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Inventor(s)

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### **Systems and methods for stimulating and/or monitoring loci in the brain to treat inflammation and to enhance vagus nerve stimulation**

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#### **Abstract**

Described herein are methods and systems for using EEG recordings to improve vagus nerve stimulation (VNS) therapy. In particular, described herein are methods and systems for using EEG recordings to detect P300 and/or activation of the nucleus basalis and/or the locus coeruleus to determine the efficacy of VNS. The EEG recordings can be used to provide feedback control to help optimize stimulation parameters and to screen for patients that respond well to VNS therapy.

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## Field of Classification Search

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2001/0002441	12/2000	Boveja	N/A	N/A
2001/0034542	12/2000	Mann	N/A	N/A
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2002/0198570	12/2001	Puskas	N/A	N/A
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2004/0002546	12/2003	Altschuler	N/A	N/A
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2004/0024422	12/2003	Hill et al.	N/A	N/A
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2004/0024439	12/2003	Riso	N/A	N/A
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2004/0059383	12/2003	Puskas	N/A	N/A
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2004/0172074	12/2003	Yoshihito	N/A	N/A
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2004/0236382	12/2003	Dinsmoor et al.	N/A	N/A
2004/0240691	12/2003	Grafenberg	N/A	N/A
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2006/0129202	12/2005	Armstrong	N/A	N/A
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2006/0142802	12/2005	Armstrong	N/A	N/A
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2006/0282121	12/2005	Payne et al.	N/A	N/A
2006/0282131	12/2005	Caparso et al.	N/A	N/A
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2006/0287679	12/2005	Stone	N/A	N/A
2006/0292099	12/2005	Milburn et al.	N/A	N/A
2006/0293720	12/2005	DiLorenzo	N/A	N/A
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2007/0025608	12/2006	Armstrong	N/A	N/A
2007/0027482	12/2006	Parnis et al.	N/A	N/A
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Levine et al.; U.S. Appl. No. 18/730,753 entitled "Treatment of inflammatory disorders," filed Jul. 19, 2024. cited by applicant

Hebb et al.; Creating the Feedback Loop: Closed-Loop Neurostimulation; *Neurosurgery Clinics of North America*; 25(1); pp. 187-204; Jan. 28, 2014. cited by applicant

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## **Background/Summary**

CROSS REFERENCE TO RELATED APPLICATIONS (1) This patent application is a divisional of U.S. patent application Ser. No. 14/922,022, titled “SYSTEMS AND METHODS FOR STIMULATING AND/OR MONITORING LOCI IN THE BRAIN TO TREAT INFLAMMATION AND TO ENHANCE VAGUS NERVE STIMULATION,” filed Oct. 23, 2015, now U.S. Pat. No. 11,311,725, which claims priority to U.S. Provisional Patent Application No. 62/068,473, titled “EXTREMELY LOW DUTY-CYCLE ACTIVATION OF THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY, AND TRAINING THEREOF, TO TREAT CHRONIC INFLAMMATION,” filed Oct. 24, 2014, which is herein incorporated by reference in its entirety. (2) Some variations of the methods and apparatuses described in this patent application may be related to the following U.S. patent applications: U.S. patent application Ser. No. 12/620,413, filed on Nov. 17, 2009 and titled, “DEVICES AND METHODS FOR OPTIMIZING ELECTRODE PLACEMENT FOR ANTI-INFLAMMATORY STIMULATION” (US-2010-0125304); U.S. patent application Ser. No. 12/874,171, filed on Sep. 1, 2010 and titled, “PRESCRIPTION PAD FOR TREATMENT OF INFLAMMATORY DISORDERS” (US-2011-0054569); U.S. patent application Ser. No. 12/917,197, filed on Nov. 1, 2010 and titled, “MODULATION OF THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY TO TREAT PAIN OR ADDICTION” (US-2011-0106208); U.S. patent application Ser. No. 12/978,250, filed on Dec. 23, 2010 and titled, “NEURAL STIMULATION DEVICES AND SYSTEMS FOR TREATMENT OF CHRONIC INFLAMMATION” (US-2011-0190849); U.S. patent application Ser. No. 12/797,452, filed on Jun. 9, 2010 and titled, “NERVE CUFF WITH POCKET FOR LEADLESS STIMULATOR” (US-2010-0312320); U.S. patent application Ser. No. 13/467,928, filed on May 9, 2012 and titled, “SINGLE-PULSE ACTIVATION OF THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY TO TREAT CHRONIC INFLAMMATION” (US-2012-0290035); and U.S. patent application Ser. No. 13/338,185, filed on Dec. 27, 2011 and titled, “MODULATION OF SIRTUINS BY VAGUS NERVE STIMULATION.” Each of these patent applications is herein incorporated by reference in its entirety. (3) Some variations of the methods and apparatuses described in this patent application may be related to the following PCT application: International Application No. PCT/US2014/033690, filed Apr. 10, 2014, which is herein incorporated by reference in its entirety.

## **INCORPORATION BY REFERENCE**

(1) All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. (2) For example, the following reference are incorporated by reference herein in their entireties: 1. Cheyuo, C., et al., The parasympathetic nervous system in the quest for stroke therapeutics. J Cereb Blood Flow Metab, 2011. 31(5): p. 1187-95. 2. Engineer, N. D., A. R. Moller, and M. P. Kilgard, Directing neural plasticity to understand and treat tinnitus. Hear Res, 2013. 295: p. 58-66. 3. Groves, D. A., E. M. Bowman, and V. J. Brown, Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. Neuroscience Letters, 2005. 379(3): p. 174-

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## FIELD

(3) Embodiments of the invention relate generally to neuromodulation of the vagus nerve for the treatment of inflammation, and more specifically to neuromodulation of the vagus nerve involving feedback and/or stimulation from the central nervous system.

## BACKGROUND

(4) Some neuromodulation devices have the ability to modulate their own stimulation settings quickly based on immediate feedback from target tissue (e.g. muscle) that they are stimulating, since the target tissue responds quickly to stimulation. For example, electromyography (EMG) can be used to record and evaluate the electrical activity of muscles, which provides information regarding the activation level and/or recruitment of the muscles. This information can be processed and used to modulate the neurostimulation parameters applied to the muscles, thereby improving the efficacy of the stimulation device.

(5) Vagus nerve stimulation (VNS) for the treatment of chronic inflammatory diseases, on the other hand, is not easily programmed for optimal result, as decreases in inflammation take hours to days to manifest. Consequently, it would be desirable to identify alternative markers or surrogates that indicate activation of the cholinergic anti-inflammatory pathway by VNS. In addition, it would be desirable to use these alternative markers or surrogates to identify patients that may be suitable for receiving VNS therapy. Furthermore, it would be desirable to directly modulate these markers or surrogates as an alternative or supplemental way to treat inflammation.

## SUMMARY OF THE DISCLOSURE

(6) The present invention relates generally to neuromodulation of the vagus nerve for the treatment of inflammation, and more specifically to neuromodulation of the vagus nerve involving feedback and/or stimulation from the central nervous system.

(7) In some embodiments, a method for inducing long term potentiation of the inflammatory reflex in a patient is provided. The method can include stimulating the vagus nerve of the patient according to a set of stimulation parameters; recording an EEG after the step of stimulating the vagus nerve; determining from the recorded EEG whether at least one of the nucleus basalis and the locus coeruleus has been activated by the vagus nerve stimulation; and adjusting the set of stimulation parameters based on the determination from the recorded EEG whether at least one of the nucleus basalis and the locus coeruleus has been activated.

(8) In some embodiments, the step of adjusting the set of stimulation parameters includes increasing a stimulation amplitude.

(9) In some embodiments, the method further includes recording a baseline EEG.

(10) In some embodiments, the step of determining from the recorded EEG whether at least one of the nucleus basalis and the locus coeruleus has been activated by the vagus nerve stimulation comprises comparing the recorded EEG with the baseline EEG.

(11) In some embodiments, a method for inducing long term potentiation of the inflammatory reflex in a patient is provided. The method can include stimulating the vagus nerve according to a set of stimulation parameters sufficient for activating at least one of the nucleus basalis and the locus coeruleus.

- (12) In some embodiments, the set of stimulation parameters includes an amplitude between about 0.1 and 3 mA, a frequency between about 1 Hz and 30 Hz, a pulse width between about 100  $\mu$ S and 500  $\mu$ S, and a duration between about 0.5 second to 10 minutes.
- (13) In some embodiments, a method for prescreening a patient is provided. The method can include noninvasively stimulating the vagus nerve; recording an EEG; and determining whether the patient will be responsive to an invasive vagus nerve stimulation based on an analysis of the EEG.
- (14) In some embodiments, the step of determining whether the patient will be responsive to an invasive vagus nerve stimulation based on an analysis of the EEG includes determining whether P300 is present in the EEG.
- (15) In some embodiments, the step of determining whether the patient will be responsive to an invasive vagus nerve stimulation based on an analysis of the EEG includes determining with the EEG whether at least one of the nucleus basalis and the locus coeruleus was activated by the noninvasive vagus nerve stimulation.
- (16) In some embodiments, the step of noninvasively stimulating the vagus nerve includes noninvasively stimulating the auricular branch of the vagus nerve.
- (17) In some embodiments, the noninvasive stimulation of the auricular branch of the vagus nerve is electrical.
- (18) In some embodiments, the noninvasive stimulation of the auricular branch of the vagus nerve is mechanical.
- (19) In some embodiments, the step of recording the ECG takes place after the step of noninvasively stimulating the vagus nerve.
- (20) In some embodiments, the step of recording the ECG takes place during the step of noninvasively stimulating the vagus nerve.
- (21) In some embodiments, a method for providing feedback control during vagus nerve stimulation of a patient is provided. The method can include stimulating the vagus nerve with a vagus nerve stimulator; recording an EEG to detect at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus; and adjusting an amplitude of the stimulation to the vagus nerve until at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is detected in the EEG.
- (22) In some embodiments, the method further includes programming the vagus nerve stimulator with a set of stimulation parameters based on the step of adjusting the amplitude of the stimulation to the vagus nerve until at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is detected in the EEG.
- (23) In some embodiments, the step of adjusting the amplitude includes increasing the amplitude when the patient is not responding to the stimulation of the vagus nerve.
- (24) In some embodiments, the step of adjusting the amplitude includes decreasing the amplitude when the patient is responding well to the stimulation of the vagus nerve.
- (25) In some embodiments, the method further includes increasing a stimulation interval after the step of adjusting the amplitude of the stimulation to the vagus nerve until at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is detected in the EEG.
- (26) In some embodiments, a system for stimulating a nerve of a patient is provided. The system can include an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of programmed stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG, and adjust the set of programmed stimulation parameters based on the determination of whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG.
- (27) In some embodiments, the controller is located in a prescription pad.



- (28) In some embodiments, the controller is located in an energizer configured to provide power to the implantable nerve stimulator.
- (29) In some embodiments, the controller is located in the EEG recording device.
- (30) In some embodiments, the set of programmed stimulation parameters includes a pulse amplitude, a pulse width, and a pulse frequency.
- (31) In some embodiments, a method for treating a patient suffering from inflammation is provided. The method can include stimulating at least one of the nucleus basalis and the locus coeruleus with an electrode implanted within the patient's brain; and reducing a level of inflammation in the patient.
- (32) In some embodiments, the step of stimulating at least one of the nucleus basalis and the locus coeruleus with an electrode implanted within the patient's brain includes delivering an electrical stimulus having a current between 10 to 100  $\mu$ A, a frequency of 1 to 500 Hz, and a duration of up to 120 minutes.
- (33) In some embodiments, a method for treating a patient suffering from inflammation is provided. The method can include stimulating at least one of the nucleus basalis and the locus coeruleus with a focused magnetic field; and reducing a level of inflammation in the patient.
- (34) In some embodiments, the step of stimulating at least one of the nucleus basalis and locus coeruleus with the focused magnetic field includes generating the focused magnetic field with a transcranial magnetic coil.
- (35) In some embodiments, the step of stimulating at least one of the nucleus basalis and locus coeruleus with the focused magnetic field includes generating the magnetic field with a frequency below 3 Hz, a field strength below 3 Tesla, and a duration between 5 to 60 minutes.
- (36) In some embodiments, the step of stimulating at least one of the nucleus basalis and locus coeruleus with the focused magnetic field includes generating the magnetic field with a frequency between 3 to 25 Hz, a field strength below 3 Tesla, and a duration between 5 to 60 minutes.
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## Description

### BRIEF DESCRIPTION OF THE DRAWINGS

- (1) The novel features of the invention are set forth with particularity in the claims that follow. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:
- (2) FIG. 1A shows one variation of a system for modulating chronic inflammation including a leadless microstimulator (shown connected to the vagus nerve) and an external charger/controller.
- (3) FIG. 1B shows another variation of a system for modulating chronic inflammation, including a microstimulator, charger ("energizer"), and system programmer/controller ("prescription pad").
- (4) FIG. 1C shows another variations of a system for modulating chronic inflammation, including a microstimulator, a securing device (POD) for securing the leadless stimulator to the nerve, an external charger, a system programmer/controller ("prescription pad") and an optional surgical tester.
- (5) FIG. 1D is a block diagram schematically illustrating the microstimulator and the charger.
- (6) FIG. 2 illustrates one variation of an external system programmer/controller wirelessly connected to a microstimulator.
- (7) FIG. 3A shows one variation of a microstimulator in a POD configured to surround a nerve of the inflammatory reflex. FIG. 3B shows an enlarged view of the microstimulator and POD. FIG. 3C shows another variation of a microstimulator; FIG. 3D shows the microstimulator of FIG. 3C within a POD. FIG. 3E shows another variation of the microstimulator.
- (8) FIG. 4 shows a schematic diagram of a microstimulator and POD around vagus nerve.

- (9) FIG. 5 illustrates an embodiment of an EEG recording system for detecting P300 and/or activation of the locus coeruleus and/or nucleus basalis.
- (10) FIG. 6 illustrates a flow chart that describes a method for modulating vagus nerve stimulation using feedback from EEG recordings.
- (11) FIG. 7 illustrates a flow chart that describes another method for modulating vagus nerve stimulation using feedback from EEG recordings.
- (12) FIG. 8 illustrates a flow chart that describes yet another method for modulating vagus nerve stimulation using feedback from EEG recordings.
- (13) FIG. 9 illustrates an embodiment of a deep brain stimulator with electrodes positioned at the nucleus basalis and locus coeruleus.
- (14) FIG. 10 illustrates an embodiment of a transcranial magnetic stimulator.
- (15) FIG. 11 illustrates an embodiment of a transcutaneous electrical nerve stimulator.

#### DETAILED DESCRIPTION

(16) Various regions or neural groups in the brain and central nervous system are linked to the vagus nerve through sympathetic and/or efferent neural pathways. Consequently, activation or stimulation of these regions or neuronal groups may initiate and/or modulate vagus nerve activity. Alternatively, activation or stimulation of the vagus nerve may initiate and/or modulate activity in these various regions or neural groups. Because activation of the vagus nerve may result in activation of these regions or neural groups, these regions or neural groups can be monitored as surrogates or proxies for determining whether the vagus nerve has been successfully activated by the VNS.

(17) For example, the nucleus basalis (NB) is composed of a neural group in the substantia innominata of the basal forebrain, next to the hypothalamus, and is a source of much of the acetylcholine in the brain. The degradation of the NB has been shown to play a role in Parkinson's and Alzheimer's disease. The NB receives noradrenergic innervation from the locus coeruleus and has neural projections to the caudate nucleus, globus pallidus, thalamus, hippocampus, cerebral cortex, and the brainstem. NB activity drives efferent vagal output [1] and activation of the NB increases attention and cortical plasticity.

(18) Another region, the locus coeruleus (LC), is composed of a neural group located in the pons within the brainstem and is the principle source of norepinephrine (NE) in the brain. The LC has neural inputs from the nucleus tractus solitaries (NTS), dorsal raphe nucleus and projects to the NTS, dorsal raphe nucleus, thalamus, hypothalamus, amygdala, cortex, and the nucleus basalis. Activation of LC increases attention and cortical plasticity. LC coordinates VNS input with sympathetic output.

(19) VNS can be used to activate both NB [2] and LC [3]. VNS causes increased firing within LC that can last for days [4]. VNS enhances recognition memory in humans [5]. Paired VNS (30 Hz, 0.8 mA, 100 uS, 0.5S, 2.5 hr duration) with tonal training results in reduction of rat tinnitus for more than 24 h [6]. These data show an increase in auditory cortical plasticity in topographically mapped brain regions with synchronous activation of NB and LC by VNS with training.

(20) P300 describes an event-related potential (ERP) component that occurs at latencies of about 250-700 msec and can be quantified by EEG recording as a positive voltage deflection. LC activity correlates with P300, as P300 is enhanced when LC activity is enhanced, and LC lesion or inhibition decreases P300 in monkeys [8]. There is a correlation between P300 activation and VNS responders in depression [9].

(21) Therefore, during and/or after VNS, electrical activity from the NB and/or LC, including the P300, can be measured with EEG in order to provide immediate feedback or feedback within seconds or minutes after stimulation, rather than obtaining feedback from reduction in inflammation levels, which may take hours or longer to manifest. In some variations simply detecting the P300 during VNS and/or afterwards is sufficient to provide feedback and/or information. Alternatively, in some variations, the P300 may be detected based on a criterion (e.g.,

at or above a threshold such as a reference amplitude) before indicating a positive reading (e.g., triggering feedback). If electrical activity and/or the P300 is not detected or does not meet threshold values, the stimulation parameters, such as amplitude, can be adjusted until the electrical activity and/or P300 is detected and meets the threshold values that indicate NB and/or LC activation. It may not be necessary to provide a stimulus other than the VNS to elicit NB or LC activity; for example, any of the methods or apparatuses (systems and devices) described herein may examine the EEG during and/or just after the VNS.

(22) Since P300 is an ERP, a predetermined stimulus can be provided to the patient to elicit P300. In some embodiments, the stimulus is the VNS itself. In other embodiments, the patient can be given a specific sensory, cognitive, or motor stimulus, and the EEG recording between about 250 msec and 700 msec after the stimulus can be analyzed for a positive voltage deflection that represents P300. Examples of a stimulus include an auditory stimulus provided using an auditory oddball paradigm and/or a visual stimulus provided using a visual oddball paradigm. The oddball paradigm presents a series of repetitive audio and/or visual stimuli that are interrupted by a deviant target stimulus, which the patient is asked to detect. Any of these stimuli can also be used to elicit electrical activity from the NB and/or LC.

### (23) Vagus Nerve Stimulation System

(24) Systems for electrically stimulating one or more nerves to treat chronic inflammation may include an implantable, wireless microstimulator such as those described herein and an external charging device (which may be referred to as a charging wand, charger, or energizer). In some variations the system also includes a controller such as a “prescription pad” that helps control and regulate the dose delivered by the system. The microstimulator may be secured in position using a securing device (which may be referred to as a “POD”) to hold the microstimulator in position around or adjacent to a nerve. These microstimulators are designed and adapted for treatment of chronic inflammation, and may be configured specifically for such use. Thus, an implantable microstimulator may be small, and adapted for the low duty-cycle stimulation to modulate inflammation. For example, the implantable microstimulator may hold a relatively small amount of power over weeks or even months and discharge it at a rate sufficient to modulate the anti-inflammatory pathway without significantly depressing heart rate or triggering any number of unwanted effects from the vagus nerve or other neural connections. Any of the nerves of the inflammatory reflex, including the vagus nerve, may be treated as described herein using the systems described.

(25) For example, FIG. 1A illustrates one variation of a system for treating chronic inflammation that includes a microstimulator contained in POD that is mounted on cervical vagus nerve and charged a programmed by an external charger/programmer unit. This variation of a system includes a microstimulator **103** that has been implanted to contact the vagus nerve as shown. The implant may be programmed, controlled and/or charged by a charger/controller **105** device. In this variation the charger/controller is a loop with a wand region.

(26) FIG. 1B shows another variation of a system for treating chronic inflammation that also includes an implantable microstimulator **103** (shown inserted into a POD to hold it in position relative to a nerve) and a charging device (“energizer” **105**) configured as a collar to be worn around the subject's neck and charge the implant. Optionally, the system may include a prescription pad **107** which may be a separate dedicated device or part of a mobile or other handheld device (e.g., an application to run on a handheld device).

(27) FIG. 1C shows another variation of a system for treating chronic inflammation. The systems described herein may also be referred to as systems for the neural stimulation of the cholinergic anti-inflammatory pathway (NCAP). These systems may be configured as chronic implantable systems. In some variations, the systems are configured to treat acutely (e.g., acute may 8 hours or less), sub-acutely (expected to occur for fewer than 30 days), or chronically (expected to occur for more than 30 days).

(28) In general, the systems described herein may be configured to apply electrical stimulation at a minimum level necessary to modulate the inflammatory reflex (e.g., modulating cytokine release) characterized by the Chronaxie and rheobase. Chronaxie typically refers to the minimum time over which an electric current double the strength of the rheobase needs to be applied in order to stimulate the neuron. Rheobase is the minimal electrical current of infinite duration that results in an action potential. As used herein, cytokines refer to a category of signaling proteins and glycoproteins that, like hormones and neurotransmitters, are used extensively in cellular communication.

(29) The NCAP Systems described herein are typically intended for the treatment of chronic inflammation through the use of implanted neural stimulation devices (microstimulators) to affect the Neural Stimulation of the Cholinergic Anti-inflammatory Pathway (NCAP) as a potential therapeutic intervention for rheumatologic and other inflammation-mediated diseases and disorders. Neurostimulation of the Cholinergic Anti-inflammatory Pathway (NCAP) has been shown to modulate inflammation. Thus, the treatment and management of symptoms manifested from the onset of disease (e.g., inflammatory disease) is based upon the concept of modulating the Cholinergic Anti-inflammatory Pathway. The NCAP pathway normally maintains precise restraint of the circulating immune cells. As used herein, the CAP is a reflex that utilizes cholinergic nerve signals traveling via the Vagus nerve between the brain, chemoreceptors, and the reticuloendothelial system (e.g., spleen, liver). Local release of pro-inflammatory cytokines (e.g., tumor necrosis factor or TNF) from resident immune cells is inhibited by the efferent, or indirectly by afferent vagus nerve signals. NCAP causes important changes in the function and microenvironment of the spleen, liver and other reticuloendothelial organs. Leukocytes which circulate systemically become “educated” as they traverse the liver and spleen are thereby functionally down regulated by the affected environment of the reticuloendothelial system. This effect can potentially occur even in the absence of an inflammatory condition.

(30) Under this model, remote inflammation is then dampened by down-regulated cytokine levels. Stimulation of the vagus nerve with a specific regiment of electrical pulses regulates production of pro-inflammatory cytokines. In-turn, the down regulation of these cytokines may reduce localized inflammation in joints and other organs of patients with autoimmune and inflammatory disorders.

(31) The NCAP System includes a neurostimulator that may trigger the CAP by stimulating the cervical vagus nerve. The NCAP System issues a timed burst of current controlled pulses with sufficient amplitude to trigger the CAP at a particular interval. These two parameters, Dose Amplitude and Dose Interval, may be used by a clinician to adjust the device. For example, the clinician may set the Dose Amplitude by modifying the current level. The Dose Interval may be set by changing the duration between Doses (e.g. 12, 24, 48 hours).

(32) In some variations, dose amplitude may be set to within the Therapy Window. The Therapy window is defined as the lower limit of current necessary to trigger the CAP, and the upper limit is the level at which the Patient feels uncomfortable. The lower limit is called the Threshold (T), and the uncomfortable level is called Upper Comfort Level (UCL).

(33) Dose Amplitude thresholds are nonlinearly dependent upon Current (I), Pulse width (PW), Pulse Frequency (PF), and Burst Duration (BD). Amplitude is primarily set by charge (Q), that is  $\text{Current (I)} \times \text{Pulse width (PW)}$ . In neurostimulation applications current has the most linear relationship when determining thresholds and working within the therapy window. Therefore, the clinician may modify Dose Amplitude by modifying current. The other parameters are held to experimentally determined defaults. Pulse width is selected to be narrow enough to minimize muscle recruitment and wide enough to be well above the chronaxie of the targeted neurons. Stimulus duration and pulse frequency was determined experimentally in Preclinical work.

(34) Dose Interval may be specific for particular diseases and the intensity of diseases experienced by a patient. Our initial research has indicated that the cervical portion of the vagus nerve may be an ideal anatomic location for delivery of stimulation. The nerve runs through the carotid sheath

parallel to the internal jugular vein and carotid artery. At this location, excitation thresholds for the vagus are low, and the nerve is surgically accessible. We have not found any significant difference in biomarker modulation (e.g., modulation of cytokines) between right and left. Even though the right vagus is thought to have lower thresholds than the left in triggering cardiac dysrhythmias, the thresholds necessary for NCAP are much lower than those expected to cause such dysrhythmias. Therefore a device delivering NCAP can safely be applied to either the right or left vagus.

(35) We have also found, surprisingly, that the Therapy Window is maximized on the cervical vagus through the use of a bipolar cuff electrode design. Key parameters of the cuff may be: spacing and shielding of the contacts. For example, the contact points or bands may be spaced 1-2 diameters of the vagus nerve apart, and it may be helpful to shield current from these contacts from other nearby structures susceptible to inadvertent triggering. The cuff may be further optimized by using bands which are as long and wide as possible to reduce neurostimulator power requirements.

(36) Thus, any variations of the systems described herein (e.g., the NCAP system) may be implemented with a Cuff, Lead and Implantable Pulse Generation (IPG), or a Leadless Cuff. The preferred implementation is a leadless cuff implemented by a microstimulator with integral electrode contacts in intimate contact with the nerve and contained within a Protection and Orientation Device (POD). This is illustrated in FIGS. 3A and 3B. The POD **301** may form a current shield, hold the microstimulator into place against the vagus nerve, and extend the microstimulator integral contacts with integral contacts in the POD itself. The POD is typically a polymer shell that encapsulates a microstimulator implant and that allows a nerve to run through the interior against the shell wall parallel to the length of the microstimulator implant. Within the shell of the POD, the microstimulator implant remains fixed against the Vagus nerve so the electrodes remain in contact with the nerve. The POD anchors the implant in place and prevents the implant from rotating or separating from the nerve, as well as maintaining contact between the electrodes and the nerve and preserving the orientation as necessary for efficient external charging of the microstimulator battery.

(37) Referring back to FIG. 1C, the system may include an implantable microstimulator contained in a POD, a Patient Charger, and a prescription pad that may be used by the clinician to set dosage parameters for the patient. This system may evaluate the efficacy, safety, and usability of an NCAP technology for chronic treatment of clinical patients. The system can employ a Prescription Pad (external controller) that may include the range of treatment options.

(38) As described in more detail in U.S. Ser. No. 12/874,171 (titled "PRESCRIPTION PAD FOR TREATMENT OF INFLAMMATORY DISORDERS"), previously incorporated by reference in its entirety, the Prescription Pad may incorporate workflows in a simplified interface and provide data collection facilities that can be transferred to an external database utilizing commercially robust and compliant methods and procedures. In use, the system may be recommended for use by a clinician after assessing a patient; the clinician may determine that treatment of chronic inflammation is warranted. The clinician may then refer the patient to an interventional doctor to implant the microstimulator. Thereafter then clinician (or another clinician) may monitor the patient and adjust the device via a wireless programmer (e.g. prescription pad). The clinician may be trained in the diagnosis and treatment procedures for autoimmune and inflammatory disorders; the interventional placement of the system may be performed by a surgeon trained in the implantation of active neurostimulation devices, with a sufficient depth of knowledge and experience regarding cervical and vagal anatomy, experienced in performing surgical dissections in and around the carotid sheath.

(39) The system may output signals, including diagnostics, historical treatment schedules, or the like. The clinician may adjust the device during flares and/or during routine visits. Examples of implantation of the microstimulator were provided in U.S. patent application Ser. No. 12/874,171, which is herein incorporated by reference in its entirety. For example, the implant may be inserted by making an incision in the skin (e.g.,  $\approx 3$  cm) along Lange's crease between the Facial Vein and

the Omohyoid muscle, reflecting the Sternocleidomastoid and gaining access to the carotid sheath. The IJV may be displaced, and the vagus may be dissected from the carotid wall ( $\leq 2$  cm). A sizing tool may be used to measure the vagus, and an appropriate Microstimulator and POD Kit (small, medium, large) may be selected. The POD may then be inserted under nerve with the POD opening facing the surgeon, so that the microstimulator can be inserted inside POD so that the microstimulator contacts capture the vagus. The POD may then be sutured shut. In some variations a Surgical Tester may be used to activate the microstimulator and perform system integrity and impedance checks, and shut the microstimulator off, during or after the implantation. In other variations the surgical tester may be unnecessary, as described in greater detail below.

(40) A physician may use the Patient Charger to activate the microstimulator, perform integrity checks, and assure sufficient battery reserve exists. Electrodes may be conditioned with sub-threshold current and impedances may be measured. A Physician may charge the microstimulator. In some variations a separate charger (e.g., an “energizer”) may be used by the patient directly, separate from the controller the physician may use. Alternatively, the patient controller may include controls for operation by a physician; the system may lock out non-physicians (e.g., those not having a key, code, or other security pass) from operating or modifying the controls.

(41) In general, a physician may establish safe dosage levels. The physician may slowly increment current level to establish a maximum limit (Upper Comfort Limit). This current level may be used to set the Dosage Level. The exact procedure may be determined during this clinical phase.

(42) The Physician may also specify dosing parameters that specify dosage levels and dosage intervals. The device may contain several concurrent dosing programs which may be used to acclimate the patient to stimulus, gradually increase dosage until efficacy is achieved, reset tachyphylaxis, or deal with unique patient situations.

(43) In some variations, the Prescription Pad may be configured to handle multiple patients and may index their data by the microstimulator Serial Number. For example, a Prescription Pad may handle up to 100,000 patients and 10,000 records per patient, and may store the data in its local memory and may be backed up on an external database. In some variations, during each charging session, accumulated even log contents will be uploaded to the Patient Charger for later transfer to Prescription Pad. The data may or may not be cleared from the microstimulator. For example, FIG. 2 shows the addition of a prescription pad **203** wirelessly connected to the charger/programmer **207**.

(44) The microstimulators described herein are configured for implantation and stimulation of the cholinergic anti-inflammatory pathway, and especially the vagus nerve. In particular the microstimulators described herein are configured for implantation in the cervical region of the vagus nerve to provide extremely low duty-cycle stimulation sufficient to modulate inflammation. These microstimulators may be adapted for this purpose by including one or more of the following characteristics, which are described in greater detail herein: the conductive capsule ends of the micro stimulator may be routed to separate electrodes; the conductive capsule ends may be made from resistive titanium alloy to reduce magnetic field absorption; the electrodes may be positioned in a polymer saddle; the device includes a suspension (e.g., components may be suspended by metal clips) to safeguard the electronics from mechanical forces and shock; the device may include an H-bridge current source with capacitor isolation on both leads; the device may include a built in temperature sensor that stops energy absorption from any RF source by detuning the resonator; the device may include a built-in overvoltage sensor to stop energy absorption from any RF source by detuning resonator; the system may include DACs that are used to calibrate silicon for battery charging and protection; the system may include DACs that are used to calibrate silicon for precision timing rather than relying on crystal oscillator; the system may include a load stabilizer that maintains constant load so that inductive system can communicate efficiently; the system may include current limiters to prevent a current rush so that the microstimulator will power up smoothly from resonator power source; the system may extract a clock from carrier OR from

internal clock; the device may use an ultra-low power accurate RC oscillator that uses stable temperature in body, DAC calibration, and clock adjustment during charging process; the device may use a solid state LIPON battery that allows fast recharge, supports many cycles, cannot explode, and is easy to charge with constant voltage; and the device may include a resonator that uses low frequency material designed not to absorb energy by high frequency sources such as MRI and Diathermy devices.

(45) Many of these improvements permit the device to have an extremely small footprint and power consumption, while still effectively modulating the vagus nerve.

(46) FIG. 3A is a perspective drawing of the Pod containing the microstimulator. Sutures (not shown) are intended to be bridged across one to three sets of holes. Electrodes integrated into the pod are not shown but would extend as bands originating and ending on the two outer pairs of suture holes.

(47) In some variations, including those described above, the microstimulator consists of a ceramic body with hermetically sealed titanium-niobium ends and integral platinum-iridium electrodes attached. The microstimulator may be designed to fit within a POD 309, as shown in FIGS. 3A-3D. As described above, the POD is a biocompatible polymer with integrated electrodes that may help the microstimulator to function as a leadless cuff electrode. In some variations, such as the variation shown in FIG. 3E, contained within the hermetic space of the microstimulator 301 is an electronic assembly that contains a rechargeable battery 321, solenoid antenna 323, hybrid circuit 325 and electrode contacts (Ti Alloy braze ring and end cap) 327 at each end to make contact with the titanium/platinum case ends.

(48) In some embodiments, the microstimulator can be batteryless. The batteryless microstimulator can be powered inductively by an external power source to deliver an electrical stimulus to the nerve. In some embodiments, the batteryless microstimulator can have a capacitor or supercapacitor instead of a battery for storing energy which can be released as an electrical stimulus.

(49) As mentioned above, some of the device variations described herein may be used with a POD to secure the implant (e.g., the leadless/wireless microstimulator implant) in position within the cervical region of the vagus nerve so that the device may be programmed and recharged by the charger/programmer (e.g., “energizer”). For example, FIG. 4 shows a schematic diagram of a POD containing a microstimulator. The cross section in FIG. 4 shows the ceramic tube containing electronic assembly that includes the hybrid, battery and coil. The rigid or semi-rigid contacts are mounted on the tube and surround the oval vagus nerve. The POD surrounds the entire device and includes a metal conductor that makes electrical contact with the microstimulator contacts and electrically surrounds the nerve.

(50) In some variations, the microstimulator may have a bipolar stimulation current source that produce as stimulation dose with the characteristics shown in table 1, below. In some variation, the system may be configured to allow adjustment of the “Advanced Parameters” listed below; in some variations the parameters may be configured so that they are predetermined or pre-set. In some variations, the Advanced Parameters are not adjustable (or shown) to the clinician. All parameters listed in Table 1 are  $\pm 5\%$  unless specified otherwise.

(51) TABLE-US-00001 TABLE 1 Microstimulator parameters Property Value Default Dosage 0-5,000  $\mu\text{A}$  in 25  $\mu\text{A}$  steps 0 Amplitude (DA) Intervals Minute, Hour, Day, Week, Month Day Number of N = 60 Maximum 1 Doses per Interval Advanced Parameters Pulse width 100-1,000  $\mu\text{S}$  in 50  $\mu\text{S}$  200 Range (PW) increments Stimulus 0.5-1000 seconds per 60 Duration (SD) dose Pulse 1-50 Hz 10 Frequency (PF) Stimulus  $\pm 3.3$  or  $\pm 5.5 \pm 1$  Volts Automatically set Voltage (SV) by software Constant  $\pm 15\%$  over supported range Current of load impedances (200- Output 2000 $\Omega$ ) Specific Dose Set a specific time between Driven by default Time 12:00 am-12:00 am in one table (TBD) minute increments for each Dose Issue Number of 4 maximum 1 Sequential Dosing Programs

(52) The Dosage Interval is defined as the time between Stimulation Doses. In some variations, to support more advanced dosing scenarios, up to four 'programs' can run sequentially. Each program has a start date and time and will run until the next program starts. Dosing may be suspended while the Prescription Pad is in Programming Mode. Dosing may typically continue as normal while charging. Programs may be loaded into one of four available slots and can be tested before they start running. Low, Typical, and High Dose schedules may be provided. A continuous application schedule may be available by charging every day, or at some other predetermined charging interval. For example, Table 2 illustrates exemplary properties for low, typical and high dose charging intervals:

(53) TABLE-US-00002 TABLE 2 low typical and high dose charging intervals

Property	Value
Low Dose Days	30 days max: 250 $\mu$ A, 200 $\mu$ S, 60 s, 24 hr, Charge Interval 10 Hz, $\pm$ 3.3 V
Typical Dose	30 days max: 1,000 $\mu$ A, 200 $\mu$ S, 120 s, 24 hr, Charge Interval 10 Hz, $\pm$ 3.3 V
High Dose Charge	3.5 days max: 5,000 $\mu$ A, 500 $\mu$ S, 240 s, Interval 24 hr, 20 Hz, $\pm$ 5.5 V

(54) The system may also be configured to limit the leakage and maximum and minimum charge densities, to protect the patient, as shown in Table 3:

(55) TABLE-US-00003 TABLE 3 safety parameters

Property	Value
Hardware DC Leakage	<50 nA
Protection Maximum Charge	30 $\mu$ C/cm.sup.2/phase
Density Maximum Current	30 mA/cm.sup.2

(56) In some variations, the system may also be configured to allow the following functions (listed in Table 4, below):

(57) TABLE-US-00004 TABLE 4 Additional functions of the microstimulator and/or controller(s)

Function	Details
Charging	Replenish Battery
Battery Check	Determine charge level
System Check	Self Diagnostics
Relative Temperature difference from Temperature baseline	Program
Read/Write/Modify a dosage Management parameter programs	Program Transfer entire dosage parameter
Up/Download programs	Electrode Bipolar Impedance (Complex) Impedances
Signal Strength	Strength of the charging signal to assist the patient in aligning the external Charge to the implanted Microstimulator.
Patient Parameters	Patient Information
Patient History	Limited programming and exception data
Implant Time/Zone	GMT + Time zone, 1 minute resolution, updated by Charger each charge session
Firmware Reload	Boot loader allows complete firmware reload
Emergency Stop	Disable dosing programs and complete power down system until Prescription Pad connected

(58) In some embodiments as shown in FIG. 11, a transcutaneous electrical nerve stimulator 50 can be used to stimulate the vagus nerve. An example of a transcutaneous electrocervical nerve stimulator is described in U.S. Pat. No. 8,843,210 to Simon et al., which is herein incorporated by reference in its entirety for all purposes. The transcutaneous electrical nerve stimulator can be used in place of the implanted microstimulator, or it can be used along with the implanted microstimulator. FIG. 11 illustrates one placement of the stimulator 50 to a target location on the patient's neck. For reference, locations of the following vertebrae are also shown: first cervical vertebra 71, the fifth cervical vertebra 75, the sixth cervical vertebra 76, and the seventh cervical vertebra 77.

(59) EEG Recording System

(60) FIG. 5 illustrates an EEG recording device 500 with electrodes 502 placed proximate the brain regions of interest, such the NB and/or LC, can be used to record the patient's EEGs. For example, one or more electrodes can be placed on the patient's forehead over the basal forebrain to record EEGs from the NB, while one or more electrodes can be placed on the lower back portion of the patient's head over the brainstem to record EEGs from the LC. P300 can be measured from electrodes being used to measure the NB and/or LC, and/or can be measured from electrodes placed over the parietal lobe. A baseline EEG can be recorded before VNS to serve as a comparison for EEGs measured after VNS.

(61) In some embodiments, the EEG recording device may be programmed to detect and analyze P300 and/or activation of the NB and/or LC. In some embodiments, the analysis of the data from



the EEG recording device can be accomplished with a separate computing device programmed to do the task. In some embodiments, the results of this analysis can be communicated to a controller that can adjust one or more stimulation parameters based on the analysis of P300 and/or activation of the NB and/or LC. The controller can be located on the microstimulator, the prescription pad, the energizer, the EEG recording device, or a separate computing device.

#### (62) Prescreening Patients Using EEG

(63) Activation of the Nucleus Basalis and/or the Locus coeruleus and/or detection of P300, all of which can be detected and/or measured with an EEG, can be used to prescreen subjects likely respond to VNS treatment prior to implantation. EEG recordings can be measured during or following stimulation of the auricular branch of the vagus nerve, or independent of any additional stimulus. The stimulation of the auricular branch of the vagus nerve can be accomplished through electrical stimulation or mechanical stimulation. In some embodiments, the stimulation can be noninvasive. For example, the electrical stimulation or mechanical stimulation can be delivered through the skin by a stimulation device placed on the skin surface of the ear. Alternatively, the stimulation can be invasive using, for example, a needle electrode to deliver electrical stimulation directly to the nerve.

(64) During or after stimulation of the auricular branch of the vagus nerve, EEG recordings can be taken of the NB and/or LC and the presence of P300 can be detected in the EEG recordings. In some embodiments, at least some of the EEG recordings can be taken after VNS without providing any other additional stimulation to elicit P300 or activity in the NB and/or LC. In some embodiments, at least some of the EEG recordings can be taken while eliciting P300 using a predetermined protocol, such as the auditory and/or visual stimulation oddball protocol. If the EEG recordings show activation of the NB and/or the LC and/or P300 is detected in the EEG recordings, then it is likely that the vagus nerve responded to the stimulation and the patient is a suitable candidate for VNS therapy. In some embodiments, for the analysis, a comparison can be made with reference to EEG recordings taken before VNS therapy.

(65) Use case example: A subject with rheumatoid arthritis is being screened for likelihood of response VNS treatment. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during electrical stimulation of the subject's auricular branch of the vagus nerve at maximum tolerated current intensity. The subject will pass the screen should P300 and/or activation of the Nucleus Basalis and/or the Locus coeruleus be detected.

#### (66) Long Term Potentiation

(67) It has been postulated that analogous to somatotopically organized brain regions that sense pain, there exists an immunological homunculus, whereby the immune system acts as a sensory organ that maps to specific regions within the central nervous system at the terminal of the afferent arm of the inflammatory reflex [7]. As activity within the NB and LC can be induced by VNS, and VNS induces long lasting plasticity within the auditory cortex via activation of the NB and LC, we reasoned that plasticity within the central neural reflexes, in part by this immunological homunculus may be induced by VNS activation of the NB and LC as well.

(68) Therefore, VNS activation of the NB and/or the LC can induce long term potentiation of the inflammatory reflex. Typical VNS parameters include an amplitude of 0.1-3 mA, frequency of 1 Hz-30 Hz, pulse width of 100  $\mu$ S-500  $\mu$ S, duration of 0.5 second to 10 minutes in duration. The off time between stimulations can be greater than 2, 4, 8, 12, 24, and 48 hours. These parameters are suitable for use in any of the embodiments described herein. For example, a 100  $\mu$ s charge balanced biphasic pulse can be delivered with a current of 0.8 mA as a train of 15 pulses at 30 Hz with a 500 ms train duration. The amplitude and other parameters can be ramped up over time, maintained at a constant level, or be modulated based on feedback, which can be based on NB and/or LC activity and/or detection of P300, for example. NB and/or LC and/or P300 activity can be detected by monitoring, measuring, and/or quantifying electrical activity from those brain regions with EEG

recordings.

(69) Feedback Control of VNS

(70) EEG measurements of P300, and/or EEG measurements to detect activation of the Nucleus Basalis and/or the Locus coeruleus can be used to provide immediate or rapid feedback on stimulation parameters during programming or reprogramming of an implanted VNS device. Various stimulation parameters may be increased, decreased or otherwise adjusted until activation of NB, LC or P300 is detected. Feedback control can be used in an open loops system or a closed loop system as described below.

(71) FIG. 6 illustrates a flow chart that describes a method for modulating vagus nerve stimulation using feedback from EEG recordings. For example, this flow chart can be used to treat a patient that is not responding well to VNS treatment. The vagus nerve can be stimulated in step **600** and then EEG recordings can be taken in step **602**. The EEG recordings can be taken during the VNS, and can also be taken after the VNS. Next, in step **604**, the EEG is analyzed for P300 and/or activation of the NB and/or LC. In some embodiments, the analysis can be performed by a physician, while in other embodiments, the analysis can be performed by a computing device with filters and algorithms tailored to detecting those specific EEG features. At step **606**, a decision is made based on the analysis in step **604** whether P300 is detected and/or activation of the NB and/or the LC is detected from the EEG recordings. If P300 and/or activation of the NB and/or the LC is not detected, then the VNS parameters are adjusted, by for example increasing the amplitude and/or the duration of the stimulation in step **608**. After the VNS parameters are adjusted, the process loops back to step **600**. If at step **606** it is determined that P300 is detected and/or activation of the NB and/or LC is detected, then the VNS parameters can be set to the current stimulation parameters. In some embodiments, this can be performed manually by the physician or health care provider, while in other embodiments, the parameters can be set automatically by a computing device performing the analysis of the EEG recordings.

(72) FIG. 7 illustrates a flow chart that describes another method for modulating vagus nerve stimulation using feedback from EEG recordings. This flow chart is particularly suited for reducing the intensity of the VNS treatment in a patient that is responding well to VNS. By reducing the intensity of the VNS treatment, the patient's pain can be reduced and comfort can be improved. In step **700**, the patient's response to VNS treatment is determined. If the patient is not responding well to VNS, then this treatment protocol is not suitable and the process ends in step **702**. If the patient is responding well to VNS, then the process proceeds to step **704** where EEG recordings are taken. Next, in step **706**, the physician or a computing device analyzes and characterizes the EEG recordings for P300 and/or activation of the NB and/or the LC. Then, in step **708**, the VNS parameters can be adjusted, by for example, decreasing the amplitude or the duration of the stimulation. In step **710**, the vagus nerve is stimulated using the adjusted parameters. In step **712**, another set of EEG recordings are taken. In step **714**, the EEG recordings can be analyzed and characterized to determine whether P300 and/or activation of the NB and/or LC are present and/or are above thresholds. The thresholds can be predetermined or can be based on the initial characterization of the EEG recordings performed in step **706**. If P300 and/or activation of the NB and/or LC is still detected and/or are still above the thresholds, then the process loops back to step **708** wherein the stimulation parameters can be further adjusted, for example, by again decreasing amplitude and/or duration. If in step **714**, P300 and/or activation of the NB and/or LC is not detected and/or falls below the threshold, then the stimulation parameters can be set to a previous set of stimulation parameters, as shown in step **716**, wherein P300 and/or activation of NB and/or LC were detected and/or above the threshold.

(73) FIG. 8 illustrates a flow chart that describes yet another method for modulating vagus nerve stimulation using feedback from EEG recordings. This flow chart is particularly suitable for a patient that is responding well to VNS therapy who wishes to increase the interval between stimulations (the off time). In step **800**, the patient is checked to determine whether the patient is

responding well to VNS. If not, the process is not suitable and is ended in step **802**. If the patient is responding well to VNS, the process proceeds to step **804** where EEG recordings are taken. In step **806**, the EEG recordings are analyzed and characterized for P300 and/or activation of the NB and/or LC. In step **808**, the vagus nerve stimulation parameters are adjusted by, for example, increasing the amplitude and/or duration. In step **810**, the vagus nerve can be stimulated using the adjusted parameters, and EEG recordings can be taken in step **812**. In step **814**, the EEG recordings are analyzed and characterized to determine whether P300 and/or activation of the NB and/or the LC is detected and/or above threshold values. The threshold values can be predetermined or can be determined based on a comparison with a baseline EEG, such as the EEG recordings taken in step **804** and analyzed and characterized in step **806**. If the determination in step **812** is that P300 and/or activation of the NB and/or the LC is not detected and/or falls below the threshold values, then the process loops back to step **808** where the VNS parameters are adjusted by, for example, further increasing the amplitude and/or duration. If the determination in step **812** is that P300 and/or activation of the NB and/or the LC is detected and/or falls above the threshold values, then the VNS parameters can be set to the current stimulation parameters and the off time between stimulations can be increased, as shown in step **816**. In some embodiments, the off time can be increased by at least 4, 6, 8, 12, 24, 36, or 48 hours.

(74) Use case example A: A subject with rheumatoid arthritis is not responding to VNS treatment. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during delivery of test doses. Stimulation dose will increase in intensity, such as amplitude, until change in P300 and activation of the Nucleus Basalis and/or the Locus coeruleus is detected. The physician will then program the applicable stimulation parameters for scheduled dosing.

(75) Use case example B: A subject with rheumatoid arthritis is responding well to once daily VNS treatment. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during delivery of test doses. Stimulation dose will decrease in intensity, such as amplitude, until change in P300 and activation of the Nucleus Basalis and/or the Locus coeruleus is detected. The physician will then program the applicable stimulation parameters for scheduled dosing.

(76) Use case example C: A subject with rheumatoid arthritis is responding well to once daily VNS treatment. The physician intends to decrease the weekly frequency of stimulation. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during delivery of test doses. Stimulation dose will increase in intensity, such as amplitude, until change in P300 and activation of the Nucleus Basalis and/or the Locus coeruleus is detected. The physician will then program a greater interval between doses of stimulation.

(77) A closed loop system can include an EEG device, an implantable nerve stimulator (e.g. vagus nerve), a prescription pad and an energizer. The EEG device can measure intracranial potentials and interpret P300, and/or activation of the Nucleus Basalis and/or the Locus coeruleus. The EEG device can communicate through wire or wirelessly, e.g. by Bluetooth protocol, to the prescription pad or energizer which programs stimulation parameters into the implantable nerve stimulator. A controller within the prescription pad, energizer, or EEG device can adjust one or more stimulation parameters, e.g. pulse width, pulse amplitude, pulse frequency, which can be programmed and carried out by the nerve stimulator. For example, the controller can be programmed to increase various stimulation parameters, such as amplitude, until P300 and/or activation of the NB and/or LC is detected by the EEG device. In some embodiments, the controller can be programmed to increase the interval, e.g. the off time, between doses of VNS when P300 and/or activation of the NB and/or LC is detected. In some embodiments, the controller can be programmed to decrease various stimulation parameters, such as amplitude, when P300 and/or activation of the NB and/or LC is detected.

(78) Deep Brain Stimulation and Transcranial Magnetic Stimulation

(79) In some embodiments, deep brain stimulation and/or transcranial magnetic stimulation of Nucleus Basalis and/or the Locus coeruleus can be used to treat chronic inflammatory disease, e.g. rheumatoid arthritis and Crohn's disease. As described above, stimulation of the NB and LC can be used to induce long term potentiation of the inflammatory reflex. In some variations, the deep brain stimulation and trans-cranial magnetic stimulation directly activates the anti-inflammatory reflex. In some embodiments, the deep brain stimulation and/or transcranial magnetic stimulation can be used in conjunction of VNS, while in other embodiments, it can be used without VNS to directly activate the inflammatory reflex through stimulation of the NB and LC. In some embodiments, if used with VNS, the deep brain stimulation and/or transcranial magnetic stimulation can be delivered prior to the VNS to first potentiate the inflammatory reflex before delivering the VNS. In other embodiments, if used with VNS, the deep brain stimulation and/or transcranial magnetic stimulation can be delivered concurrently with the VNS to potentiate the inflammatory reflex while delivering the VNS.

(80) FIG. 9 illustrates a deep brain stimulator **900** that can be implanted with electrodes **902**, **904** positioned at the NB and/or LC, thereby allowing the stimulator **900** to deliver electrical stimulation to the NB and/or LC. The stimulation can be delivered using stimulation parameters of about 10-10,000 uA, 50-500 Hz for 5-120 minutes per session. Sessions can be given at a frequency of twice/day, once/day, once/two days, once/three days, once/four days, once/five days, once/six days, and once/seven days, once/14 days, and once/month.

(81) In some embodiments, as illustrated in FIG. 10, a transcranial magnetic stimulator **1000** can be used to stimulate the NB and/or LC. The transcranial magnetic stimulator can have one or more coils **1002**, **1004** that generate a magnetic field for stimulating the NB and/or LC. The depth of penetration of the magnetic field can be tailored to focus the magnetic field on the NB and/or LC. The stimulation can be provided at either low frequency (<3 Hz) or high frequency (3-25 Hz) for 5 minutes to 120 minutes per session with a magnetic field of up to about 3 Tesla. Sessions can be given at a frequency of twice/day, once/day, once/two days, once/three days, once/four days, once/five days, once/six days, and once/seven days, once/14 days, and once/month.

(82) Use case example A: At least one electrode is implanted into the Nucleus Basalis and/or the Locus coeruleus of a subject with a chronic inflammatory disease, e.g. rheumatoid arthritis. The brain, specifically the NB and/or LC, is stimulated with electrical current, eg. 10-100 uA, 50-500 Hz for 5 minutes to 1 hr per session.

(83) Use case example B: A trans-cranial magnetic coil is oriented for stimulation into the Nucleus Basalis and/or the Locus coeruleus of a subject with a chronic inflammatory disease, e.g. rheumatoid arthritis. The brain, specifically the NB and/or the LC, is stimulated with at either low frequency (<3 Hz) or high frequency (3-25 Hz) for 5 minutes to 1 hr per session with a magnetic field of up to about 3 Tesla.

(84) It is understood that this disclosure, in many respects, is only illustrative of the numerous alternative device embodiments of the present invention. Changes may be made in the details, particularly in matters of shape, size, material and arrangement of various device components without exceeding the scope of the various embodiments of the invention. Those skilled in the art will appreciate that the exemplary embodiments and descriptions thereof are merely illustrative of the invention as a whole. While several principles of the invention are made clear in the exemplary embodiments described above, those skilled in the art will appreciate that modifications of the structure, arrangement, proportions, elements, materials and methods of use, may be utilized in the practice of the invention, and otherwise, which are particularly adapted to specific environments and operative requirements without departing from the scope of the invention. In addition, while certain features and elements have been described in connection with particular embodiments, those skilled in the art will appreciate that those features and elements can be combined with the other embodiments disclosed herein.

## Claims

1. A system for stimulating a nerve of a patient, the system comprising: an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of programmed stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of: a presence of P300, an activation of a nucleus basalis, and an activation of a locus coeruleus is indicated by the EEG, and adjust the set of programmed stimulation parameters based on the determination of whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG, wherein adjusting the set of programmed stimulation parameters includes decreasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of stimulation if the EEG indicates at least one of: the presence of P300, the activation of the nucleus basalis, and the activation of the locus coeruleus.
2. The system of claim 1, wherein the controller is located in a prescription pad.
3. The system of claim 1, wherein the controller is located in an energizer configured to provide power to the implantable nerve stimulator.
4. The system of claim 1, wherein the controller is located in the EEG recording device.
5. The system of claim 1, wherein the set of programmed stimulation parameters comprises a pulse amplitude, a pulse width, and a pulse frequency.
6. The system of claim 1, wherein the system is configured to induce long term potentiation of an inflammatory reflex in the patient.
7. The system of claim 1, wherein the controller is configured to wirelessly communicate with the implantable nerve stimulator.
8. The system of claim 1, wherein the implantable nerve stimulator is configured to be positioned around the nerve of the patient.
9. A system for stimulating a nerve of a patient, the system comprising: an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of programmed stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of: a presence of P300, an activation of a nucleus basalis, and an activation of a locus coeruleus is indicated by the EEG, and adjust the set of programmed stimulation parameters based on the determination of whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG, wherein adjusting the set of programmed stimulation parameters includes increasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of stimulation if the EEG does not indicate at least one of: the presence of P300, the activation of the nucleus basalis, and the activation of the locus coeruleus.
10. A system for stimulating a nerve of a patient, the system comprising: an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of a nucleus basalis and a locus coeruleus is activated as indicated by the EEG, and adjust the set of stimulation parameters based on the determination of whether at least one of the nucleus basalis and the locus coeruleus is activated as indicated by the EEG, wherein adjusting the set of stimulation parameters includes decreasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of stimulation if the EEG indicates activation of at least one of the nucleus basalis and the locus coeruleus, wherein the controller is configured to repeatedly determine whether at least one of the nucleus basalis and the

locus coeruleus is activated, and adjust the set of stimulation parameters until a dose of stimulation is at a level necessary to modulate an inflammatory reflex of the patient.

11. The system of claim 10, wherein the controller is configured to wirelessly communicate with the implantable nerve stimulator.

12. The system of claim 10, wherein the controller is located in a prescription pad.

13. The system of claim 10, further comprising an energizer configured to provide power to the implantable nerve stimulator.

14. The system of claim 13, wherein the energizer is configured to inductively charge the implantable nerve stimulator.

15. The system of claim 10, wherein the set of programmed stimulation parameters comprises a pulse amplitude, a pulse width, a pulse frequency, and a duration.

16. The system of claim 10, wherein the implantable nerve stimulator is configured to be positioned around the nerve of the patient.

17. A system for stimulating a nerve of a patient, the system comprising: an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of a nucleus basalis and a locus coeruleus is activated as indicated by the EEG, and adjust the set of stimulation parameters based on the determination of whether at least one of the nucleus basalis and the locus coeruleus is activated as indicated by the EEG, wherein the controller is configured to repeatedly determine whether at least one of the nucleus basalis and the locus coeruleus is activated, and adjust the set of stimulation parameters until a dose of stimulation is at a level necessary to modulate an inflammatory reflex of the patient, wherein adjusting the set of stimulation parameters includes increasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of the stimulation if the EEG does not indicate activation of at least one of the nucleus basalis and the locus coeruleus.

18. A system for stimulating a nerve of a patient, the system comprising: an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of a nucleus basalis and a locus coeruleus is activated as indicated by the EEG, and adjust the set of stimulation parameters based on the determination of whether at least one of the nucleus basalis and the locus coeruleus is activated as indicated by the EEG, wherein the controller is configured to repeatedly determine whether at least one of: the presence of P300, the activation of the nucleus basalis, and the activation of the locus coeruleus is indicated by the EEG, and adjust the set of stimulation parameters until a dose of stimulation is at a minimum level necessary to modulate an inflammatory reflex of the patient.

19. The system of claim 18, further comprising an energizer configured to provide power to the implantable nerve stimulator.

20. The system of claim 19, wherein the energizer is configured to inductively charge the implantable nerve stimulator.

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