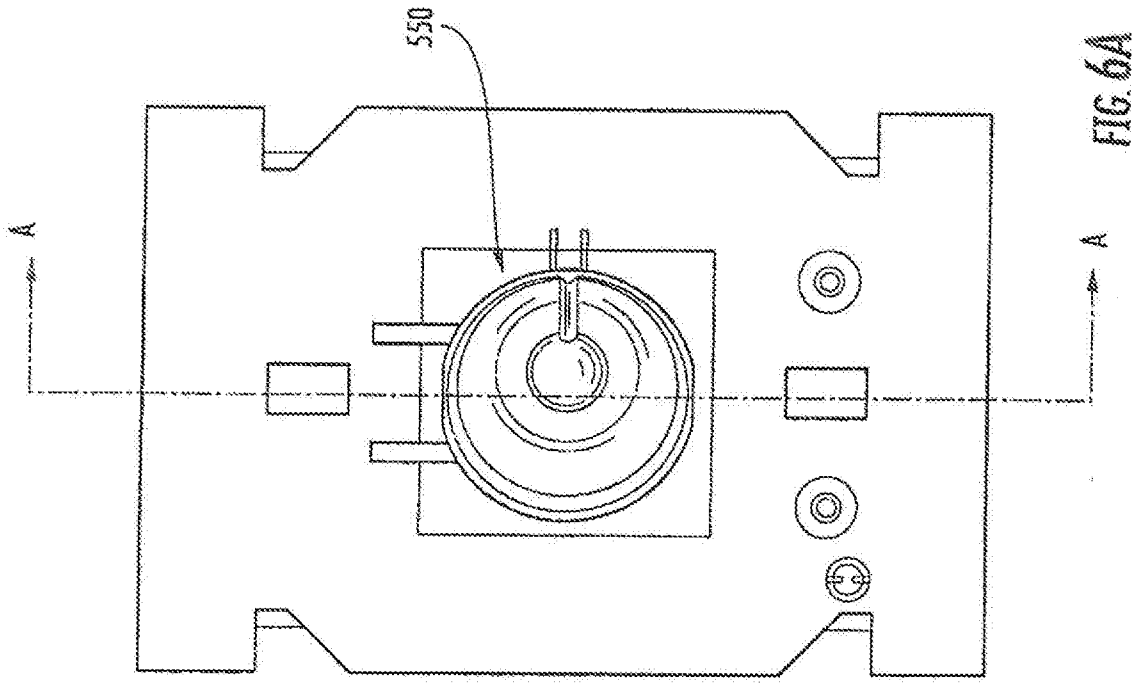


FIG. 6A

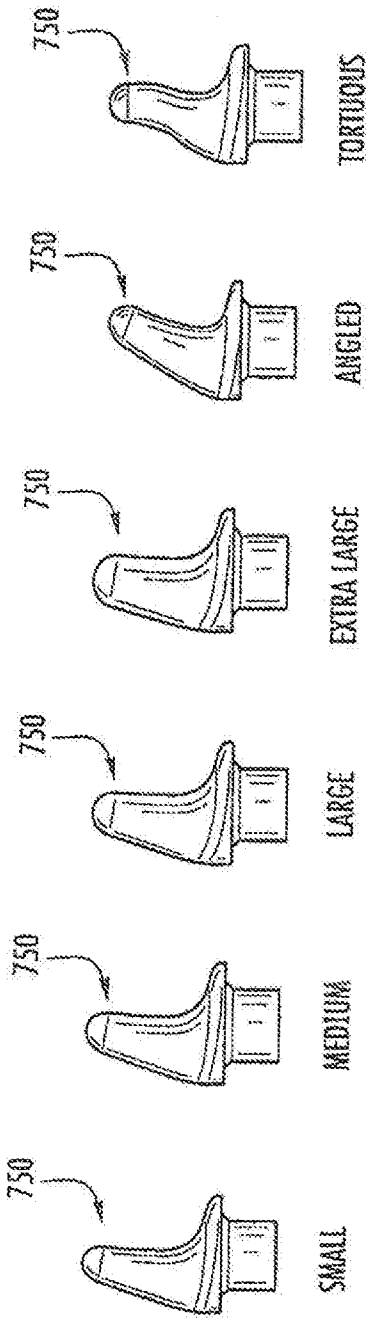

750
SMALL
750
MEDIUM
750
LARGE
750
EXTRA LARGE
750
ANGLED
750
TORTUOUS

FIG. 7

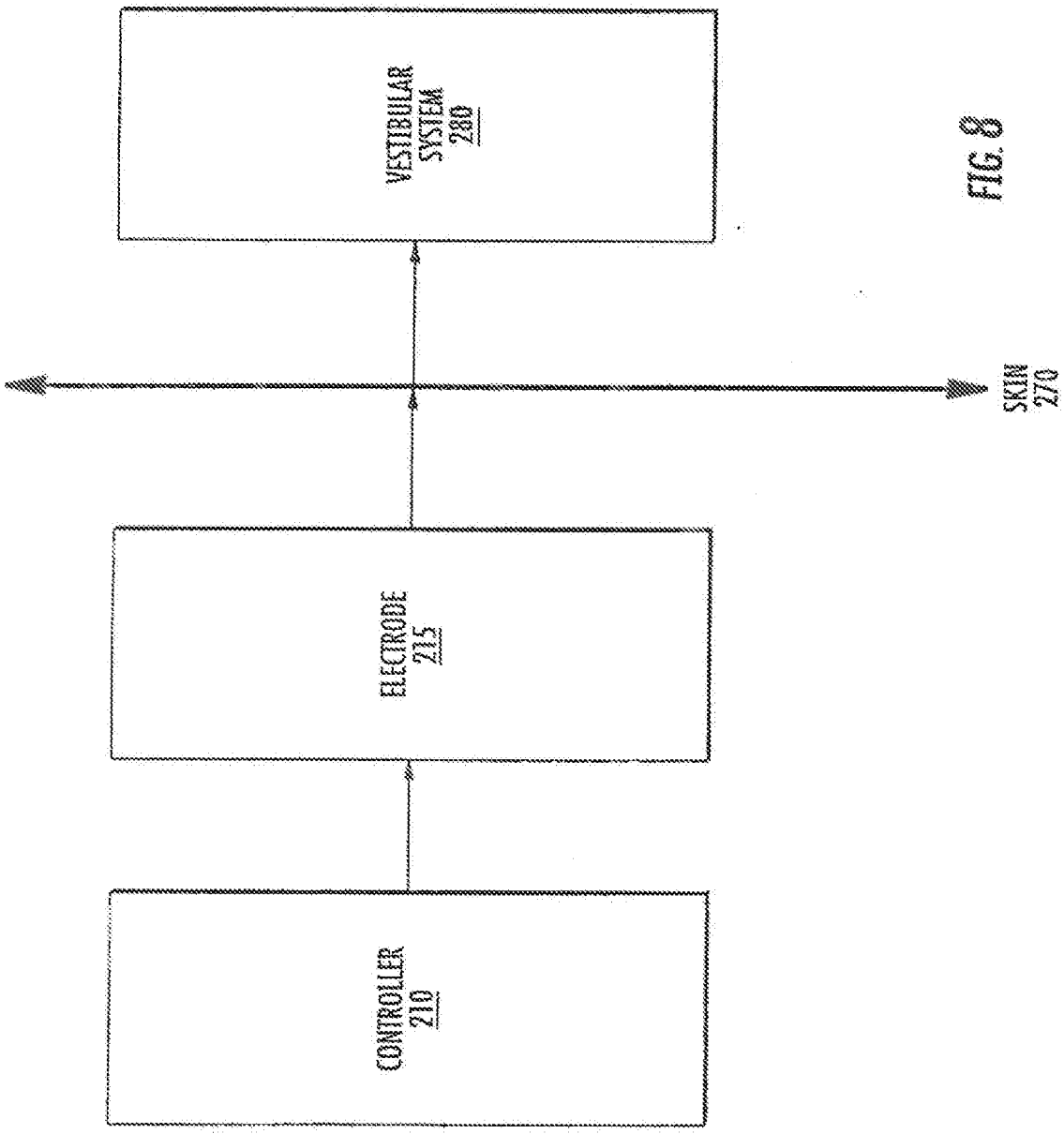

VESTIBULAR SYSTEM 280
SKIN 270
ELECTRODE 215
CONTROLLER 210

FIG. 8

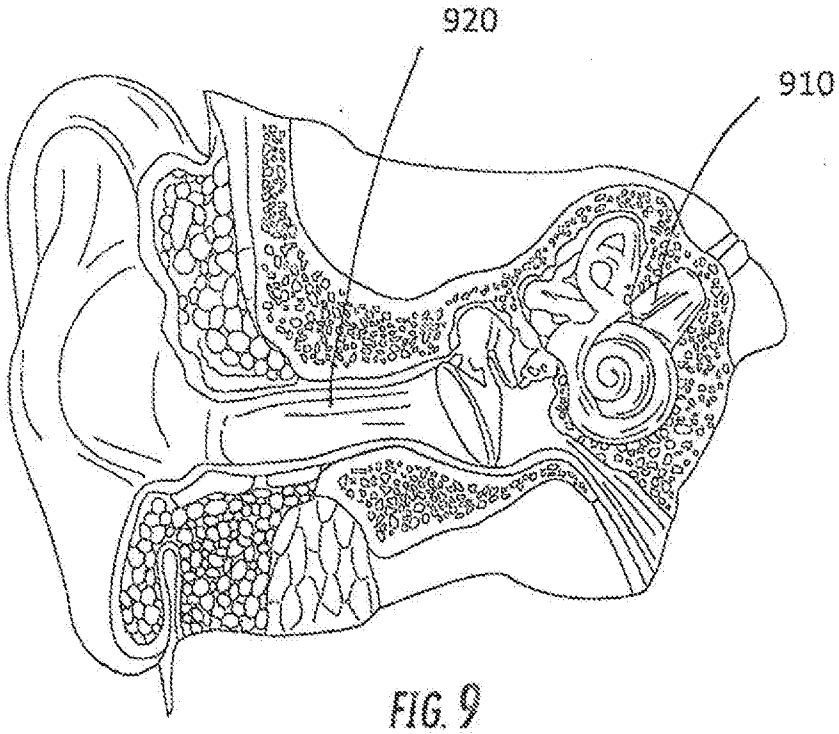


FIG. 9

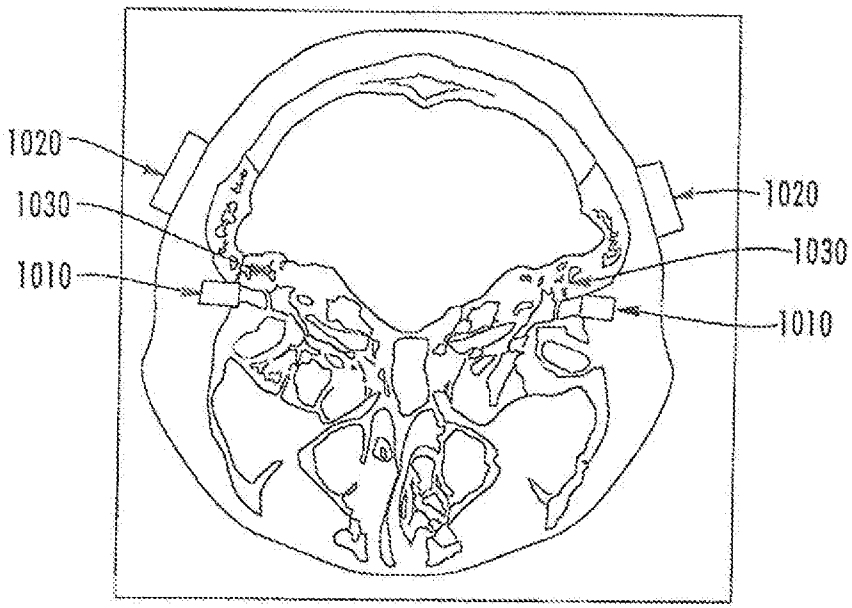


FIG. 10

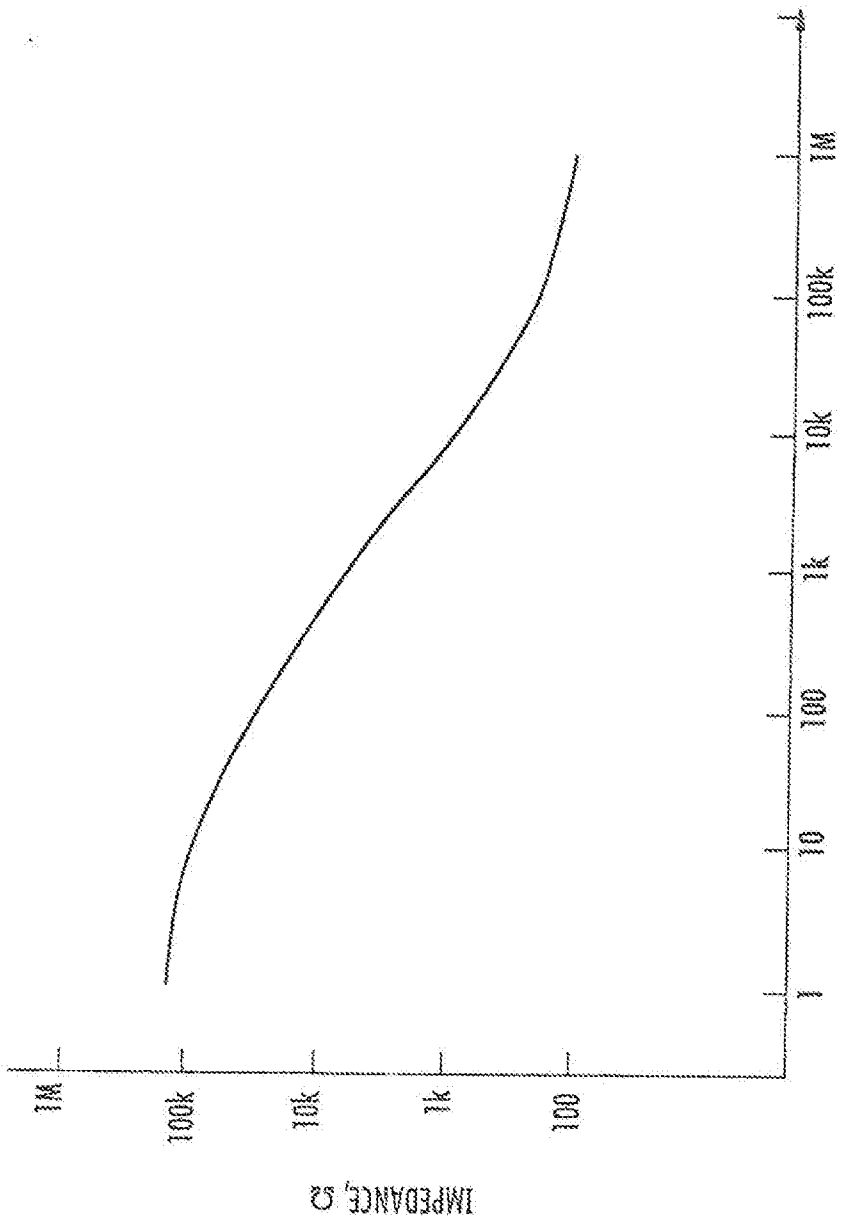

IMPEDANCE, Ω
1M
100k
10k
1k
100
1
10
100
1k
10k
100k
1M
FREQUENCY, Hz

FIG. 11

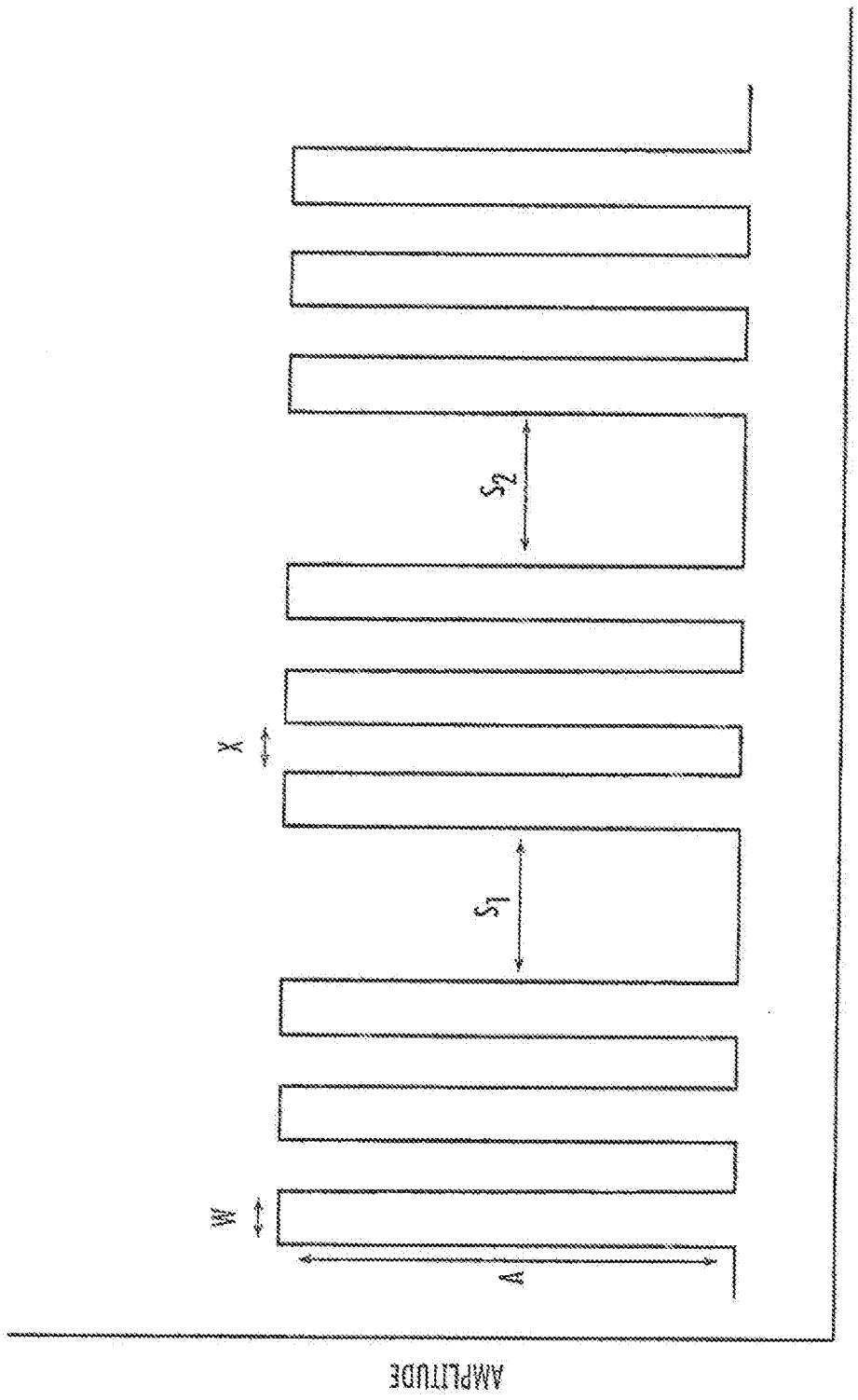


FIG. 12

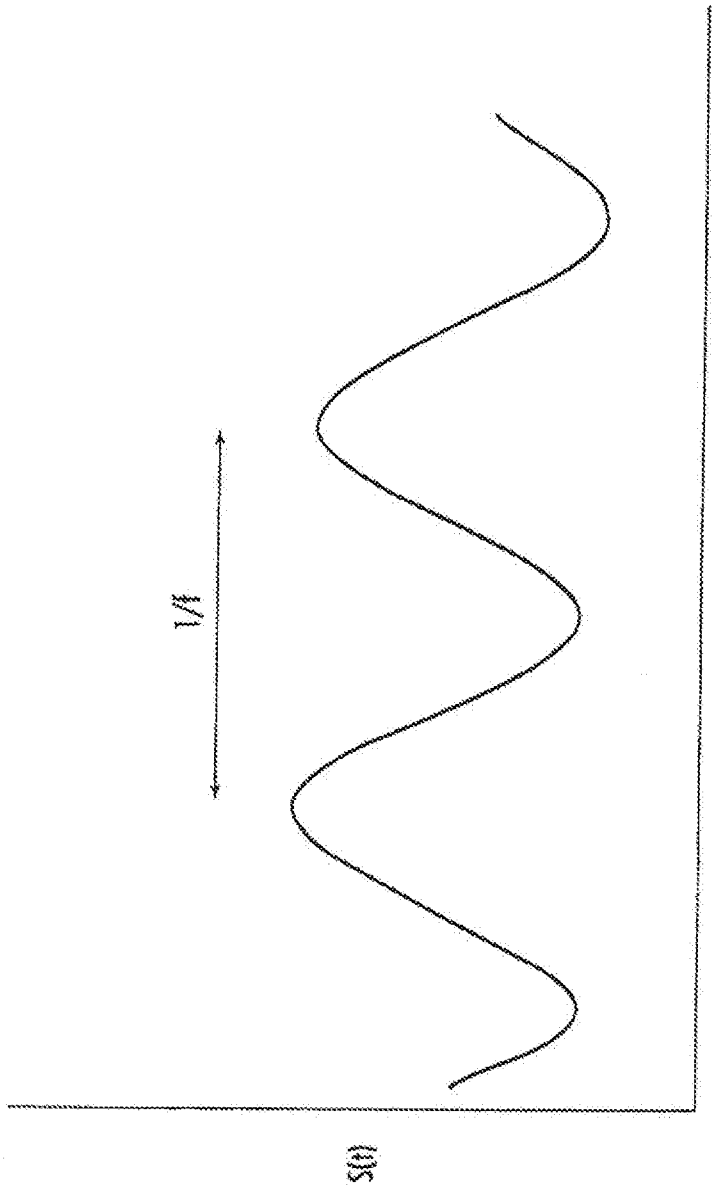


FIG. 13

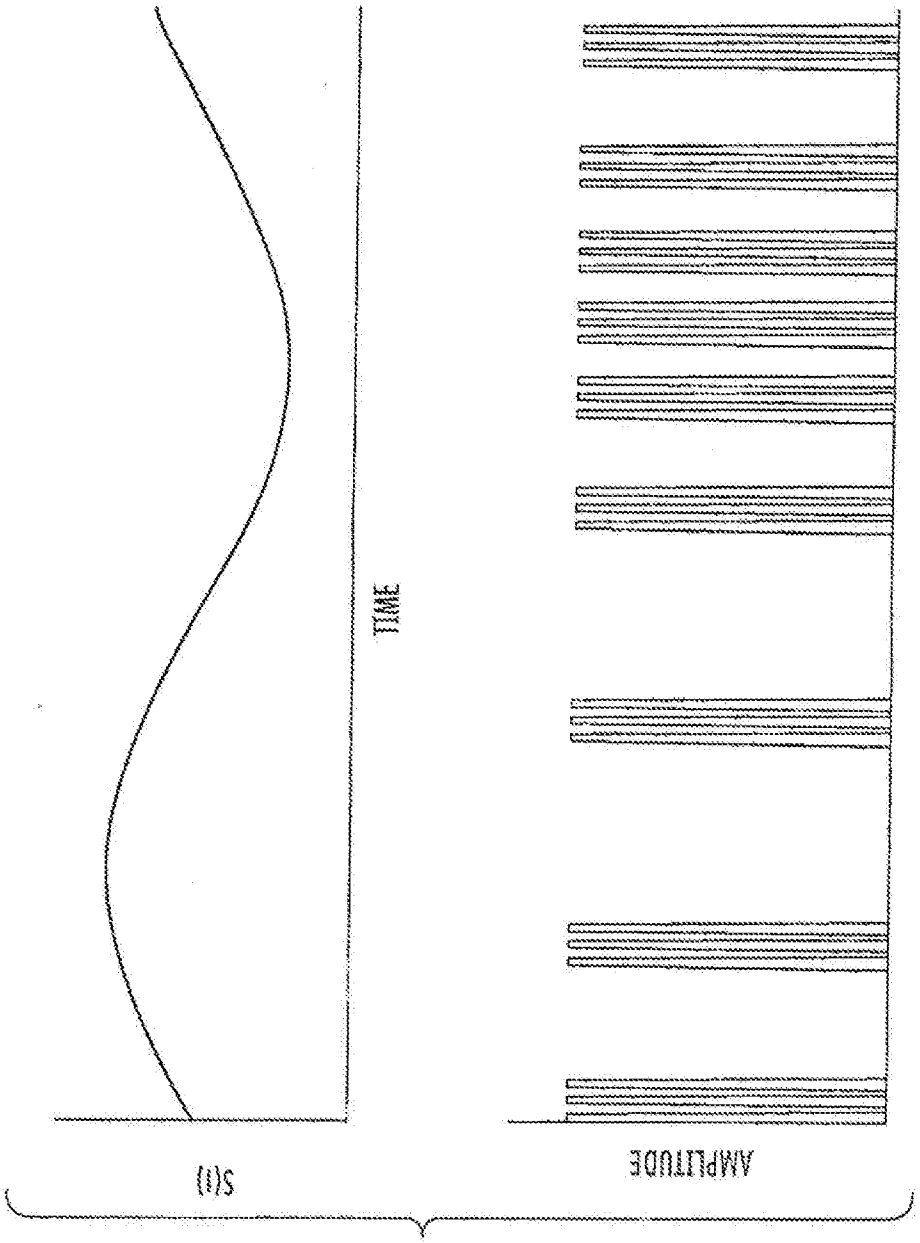


FIG. 14

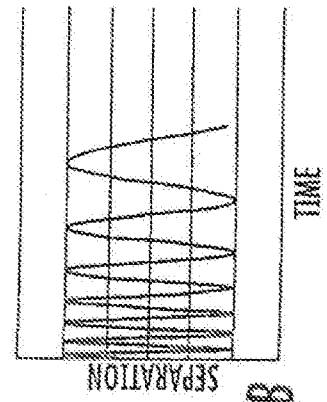


FIG. 15B

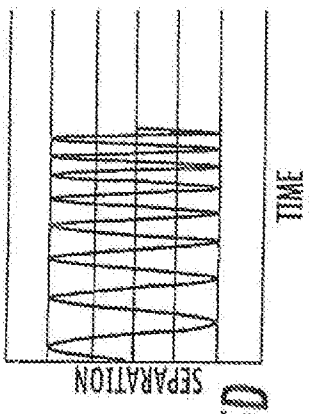


FIG. 15D

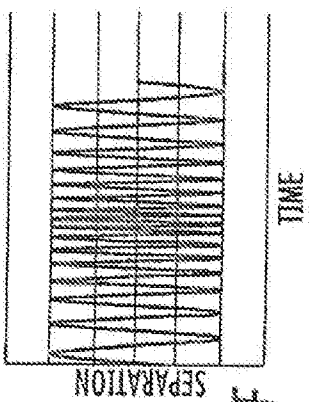


FIG. 15F

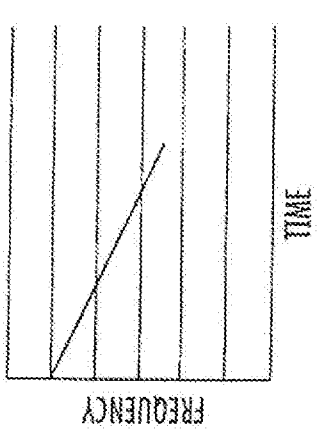


FIG. 15A

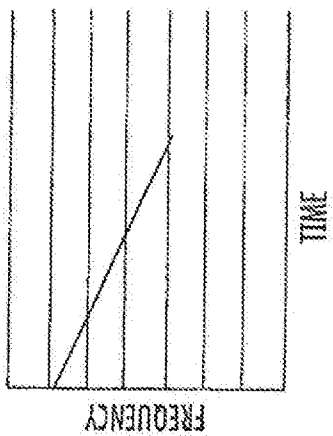


FIG. 15C

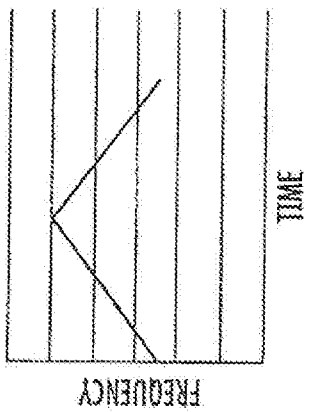


FIG. 15E

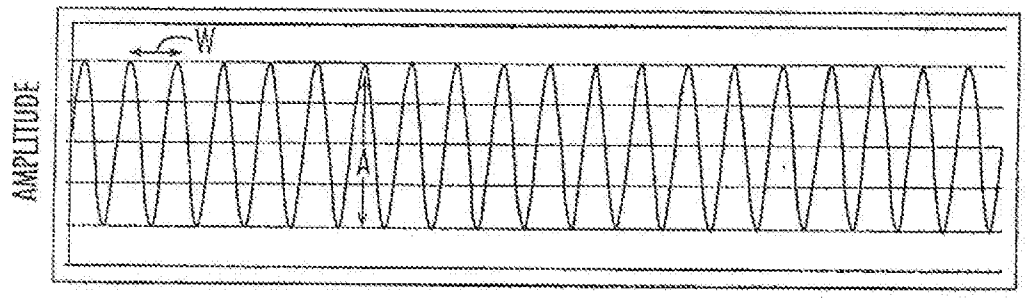


FIG. 16A

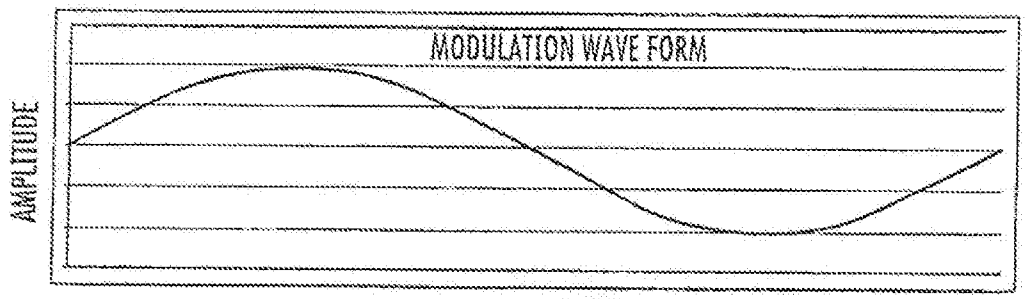


FIG. 16B

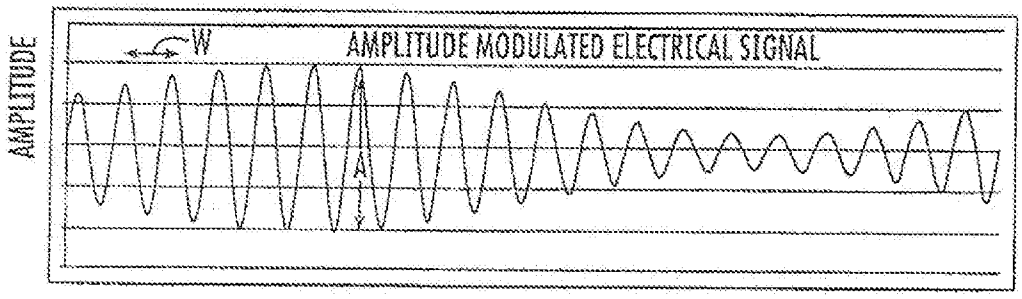


FIG. 16C

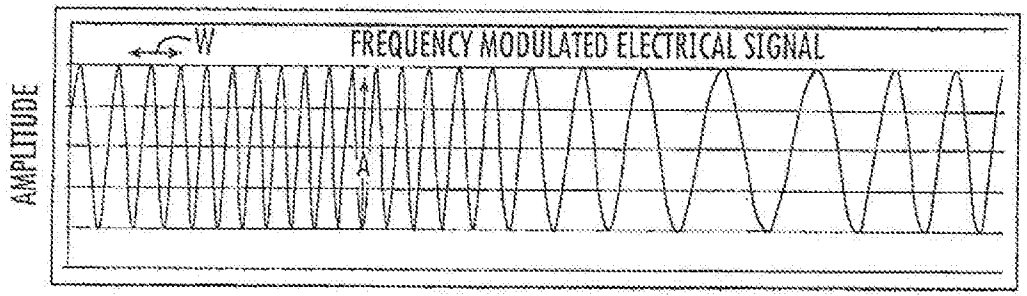


FIG. 16D

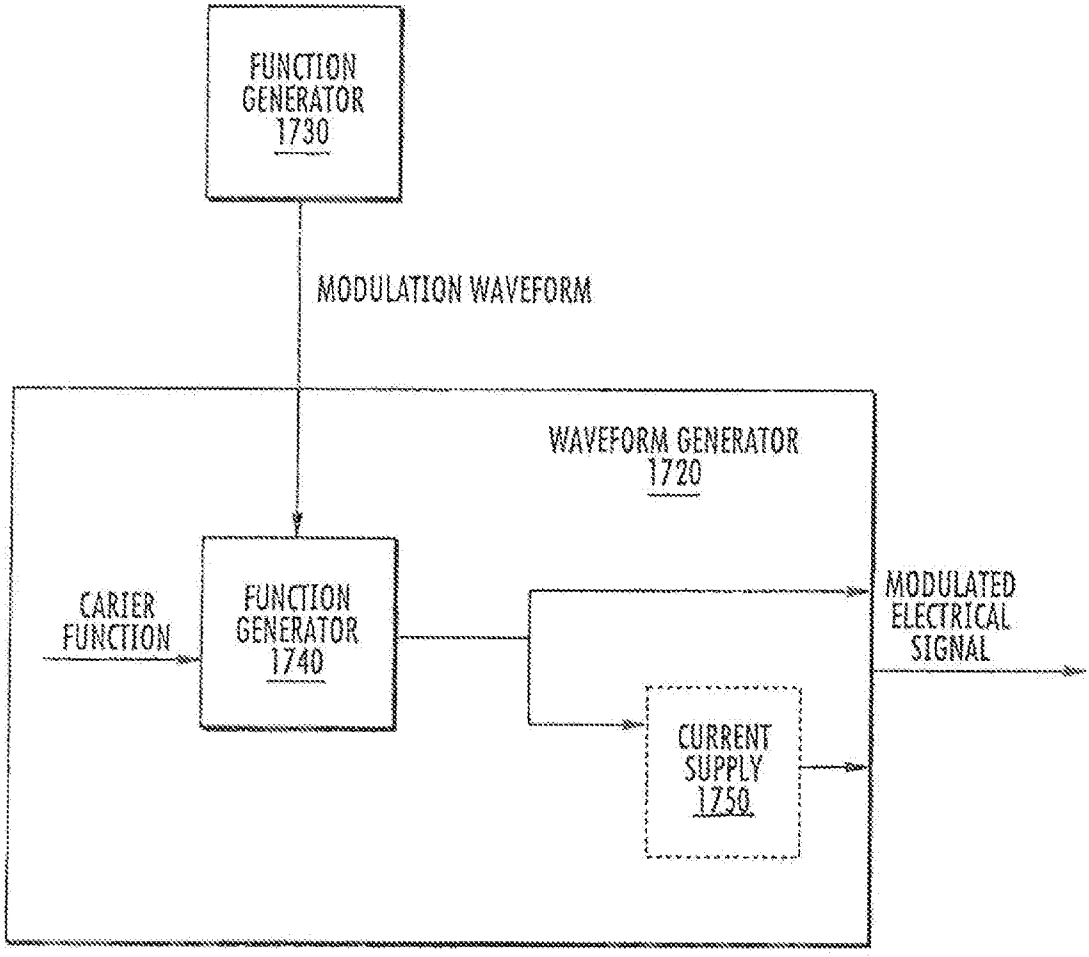

FUNCTION GENERATOR 1730
MODULATION WAVEFORM
WAVEFORM GENERATOR 1720
CARIER FUNCTION
FUNCTION GENERATOR 1740
MODULATED ELECTRICAL SIGNAL
CURRENT SUPPLY 1750

FIG. 17

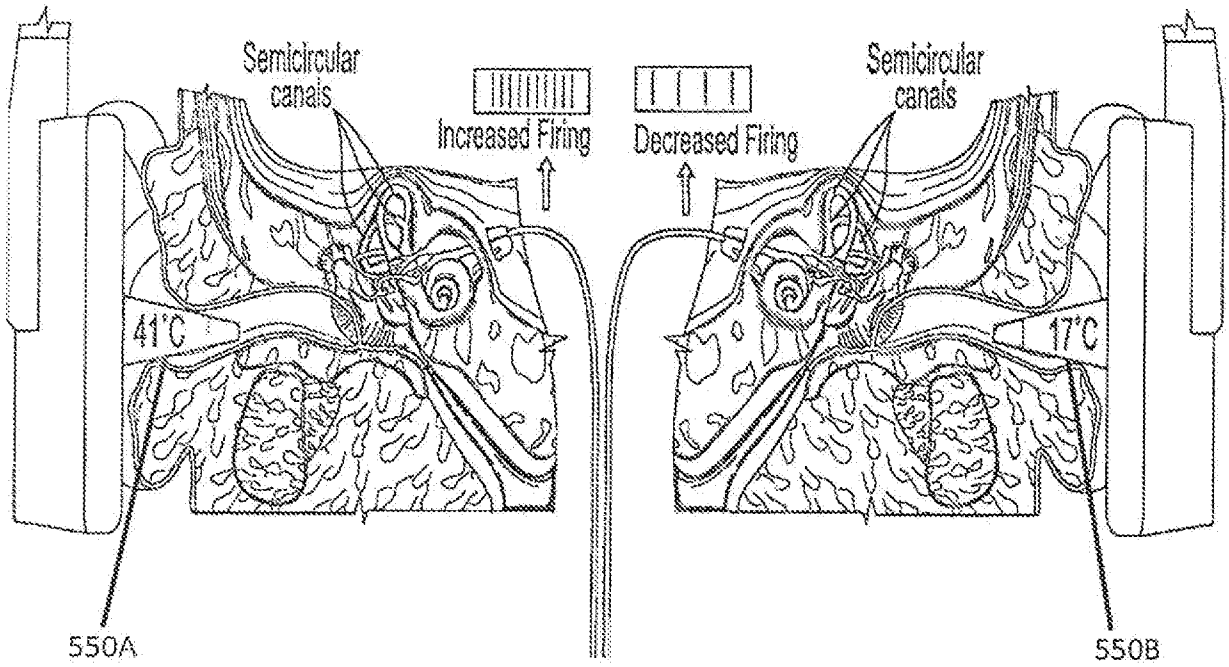

Semicircular canals
Increased Firing
Decreased Firing
Semicircular canals
41°C
17°C
550A
550B

FIG. 18

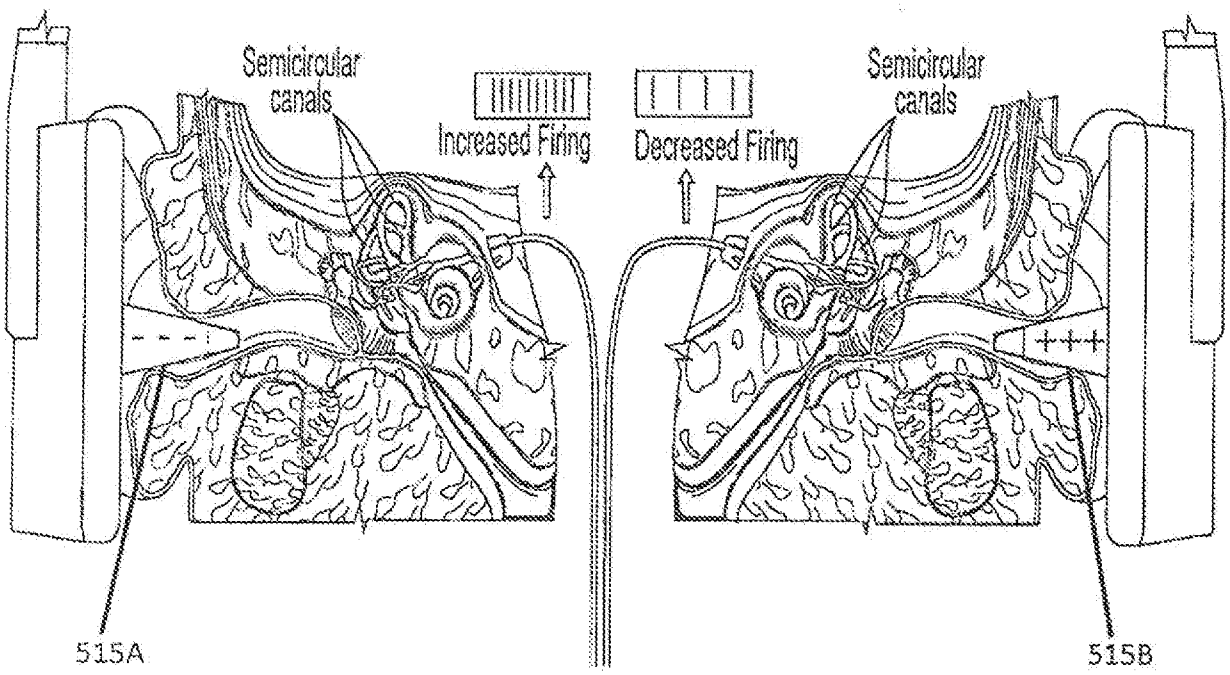

Semicircular canals
Increased Firing
Decreased Firing
Semicircular canals
515A
515B

FIG. 19

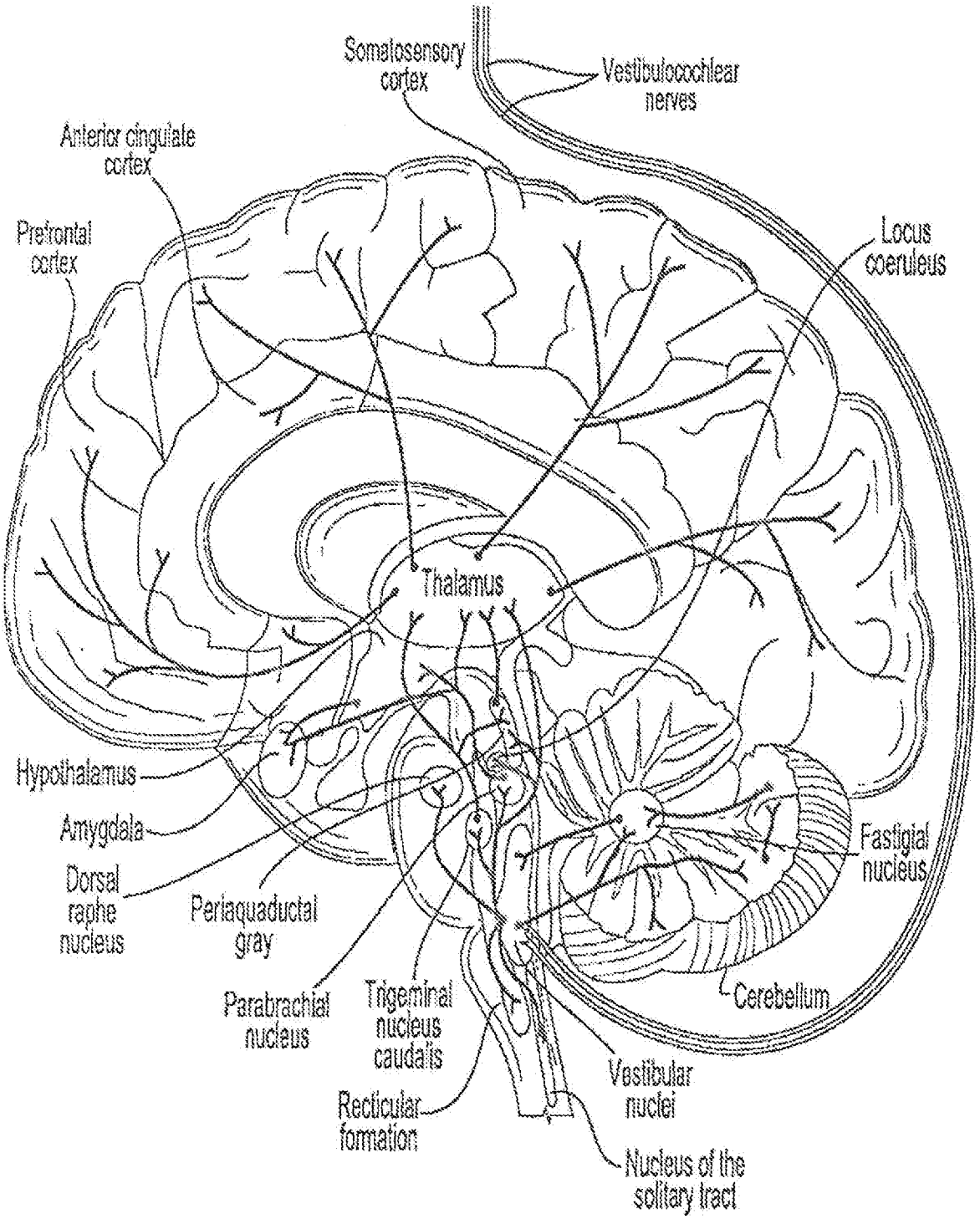

Somatosensory cortex
Vestibulocochlear nerves
Anterior cingulate cortex
Prefrontal cortex
Locus coeruleus
Thalamus
Hypothalamus
Amygdala
Dorsal raphe nucleus
Periaquaductal gray
Parabrachial nucleus
Trigeminal nucleus caudalis
Reticular formation
Vestibular nuclei
Nucleus of the solitary tract
Fastigial nucleus
Cerebellum

FIG. 20

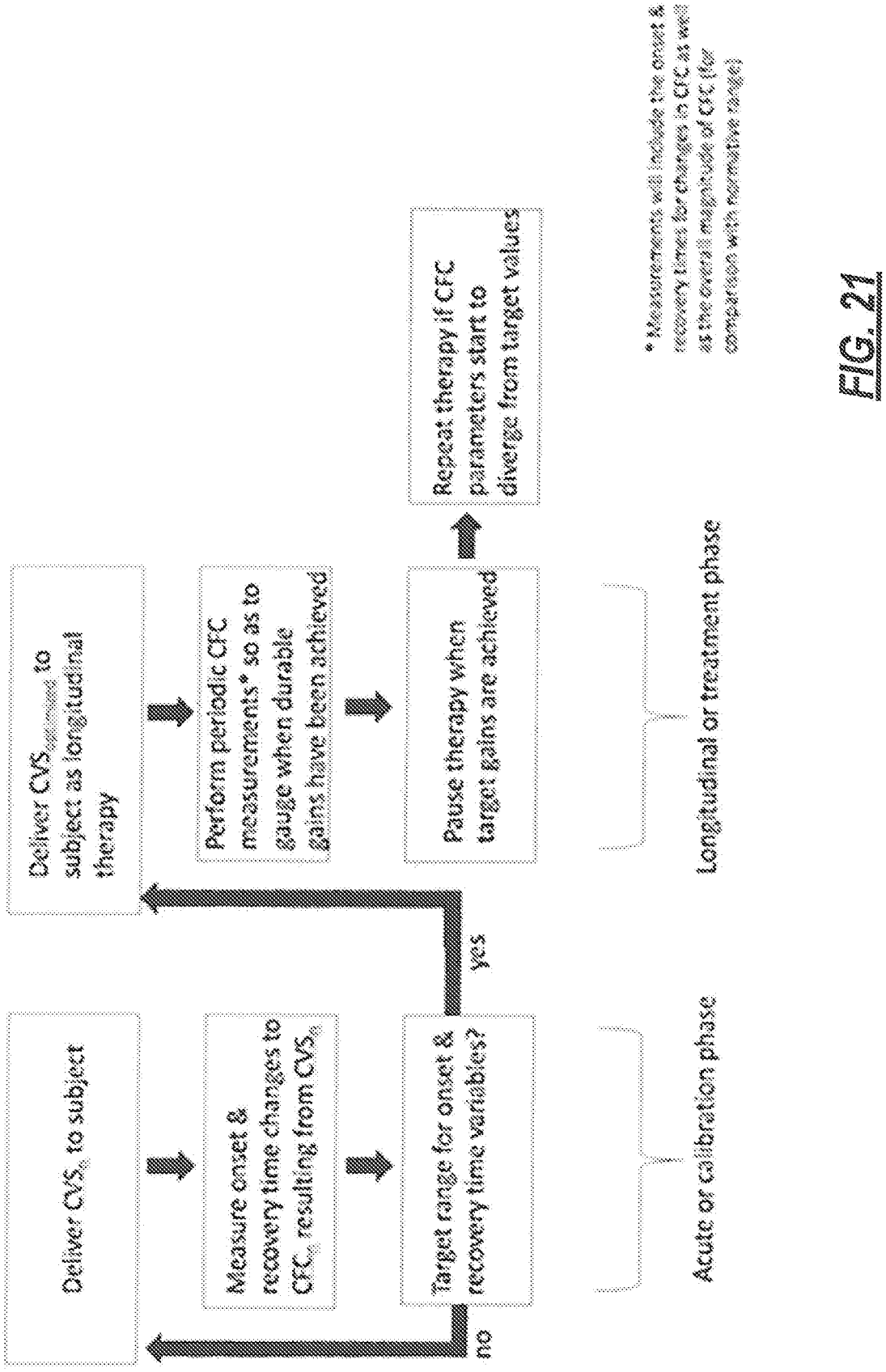

Deliver CVS$_x$ to subject
Measure onset & recovery time changes to CFC$_x$ resulting from CVS$_x$
Target range for onset & recovery time variables?
no
yes
Deliver CVS$_{x,\text{optimized}}$ to subject as longitudinal therapy
Perform periodic CFC measurements* so as to gauge when durable gains have been achieved
Pause therapy when target gains are achieved
Repeat therapy if CFC parameters start to diverge from target values
Acute or calibration phase
Longitudinal or treatment phase
* Measurements will include the onset & recovery times for changes in CFC as well as the overall magnitude of CFC (for comparison with normative range)

FIG. 21

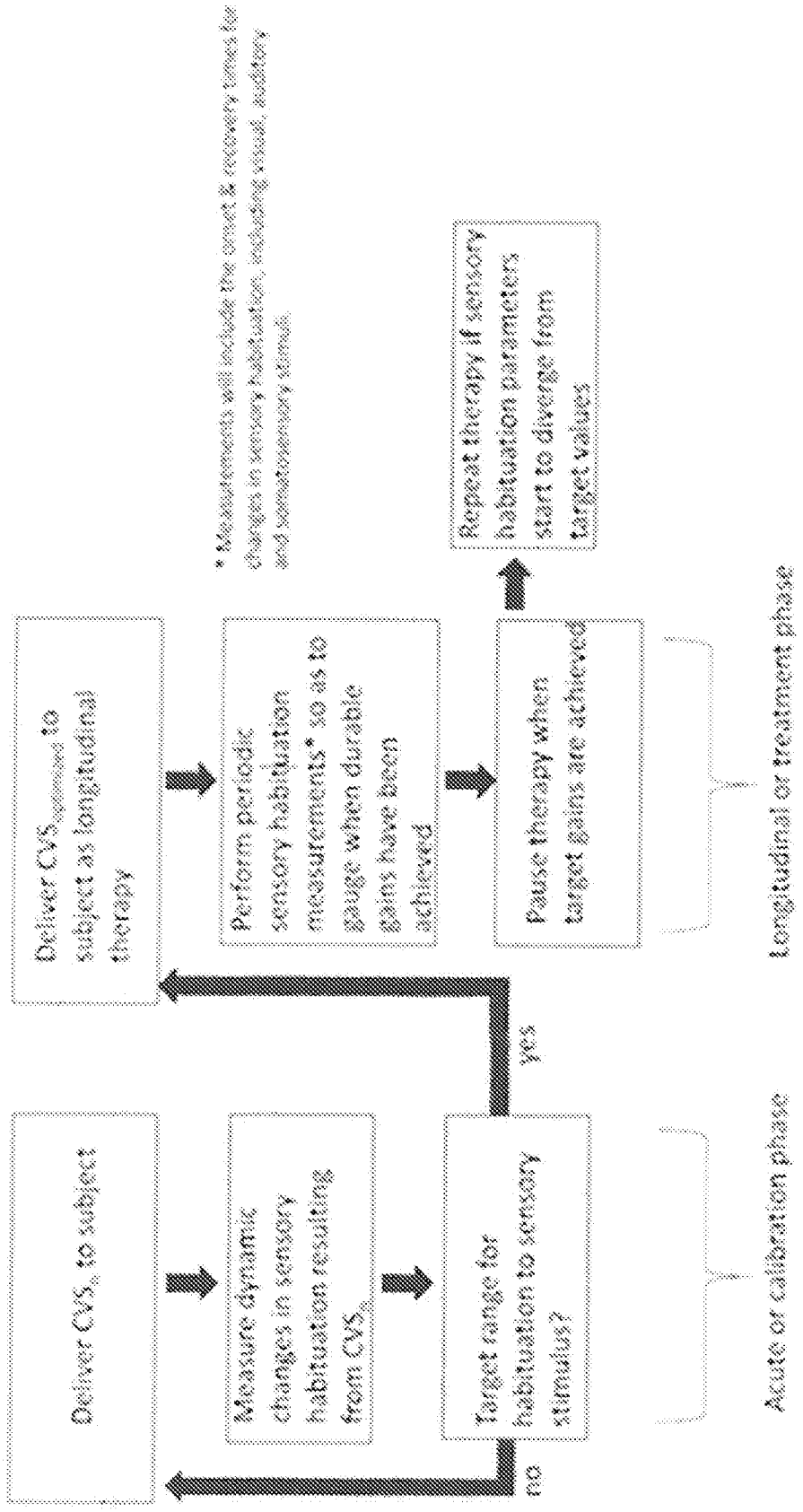

Deliver CVS$_{x}$ to subject
Measure dynamic changes in sensory habituation resulting from CVS$_{x}$
Target range for habituation to sensory stimulus?
no
yes
Deliver CVS$_{x,mod}$ to subject as longitudinal therapy
Perform periodic sensory habituation measurements* so as to gauge when durable gains have been achieved
Pause therapy when target gains are achieved
Repeat therapy if sensory habituation parameters start to diverge from target values
* Measurements will include the onset & recovery times for changes in sensory habituation, including visual, auditory and somatosensory stimuli.
Acute or calibration phase
Longitudinal or treatment phase

FIG. 22

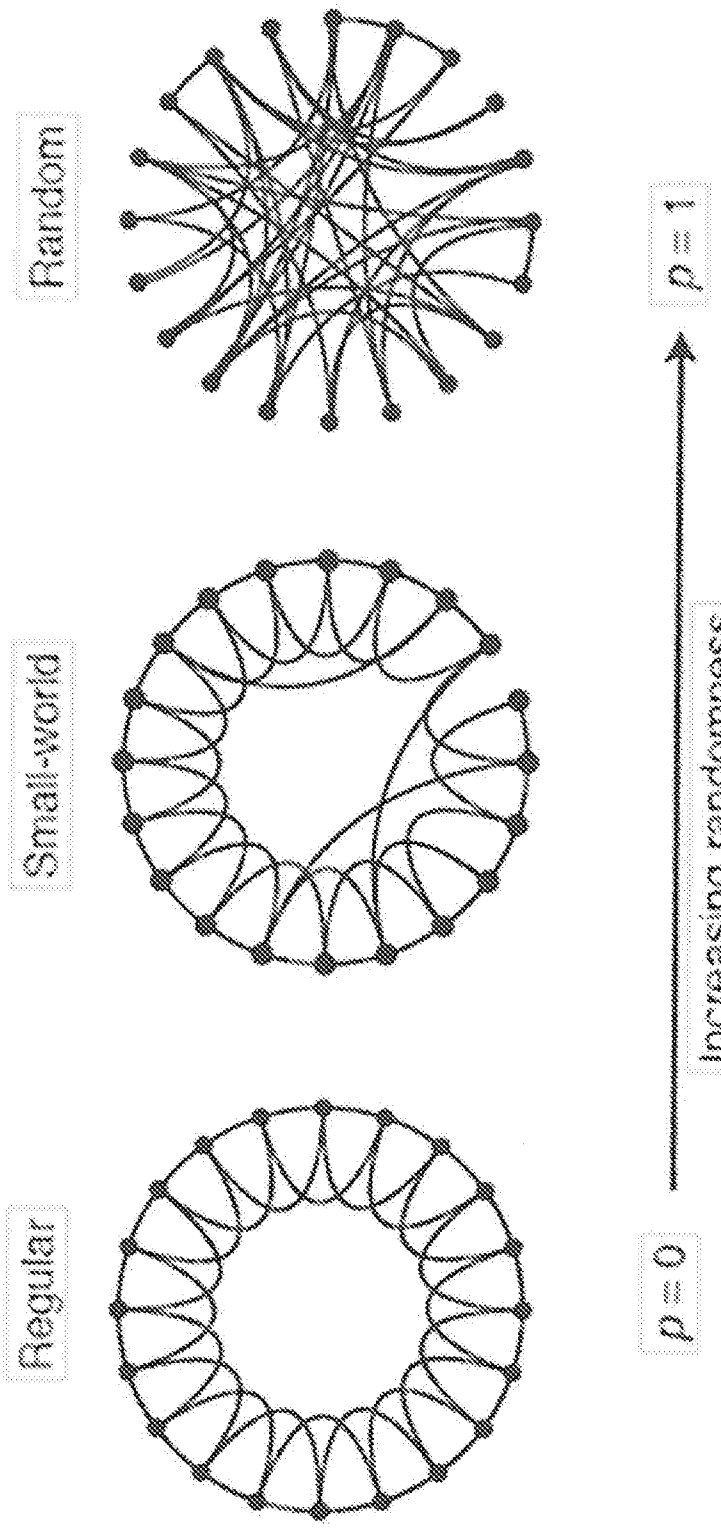


FIG. 23

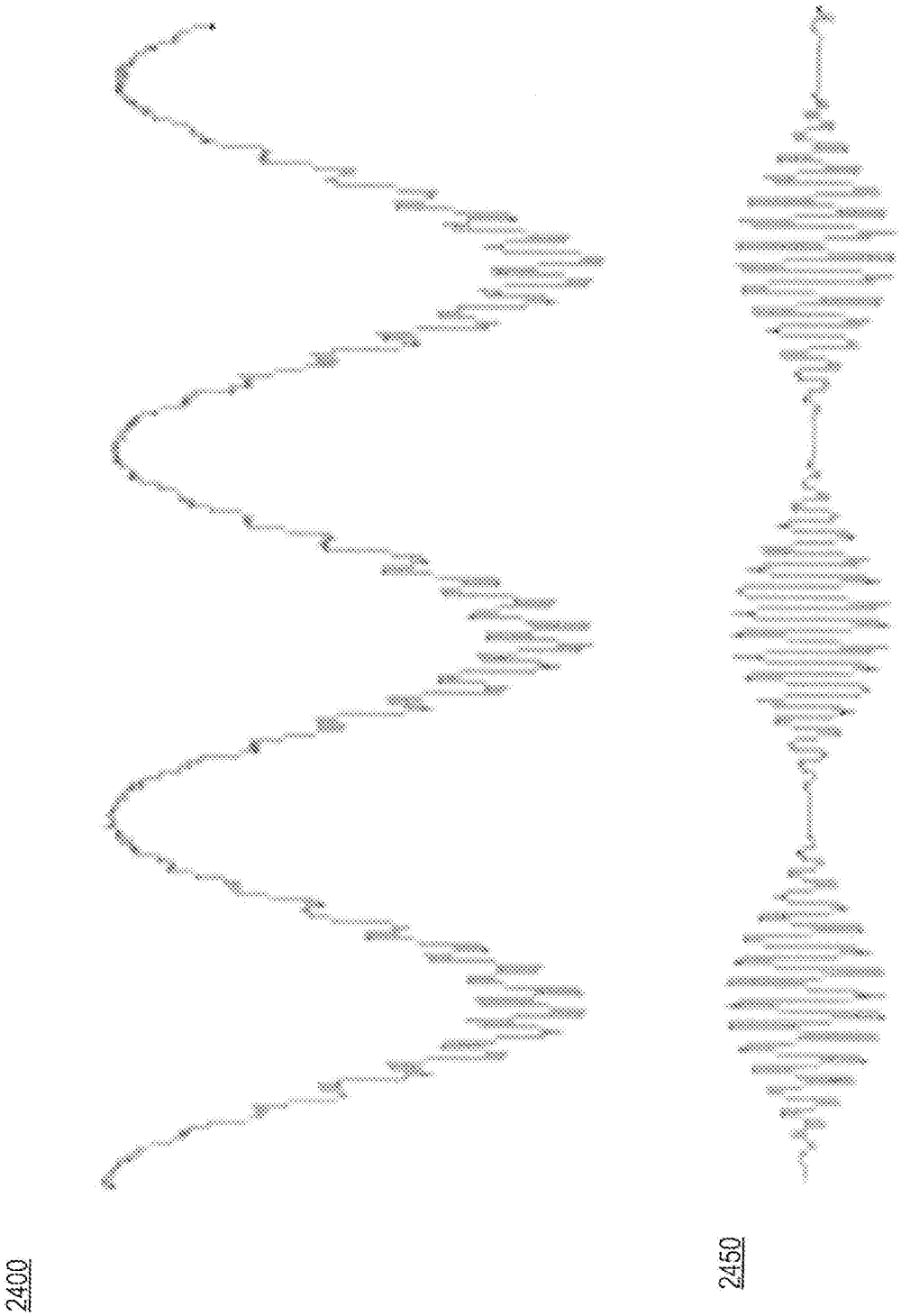


FIG. 24

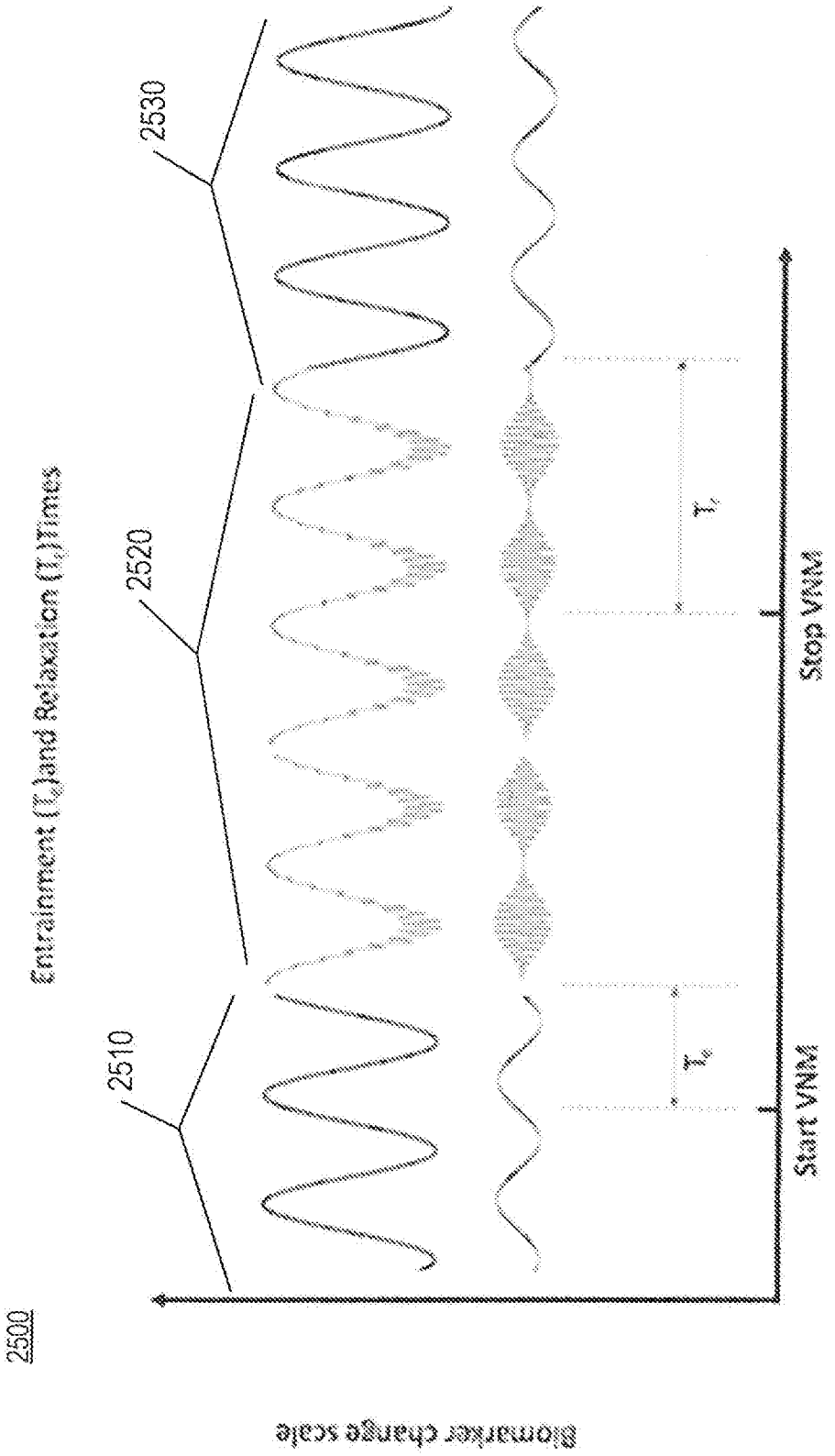

2500
Entrainment (T_e) and Relaxation (T_r) Times
2510
2520
2530
T_e
T_r
Start VNM
Stop VNM
Biomarker change scale

FIG. 25

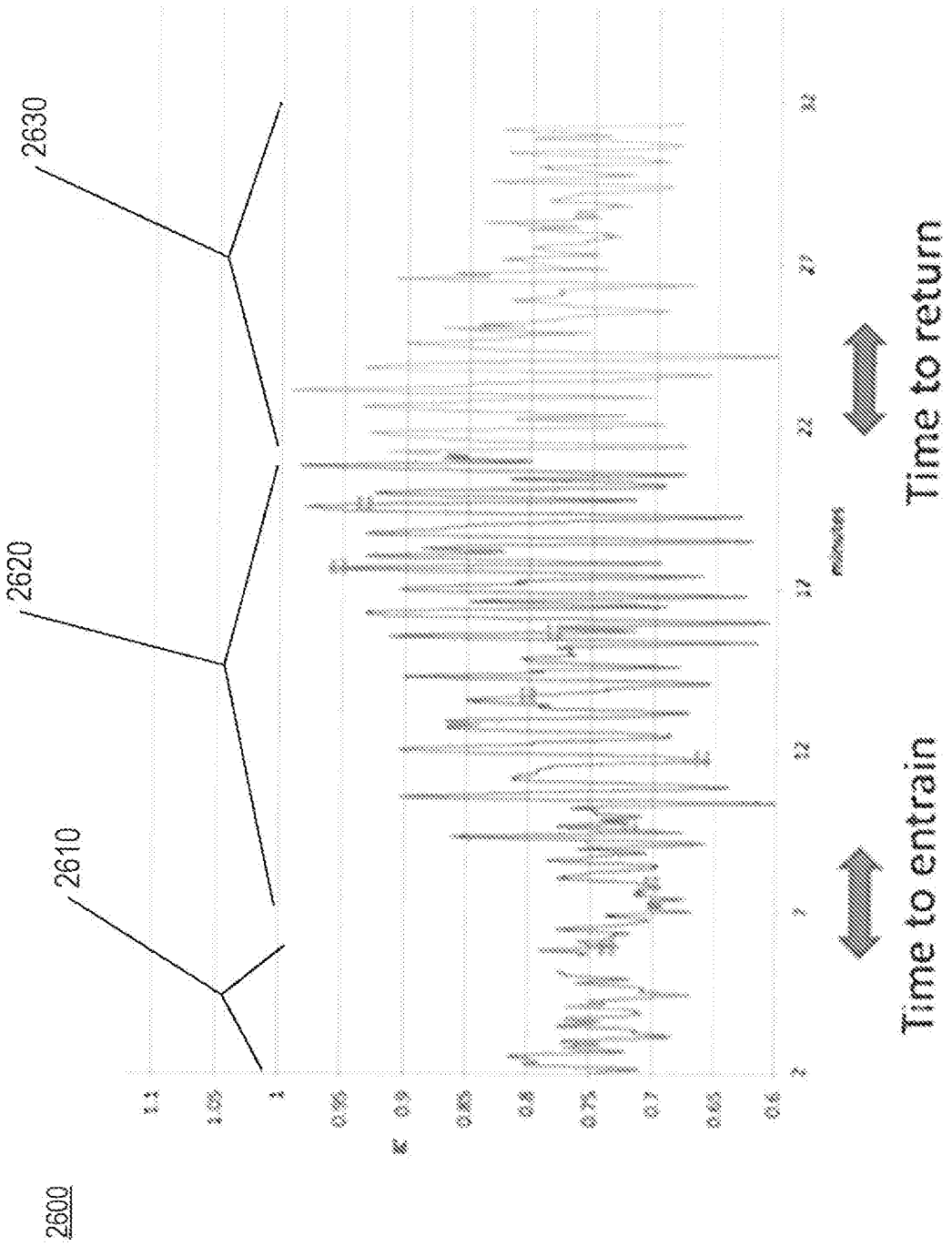


FIG. 26

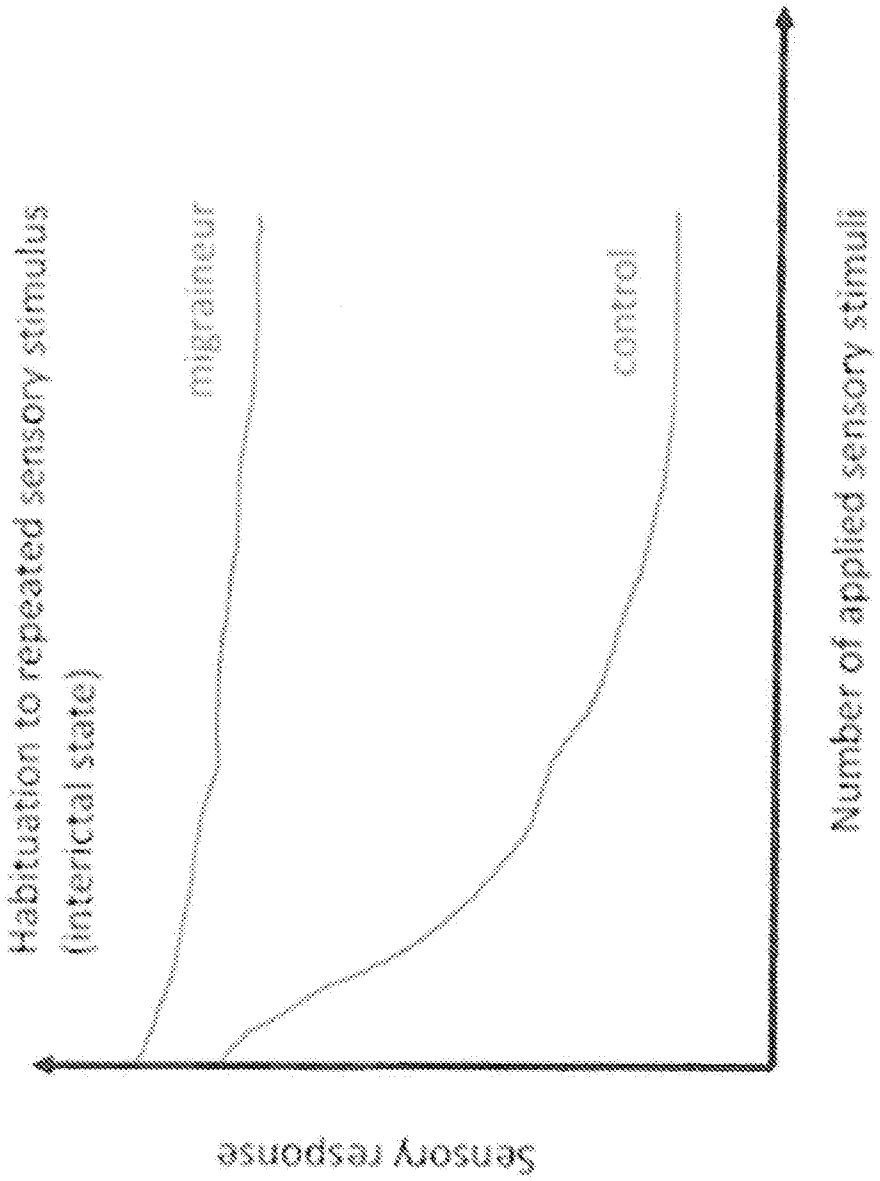

Habituation to repeated sensory stimulus
(interictal state)
migraineur
control
Sensory response
Number of applied sensory stimuli

FIG. 27

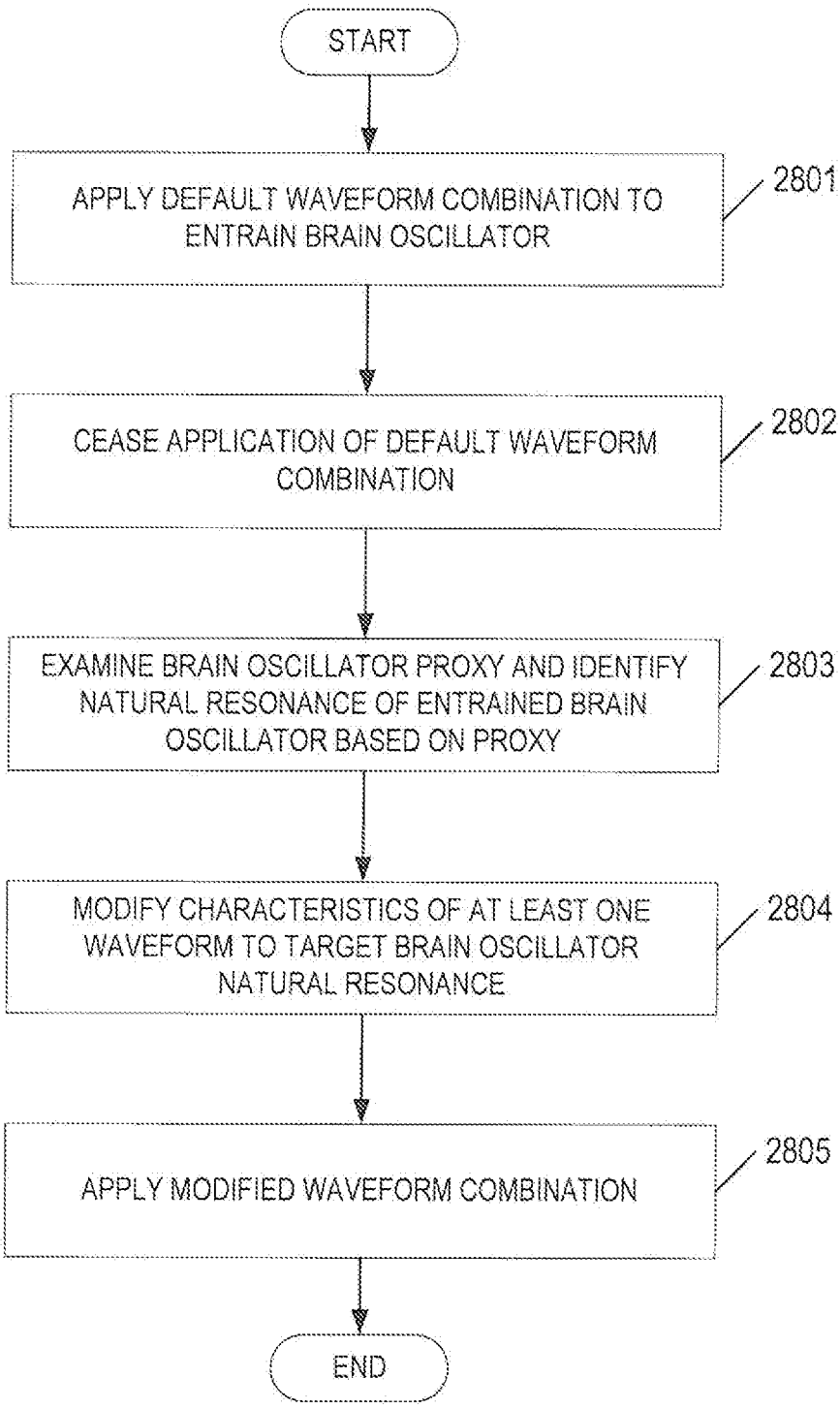

START
APPLY DEFAULT WAVEFORM COMBINATION TO ENTRAIN BRAIN OSCILLATOR
2801
CEASE APPLICATION OF DEFAULT WAVEFORM COMBINATION
2802
EXAMINE BRAIN OSCILLATOR PROXY AND IDENTIFY NATURAL RESONANCE OF ENTRAINED BRAIN OSCILLATOR BASED ON PROXY
2803
MODIFY CHARACTERISTICS OF AT LEAST ONE WAVEFORM TO TARGET BRAIN OSCILLATOR NATURAL RESONANCE
2804
APPLY MODIFIED WAVEFORM COMBINATION
2805
END

FIG. 28

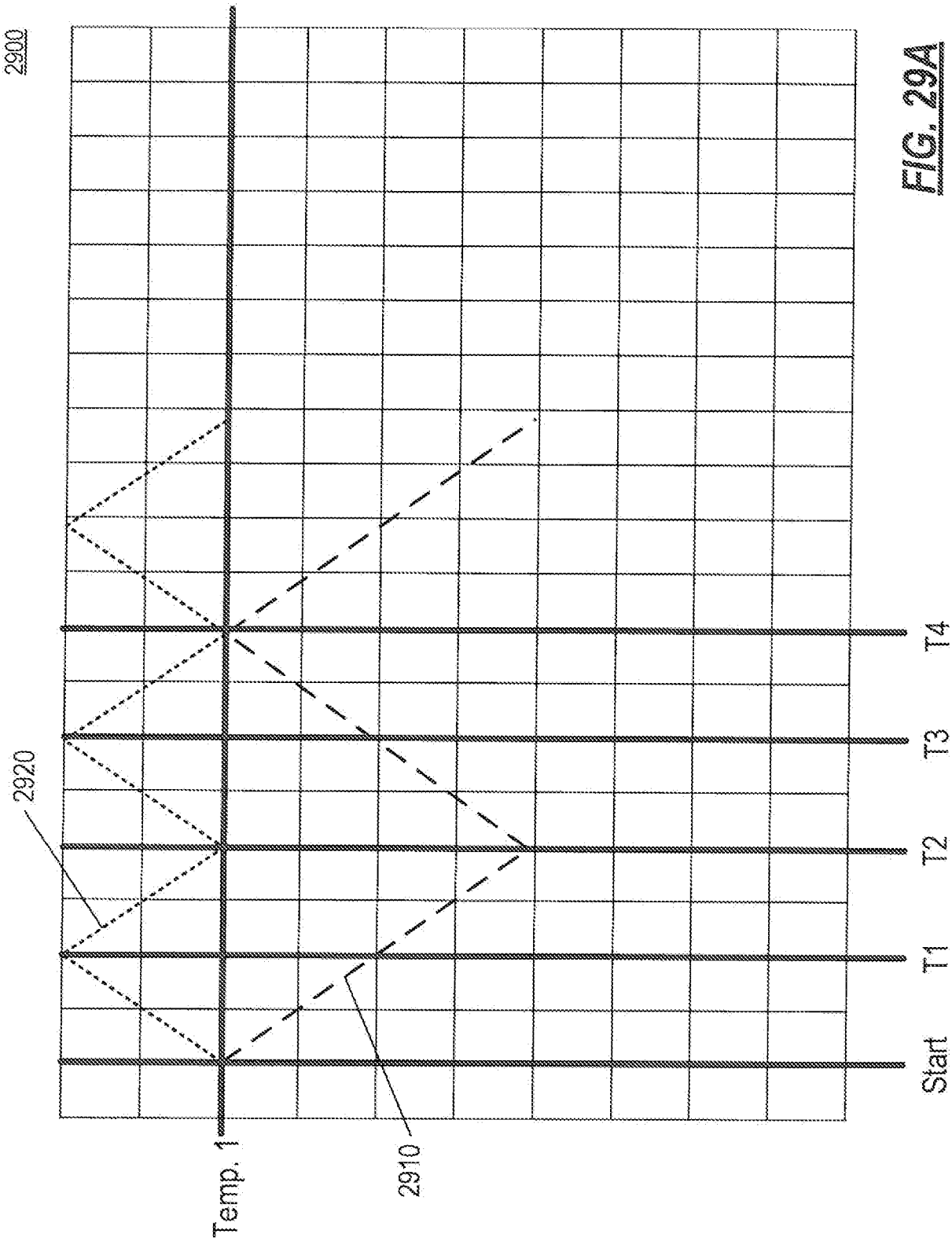


FIG. 29A

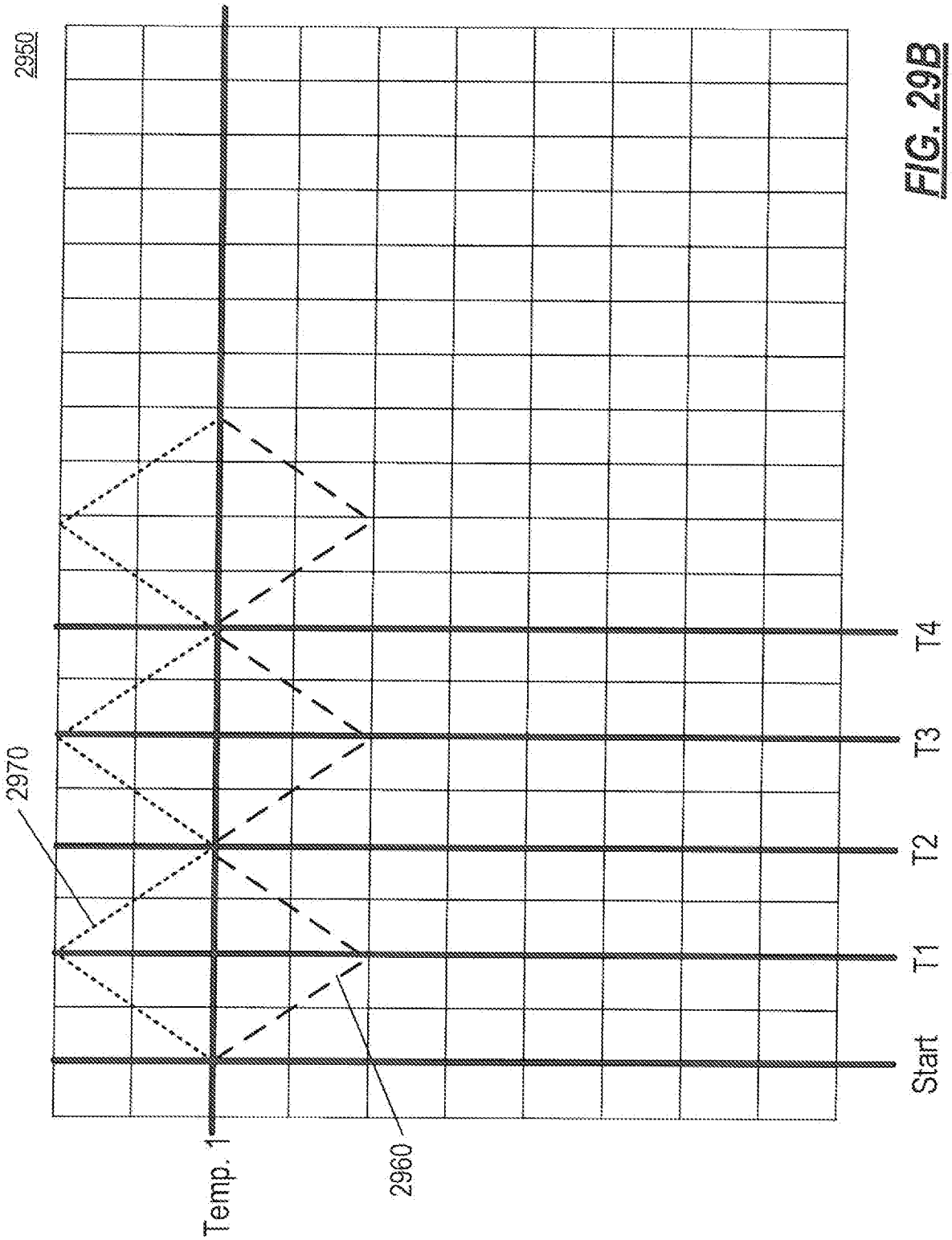


FIG. 29B

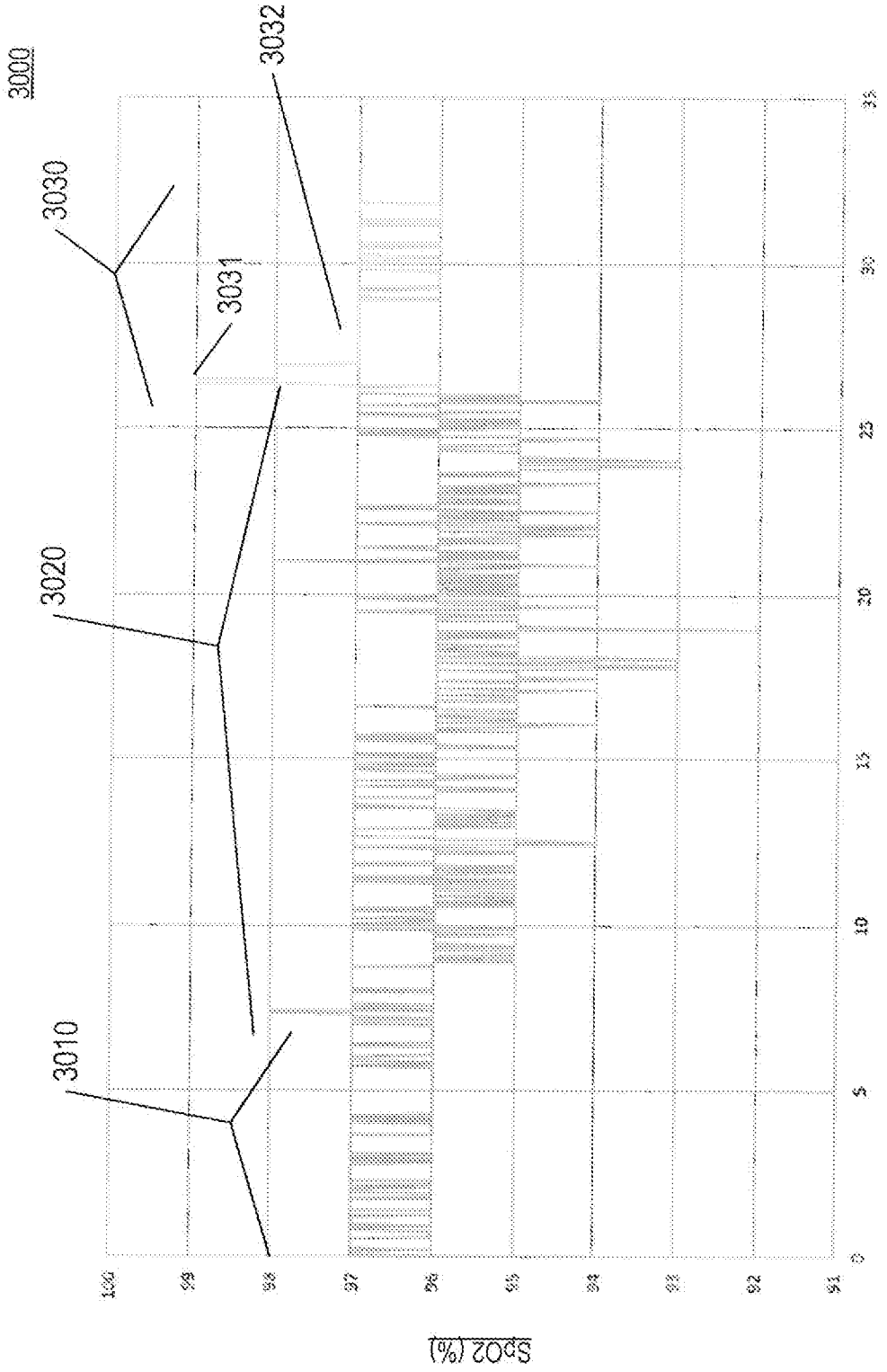


FIG. 30A

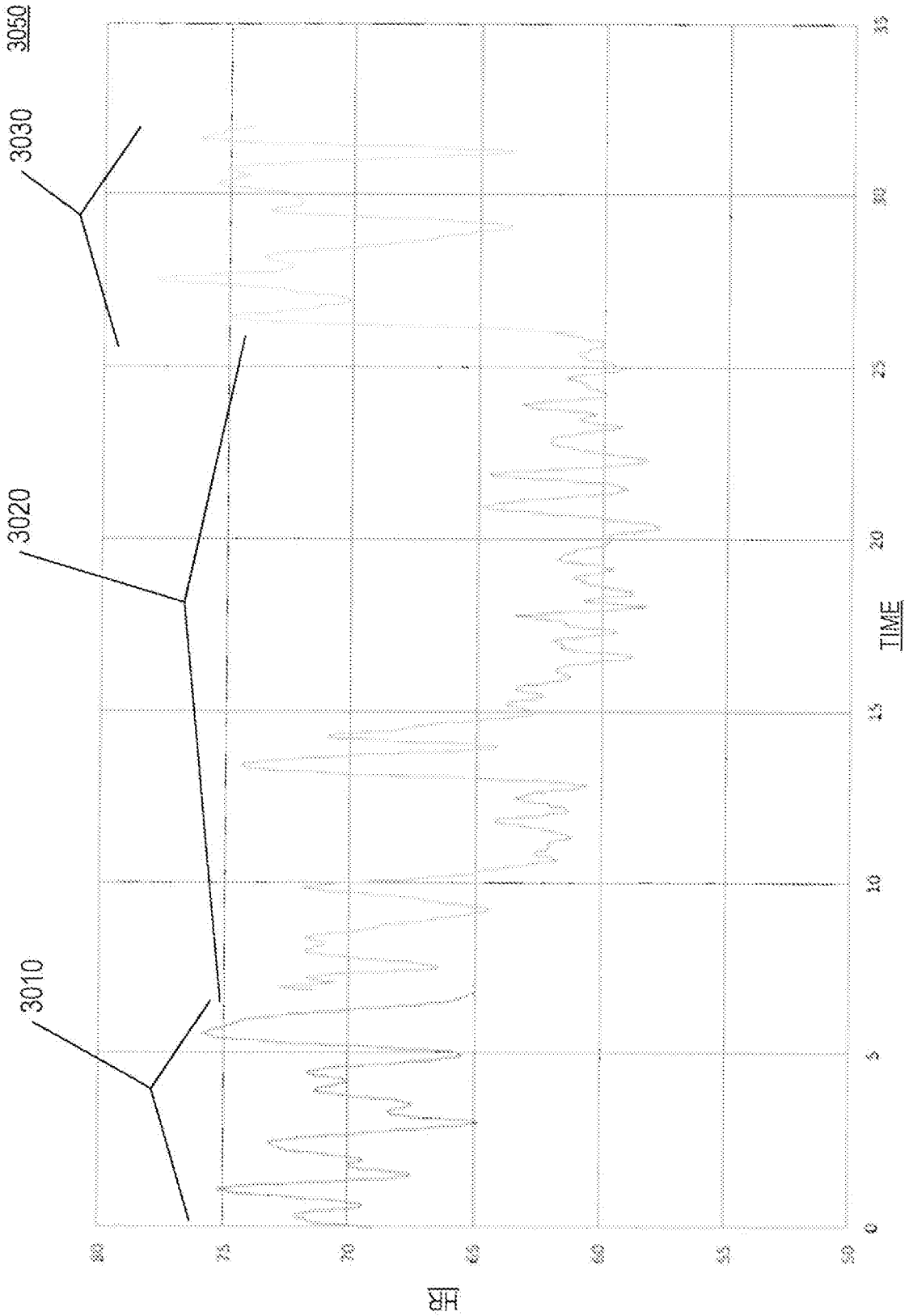


FIG. 30B