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NEUROMODULATION SYSTEM

Background of the Invention

[0001] The present invention relates to a modulation system and in one particular example, to a neuromodulation system for modulating a nerve.

Description of the Prior Art

[0002] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[0003] The vagus nerve is made up of an intricate neural network that maintains homeostasis and equilibrium in important processes. Reciprocal neural connections with several brain areas serve as a control centre that responds to new information (stimulus) with appropriate adaptive feedback for modulation. The vagus nerve has four vagal nuclei that provide key controls to the cardiovascular, respiratory, and alimentary systems with respective neurotransmitters. It is tenth of twelve cranial nerves, being the main nerve interfacing with the parasympathetic division of the autonomic nervous system. Recent clinical studies have revealed that the vagus nerve is also involved in inflammation, mood, and pain regulation, all of which can be potentially modulated by stimulating or inhibiting nerve activity with micropulses of electrical current targeted to nerve fibres that signal the brain via the brainstem, known as neuromodulation.

[0004] The development of vagal neuromodulation and vagus nerve stimulation (VNS) as therapy began with the investigations of James Corning who developed the first basic functioning VNS device. In the late 1990's, after the success of several clinical trials illustrating the beneficial use of VNS for treatment resistant epilepsy and depression, the FDA approved its use for these applications. This illustrated the safe and effective use of this treatment modality.

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[0005] Stimulation of the vagus utilises several modulatory actions in the nervous, immune, autonomic, endocrine, cardiorespiratory, and gastrointestinal systems. The exact mechanisms of action in VNS are still being theorised however this has not hindered its ability to demonstrate safe and effective use for individuals suffering from conditions which interface vagal pathways. For example, vagus nerve stimulation therapies have already been approved by regulatory bodies for applications such as mood enhancement, pain relief, improving sleep and reducing anxiety; with investigations underway in assessing the cardiac and inflammatory modulation properties as well as those utilising effects of neuroplasticity.

[0006] In this regard, the vagus nerve is the main nerve of the parasympathetic division of the autonomic nervous system, which regulates unconscious processes in the body. The Parasympathetic Nervous System (PNS) is often referred to as the 'rest and digest' system, whereas the Sympathetic Nervous System (SNS) is thought of as the 'fight or flight' system. Stimulation of the vagus nerve has been shown to increase PNS activity/decrease SNS activity. Further through this regulation of metabolic homeostasis, the vagus nerve also controls heart rate, where increasing vagal activity has been associated with decreases in heart rate. This is significant as autonomic dysfunction, as characterised by an overactive SNS response, is thought to underpin several high impact chronic conditions, illustrating the value of an intervention which can modulate this.

[0007] Neurotransmitters are chemical substances released by nerve fiber impulses to surrounding areas of this electrical activity. Examples of neurotransmitters are Serotonin, Noradrenaline/Norepinephrine and Gamma-Aminobutyric acid (GABA). Research in this area indicates stimulating the vagus nerve can influence the release of neurotransmitters in the brain. Clinical studies indicate that VNS likely results in changes in serotonin, norepinephrine, GABA, and glutamate, these are all neurotransmitters implicated in the pathogenesis of major depression. This influence on neurotransmitters, along with a number of other theorised mechanisms, are thought to explain the mood enhancing effects arising from stimulation of the vagus nerve.

[0008] It is now understood that the nervous system reflexively regulates the inflammatory response in real time, in much the same way that it controls heart rate and other vital functions.

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This is thought to occur via the vagus nerve through a neural reflex mechanism known as the 'inflammatory reflex'. The brain receives signals from the immune system for the purposes of optimally controlling inflammation in the body, however, dysfunction in these signals can lead to excess inflammation. It has been observed that without vagus nerve activity (either due to a vagotomy or neural lesions) there is an absence of the inflammatory reflex which can result in excessive innate immune responses and cytokine toxicity (excessive inflammation). This led to clinical study and demonstration that stimulation of the vagus nerve can lead to decreases in inflammatory cytokines. The anti-inflammatory properties of (stimulating) the vagus nerve are thought to be through the Cholinergic Anti-inflammatory Pathway (CAP) as well as mediated through the Hypothalamic pituitary adrenal (HPA) axis. These insights have led to new opportunities in the treatment of inflammation through these selective and reversible 'hard-wired' neural systems.

[0009] Research towards the end of the 20th century has shown that many aspects of the brain can be altered, or are 'plastic', even through adulthood. Neuroplasticity is the brain's ability to restructure itself by generating new neural connections. It allows the neurons or nerve cells in the brain to compensate for injury or disease and amend their processes in response to new situations or environmental changes. The promotion of neuroplastic effects from VNS through alterations in central nervous system neurotransmitter levels and/or processing have led to greater focus on the use of VNS as therapy for stroke rehabilitation. This application utilises the mechanisms of 'targeted plasticity', by stimulating the vagus to promote neuroplasticity and pair this with a specific stimulus, eg. rehabilitative exercise (for stroke recovery), which targets this effect of plasticity in the specific region of the brain associated with each condition. This has led to outcomes such as accelerated and improved recovery from stroke.

[0010] Traditionally VNS as a treatment method has been limited by the need for surgical implantation. This ultimately restricted access geographically (centres specialising in the procedure), by condition severity (to warrant surgery), and financially (those who could afford the procedure). More recently a number of non-invasive devices have been proposed. Specifically, this can be achieved utilising the auricular branch of the vagus nerve which runs past the outer ear, allowing this to be used to provide non-invasive vagal neuromodulation (nVN). This method has now been shown to activate vagal pathways in the same way as with

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the surgical procedure, making it an accessible, low risk and lower cost route to vagal neuromodulation.

[0011] US 20050165460 describes a self-contained, portable headset carries a waveform source device and tissue interface circuits in a self-locating position for delivering treatment signals to a preselected area in the conch of the ear of a human subject. An electronics housing carries a waveform source device in communication with right and left tissue interface circuits, carried respectively in right and left earpiece housings. The headset carries each earpiece housing at a rearward and downward angle so that a protruding trunk enters the conch of the outer ear and contacts the conch generally below and rearwardly of the ear canal. An audio speaker delivers associated tones during treatment. An end wall of the trunk carries an array of electrodes contacts the preselected area in the conch of the ear.

[0012] US 10130809 describes an electrostimulation device includes a computer generating an electrostimulation generator control signal and outputting a music signal, a transcutaneous electrostimulation generator, an electronic signal conduit, and an electrode coupler. The generator receives the generator control signal and the music signal, generates a nerve electrostimulation signal dependent upon the generator control signal, and outputs the nerve electrostimulation signal at the stimulation output and the music signal at an audio output. The coupler fits in an ear canal, has a speaker connected to the audio output to output the music signal into the ear canal when worn, and has electrostimulation electrodes conductively connected to the stimulation output through the electronic signal conduit to receive the nerve electrostimulation signal and positioned to contact tissue within the canal to transcutaneously apply the nerve electrostimulation signal thereto. The coupler supplies the nerve electrostimulation signal while music outputs from the speaker.

[0013] US 8457765 describes an ear clip electrode used to conduct a minute amount of electricity from a stimulator to the ear lobes of a patient. The ear clip electrode is provided with an inner and outer plastic piece onto which separate metallic plates are placed. Both the metallic plate as well as the plastic pieces are provided with a circular end onto which a metallic pole is placed. Electrode pads are placed upon these metallic poles and electricity is conducted from each of the plates to the electrode pad and then to the patient's ear lobe. A plastic shroud is

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placed over a substantial length of each of the metallic plates. Plastic material also covers the end surface of each of the metallic poles. The ear clip electrode is connected to a source of minute electrical energy.

[0014] US 20070250145 describes a device (1) for transcutaneous stimulation of a nerve of the human body, which device (1) comprises at least one stimulation electrode (2) and at least one reference electrode (3) for transcutaneous nerve stimulation, the at least one stimulation electrode (2) and the at least one reference electrode (3) being connected to a control unit (4) and being able to be supplied with an electrical current from the latter, and the at least one stimulation electrode (2) and the at least one reference electrode (3) being arranged in or on a housing (5) which is designed to be fitted on or in the human ear. To make the nerve stimulation effective and to make it easier to manage for the patient, it is proposed, according to the invention, that the housing (5) has a bow-shaped extension piece (6) designed to be inserted into the auditory canal, said bow-shaped extension piece (6) matching the shape of the entrance to the auditory canal or of the external auditory canal, and with an electrode head (7) which is arranged at the end of the bow-shaped extension piece (6) and which has two contact points (8, 9) for the two electrodes (2, 3).

[0015] US 20180021564 describes a nerve stimulation system includes a headset and an earpiece which includes two or more ear-contacting elements, for example an ear canal insert, and a concha insert. Ear-contacting elements may be mounted onto an earpiece housing have projecting mounting structures, which provide mechanical and electrical connection between ear-contacting elements and housing through various materials and configurations. In an embodiment, a nerve stimulation system includes a neural stimulation subsystem including neural stimulation device control circuitry for use in combination with a personal computing device to control a neural stimulation device.

[0016] However, these typically require devices that electrically interface with internal and/or external surfaces of the concha, which can be uncomfortable for users, and difficult to achieve a device that remains in situ during use. Furthermore, the systems suffer from issues associated with safety, efficacy and usability. For example, some electrode configurations and current densities can give rise to skin burns, whilst others fail to achieve effective neurostimulation.

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Summary of the Present Invention

[0017] In one broad form, an aspect of the present invention seeks to provide a neuromodulation system for treating a condition, the system including: electrodes configured to be attached to a subject; and, a signal generator electrically connected to the electrodes, the signal generator being configured to generate at least one therapy signal that is applied to the subject via the electrodes to thereby modulate the nerve, and wherein the at least one therapy signal includes at least one sequence of different types of waveforms.

[0018] In one embodiment the at least one sequence of different types of waveforms includes: a single repeating sequence of different types of waveforms; multiple different sequences of waveforms; and, multiple repeating different sequences of waveforms.

[0019] In one embodiment the at least one sequence of different types of waveforms is at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; an autonomic dysfunction being treated; a responsiveness to treatment; biofeedback; and, user input.

[0020] In one embodiment the types of waveforms include at least one of: a rectangular pulse waveform; a triangular pulse waveform; a spike waveform; a sine waveform; a ramp waveform; an exponential ramp waveform; an exponential decay waveform; a burst waveform; an arbitrary waveform; a premodulated waveform; a linear waveform; an increasing or decreasing, zeta waveform; an increasing or decreasing sawtooth waveform; a direct current waveform; a damped sine waveform; a bi-sigmoidal waveform; a complex waveform; a pulse waveform; a square waveform; a random noise waveform; a custom waveform; a differential waveform; and, a rest.

[0021] In one embodiment the at least one therapy signal is triggered by at least one of: a user input; a sensor input; an electrical signal; a bioelectric signal; a movement of the subject; an audio signal; a vibration; and, a physiological state of the subject.

[0022] In one embodiment the at least one therapy signal at least one of: are symmetrical; are asymmetrical; are monophasic; are bi-phasic; are tri-phasic; are poly-phasic; and, include multiple phases with at least one interspersed dwell.

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[0023] In one embodiment the sequence of different types of waveforms includes at least a time interval between the different types of waveforms.

[0024] In one embodiment the time interval is at least one of: variable; fixed; 0 μ s; 0 μ s to 200000 μ s; 200 μ s to 2000 μ s; 100 μ s to 500 μ s; at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; an autonomic dysfunction being treated; a responsiveness to treatment; biofeedback; and, user input.

[0025] In one embodiment the sequence of different types of waveforms repeats, with a dwell time between each repeat.

[0026] In one embodiment the dwell time is at least one of: variable; fixed; 0 μ s; 1 μ s to 10000 μ s; 10000 μ s to 10000000 μ s; approximately 50000 μ s; and, at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; an autonomic dysfunction being treated; a responsiveness to treatment; biofeedback; and, user input.

[0027] In one embodiment at least one of: a magnitude of at least one of the different types of waveforms is at least one of: variable; fixed; at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; an autonomic dysfunction being treated; a responsiveness to treatment; biofeedback; and, user input; and, relative magnitudes of the waveforms in the sequence of different types of waveforms are at least one of: variable; fixed; at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; an autonomic dysfunction being treated; a responsiveness to treatment; biofeedback; and, user input.

[0028] In one embodiment at least one of: a duration of each waveform in the sequence of waveforms is at least one of: variable; fixed; 1 μ s to 20000 μ s; 200 μ s to 500 μ s; and, at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; a responsiveness to treatment; an autonomic dysfunction being treated; biofeedback; and, user input; and, relative durations of the waveforms in the sequence of different types of waveforms are at least one of: variable; fixed; at least one of selected and adjusted based on at least one of: a cardiovascular disease being treated; an autonomic dysfunction being treated; a responsiveness to treatment; biofeedback; and, user input.

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[0029] In one embodiment the sequence of different types of waveforms includes a first waveform followed by a second waveform.

[0030] In one embodiment at least one of: the first waveform has a longer duration than the second waveform; the first waveform has a shorter duration than the second waveform; the first waveform has the same duration as the second waveform; the first waveform has a greater magnitude than the second waveform; the first waveform has a lesser magnitude than the second waveform; and, the first waveform has the same magnitude as the second waveform.

[0031] In one embodiment the sequence of different types of waveforms includes a rectangular pulse waveform and an exponential ramp waveform.

[0032] In one embodiment the sequence of different types of waveforms includes a rectangular pulse waveform at a subthreshold, a spike waveform and an exponential decay waveform.

[0033] In one embodiment the rectangular pulse waveform is a pre-pulse at a subthreshold, In one embodiment the subthreshold is at least one of: less than a threshold; larger than 0% and less than 100% of a threshold; between 50% and 70% of a threshold; approximately 60% of a threshold; and, approximately 50% of a threshold.

[0034] In one embodiment the nerve modulation system is configured to stimulate the nerve to modulate at least one of: a presence, absence or concentration of an inflammatory biomarker; an electrocardiographic biomarker; a temperature; a blood oxygen level; a heart rate; a heart rate variability; an impedance; and, a galvanic skin response.

[0035] In one embodiment the condition includes at least one of: cardiovascular disease, including at least one of: a cardiovascular disease with an inflammatory phenotype; a coronary heart disease; a cerebrovascular disease; a peripheral arterial disease; a rheumatic heart disease; a congenital heart disease; an ischemic heart disease; an arrhythmia; atrial fibrillation; hypertension; heart failure with reduced ejection fraction; acute heart failure; heart failure with mildly reduced ejection fraction; heart failure with preserved ejection fraction; diastolic dysfunction; postural orthostatic tachycardia syndrome; myocardial infarction; and, stroke; chronic fatigue; long COVID; rheumatoid arthritis; autonomic nervous system dysfunction; dysautonomia; mental health disorders; inflammatory disorders; autoimmune disorders;

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cognitive dysfunction; post viral syndromes including long COVID; pain disorders; stress including acute stress and chronic stress; post-traumatic stress disorder; systemic lupus erythematosus; diabetes; and, cancer.

[0036] In one embodiment the system enhances at least one of: concomitant therapy delivery; cognition; memory; mobility; physical performance; recovery after physical activity; sleep quality; and, divergent thinking.

[0037] In one embodiment the nerve is at least one of: a cranial nerve including at least one of Cranial nerve I to XII; a vagus nerve, including at least one of: an auricular branch; a cervical branch; an efferent branch; and, an afferent branch; a central neural nerve; and, a peripheral nerve, including at least one of: a median nerve; and, a radial nerve.

[0038] In one embodiment the signal generator modulates the nerve including modulating at least one target of the nerve.

[0039] In one embodiment the at least one target of the nerve includes: an auricular branch of the nerve; a cervical branch of the nerve; a radial branch of the nerve; a specific neural fibres; efferent fibres; afferent fibres; A-alpha ($A\alpha$) fibres; A-beta ($A\beta$) fibres; A-delta ($A\delta$) fibres; B fibres including at least a myelinated B fibres; and, C fibres.

[0040] In one embodiment the electrodes are configured to be attached to the subject in a form of at least one of: a clip; a collar; a wrist band; a headband; an earpiece; an auricular attachment; a textile attachment; a handheld attachment; an ankle band; a ring; a wearable piece; a wearable jewellery; a neckpiece; and, invasively.

[0041] In one embodiment the electrodes are configured to be attached to an ear of the subject via an attachment, wherein the attachment includes a housing biased against the ear and is positioned proximate to a target nerve of the subject.

[0042] In one embodiment the electrodes are configured to be attached to a tragus of the subject, the attachment or earpiece including: opposing arms configured so that a distal end of the arms are biased towards each other; and, the electrodes positioned proximate a distal end

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of the arms on opposing faces so that the electrodes are urged into engagement with opposing faces of the tragus.

[0043] In one embodiment the system includes a hook extending over and behind an ear of the subject to at least partially support the attachment.

[0044] In one embodiment the hook is configured to extend laterally from the earpiece so that the lead can loop over and behind an ear of the subject.

[0045] In one embodiment the system includes a lead extending from the earpiece, the lead including connections configured to electrically connect the electrodes to the signal generator.

[0046] In one embodiment the lead is configured to extend laterally from the earpiece so that the lead can loop over and behind an ear of the subject.

[0047] In one embodiment the lead is configured to extend from a distal end of one of the arms.

[0048] In one embodiment the lead includes a sheath extending at least part way along a length of the lead and wherein the sheath defines a hook shaped to loop over and behind an ear of the subject.

[0049] In one embodiment one of the arms is configured to be positioned within a concha of the user.

[0050] In one embodiment the arms are pivotally connected about a mid-portion.

[0051] In one embodiment a distal ends of the arms are biased together using a biasing mechanism.

[0052] In one embodiment the biasing mechanism includes at least one of: a pivot; a spring; a rubber member; a malleable member interconnecting the arms; at least partially malleable arms; an at least partially elastic member interconnecting the arms; at least partially elastic arms; and, magnets provided on the arms.

[0053] In one embodiment a proximal outer face of the arms include a depression configured to allow a subject to engage the arms and bias the arms apart.

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[0054] In one embodiment the arms have at least one of: a length that is at least one of: greater than 15mm; greater than 16mm; greater than 17mm; greater than 18mm; greater than 19mm; greater than 20mm; greater than 21mm; less than 30mm; less than 28mm; less than 27mm; less than 26mm; less than 25mm; less than 24mm; less than 23mm; and, about 22mm; and, a width that is at least one of: greater than 5mm; greater than 6mm; greater than 7mm; greater than 8mm; greater than 9mm; greater than 10mm; less than 16mm; less than 15mm; less than 14mm; less than 13mm; less than 12mm; and, about 11mm.

[0055] In one embodiment the electrodes are: substantially circular; rounded rectangular; rounded square; at least partially dome shaped; and, have a diameter of at least one of: greater than 4mm; greater than 5mm; greater than 6mm; greater than 7mm; less than 12mm; less than 11mm; less than 10mm; less than 9mm; and, about 8mm.

[0056] In one embodiment a surface of the electrodes at least one of: is roughened; includes grooves; includes ridges; and, is coated.

[0057] In one embodiment a surface of the electrodes is coated with at least one of: an inert metal; and, gold.

[0058] In one embodiment therapy signals are signals having a frequency that is at least one of: less than 20kHz; less than 10kHz; less than 1Hz; less than 500Hz; less than 200Hz; less than 150Hz; less than 100Hz; less than 75Hz; greater than 1Hz; greater than 2Hz; greater than 5Hz; greater than 10Hz; greater than 20Hz; about 20Hz; and, about 50Hz.

[0059] In one embodiment therapy signals are signals having a pulse width of at least one of: less than 5,000µs; less than 2,500µs; less than 1,000µs; less than 500µs; less than 200µs; less than 100µs; less than 75µs; greater than 1µs; greater than 2µs; greater than 5µs; greater than 10µs; greater than 20µs; and, about 50µs.

[0060] In one embodiment the therapy signals are signals having a voltage that is at least one of: less than 50V; less than 25V; less than 10V; less than 5V; less than 2V; less than 1V; greater than 0.1V; greater than 0.2V; greater than 0.5V; and, greater than 1V.

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[0061] In one embodiment the therapy signals are signals having a current that is at least one of: less than 50mA; greater than 0.1mA; and, between 0.1mA and 36mA.

[0062] In one embodiment the therapy signals at least one of: are symmetrical; are asymmetrical; are monophasic; are bi-phasic; are tri-phasic; are poly-phasic; and, include multiple phases with at least one interspersed dwell.

[0063] In one embodiment a respective therapy signal is applied to each of the electrodes.

[0064] In one embodiment the respective therapy signals are at least one of: in phase; and, out of phase.

[0065] In one embodiment the lead includes at least one of: a respective conductor for each electrode; at least one insulating layer; and, a braided shield.

[0066] In one embodiment the therapy signals are configured to at least one of: stimulate activity of the vagus nerve; and, inhibit activity of the vagus nerve.

[0067] In one embodiment the signal generator is mounted on the earpiece.

[0068] In one embodiment the system includes a control system having a housing containing at least one of: the signal generator; a power supply; and, a controller.

[0069] In one embodiment a lead extends from the earpiece to the housing.

[0070] In one embodiment the system includes a controller configured to control the signal generator.

[0071] In one embodiment the controller is configured to: determine therapy signal parameters; and, control the signal generator in accordance with the therapy signal parameters.

[0072] In one embodiment the controller is configured to determine the therapy signal parameters in accordance with at least one of: defined therapy signal parameters stored in a memory; user input commands; biofeedback; signals from a sensor; and, a selected therapy mode.

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[0073] In one embodiment the system includes a sensor configured to sense at least one subject parameter and In one embodiment the controller is configured to: determine at least one subject parameter using signals from the sensor; and, cause the signal generator to generate therapy signals in accordance with the at least one subject parameter.

[0074] In one embodiment the sensor is at least one of: mounted on the earpiece proximate at least one electrode; and, electrically coupled to at least one of the electrodes.

[0075] In one embodiment the sensor is at least one of: an inflammatory biomarker sensor; a temperature sensor; a blood oxygen sensor; a pulse oximeter; a heart rate sensor; and, an impedance sensor.

[0076] In one embodiment the at least one subject parameter includes at least one of: a presence, absence or concentration of an inflammatory biomarker; a temperature; a blood oxygen level; a heart rate; a heart rate variability; an impedance; and, a galvanic skin response.

[0077] In one embodiment the controller is configured to: determine feedback using user input commands; and, cause the signal generator to generate the therapy signals in accordance with the feedback.

[0078] In one embodiment the controller is configured to: cause the signal generator to generate therapy signals having progressively increasing magnitudes; and, selecting a therapy signal magnitude in response to user input commands.

[0079] In one embodiment the controller is configured to progressively increase the therapy signal in steps of at least one of: 0.1mA; 0.2mA; 0.5mA; 0.8mA; 1mA; 1.5mA; and, 2mA.

[0080] In one embodiment the controller is configured to: determine selection of a therapy mode in accordance with user input commands; and, control the signal generator in accordance with the selected mode.

[0081] In one embodiment the system includes a number of therapy modes stored in a store, each therapy mode defining a sequence of therapy signals and wherein the controller is configured to cause the signal generator to generate the sequence of therapy signals.

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[0082] In one embodiment in a research mode the controller is configured to: selecting a therapy signal magnitude in response to user input commands; and, progressively decrease the therapy signal magnitude to zero.

[0083] In one broad form, an aspect of the present invention seeks to provide a neuromodulation method for treating a condition, the method including: placing electrodes to be approximate to a subject; and, using a signal generator electrically connected to the electrodes to generate at least one therapy signal that is applied to a nerve via the electrodes to thereby modulate the nerve, and In one embodiment the at least one therapy signal includes at least one sequence of different types of waveforms

[0084] It will be appreciated that the broad forms of the invention and their respective features can be used in conjunction and/or independently, and reference to separate broad forms is not intended to be limiting. Furthermore, it will be appreciated that features of the method can be performed using the system or apparatus and that features of the system or apparatus can be implemented using the method.

Brief Description of the Drawings

[0085] Various examples and embodiments of the present invention will now be described with reference to the accompanying drawings, in which: -

[0086] Figure 1A is a schematic plan view of an example of a vagus nerve modulation system;

[0087] Figure 1B is a schematic side view of the nerve modulation system of Figure 1A;

[0088] Figure 1C is a schematic plan view of the earpiece of Figure 1A in use;

[0089] Figure 1D is a schematic side view of the earpiece of Figure 1A in use;

[0090] Figure 2 is a schematic diagram of an example of a control system for the nerve modulation system of Figure 1A;

[0091] Figure 3 is a flow chart of an example of a neuromodulation process;

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[0092] Figure 4A is schematic side view of a specific example of an earpiece for a vagus nerve modulation system;

[0093] Figure 4B is a schematic plan view of the earpiece of Figure 4A;

[0094] Figure 4C is a schematic perspective view of the earpiece of Figure 4B;

[0095] Figure 4D is a schematic front view of the earpiece of Figure 4A;

[0096] Figure 4E is a schematic rear view of the earpiece of Figure 4A;

[0097] Figure 4F is a schematic close up view of a pivot of the earpiece of Figure 4A;

[0098] Figure 4G is a schematic plan view of the earpiece of Figure 4A in use;

[0099] Figure 5A is a schematic perspective view of an example of a control system;

[0100] Figure 5B is a schematic side view of the control system of Figure 5A;

[0101] Figure 5C is a schematic plan view of the control system of Figure 5A;

[0102] Figure 6 is a schematic diagram of a second example of a control system for a neuromodulation system;

[0103] Figure 7 is a flow chart of a specific example of a neuromodulation process;

[0104] Figure 8 is a schematic diagram of a neuromodulation system;

[0105] Figure 9 is a flow chart of an example of a neuromodulation process;

[0106] Figure 10 illustrates results of an example of a neuromodulationsystem and process; and,

[0107] Figures 11A to 11AE are schematic diagrams of example therapy signal waveforms.

Detailed Description of the Preferred Embodiments

[0108] An example of a neuromodulation system 800 will now be described with reference to Figure 8.

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[0109] In this example, the neuromodulation system 800 for treating a condition. The system 800 includes electrodes 821, 822 configured to be attached to a subject and a signal generator 830 electrically connected to the electrodes 821, 822, for example via respective connections 831, 832. The signal generator 830 is configured to generate at least one therapy signal that is applied to the subject via the electrodes 821, 822 to thereby modulate the nerve.

[0110] Thus, in use, the system is configured to be attached to a subject for modulating a nerve. As a result, therapy signals applied to the electrodes 821, 822 are applied to the nerve, which in turn results in an electric field being generated surrounding the nerve. This field can elicit or inhibit action potentials, in turn leading to modulation of the nerve. The signal is typically applied to the subject in a location where part of a nerve, such as the vagus nerve is near the surface of the subject, thereby maximising the modulation. Example locations for neuromodulation include the ear, tragus, cymba concha, wrist, back, and neck for vagus nerve, median nerves, radial nerves or other target nerves. In one example, locations for vagus nerve modulation may include the tragus and/or neck, and locations for the median or radial nerves may include the wrist and these locations may be used at the same time.

[0111] The at least one therapy signal includes at least one sequence of different types of waveforms. The nature of the different waveforms will vary depending on the implementation and the type of modulation to be performed, and examples of this will be described in more detail below. It will be appreciated that the different waveforms can be configured to provide a different modulatory effect, and so the use of a sequence of different waveforms can enhance the effectiveness of the modulation and allow different conditions to be more effectively targeted.

[0112] Accordingly, the therapy signal of a sequence of waveforms including multiple types of waveforms is applied to the nerve of the subject to modulate the nerve, and to modulate a subject parameter, which in turn can be used to treat conditions such as cardiovascular disease and/or an autonomic dysfunction.

[0113] The above arrangement can help maximising neural recruitment and/or improve parasympathetic activation while minimising side effects, such as discomfort, or burns. Additionally, the above described arrangement increases 'memory effect' of the therapy, and

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helps maintain safety and efficacy. 'Memory effect' may be described as the length of time that treatment effects are experienced after treatment has ceased. A longer memory effect can have advantages in that a shorter duration of treatment may be required or intervals between treatment sessions can be extended. In one example, a triggered treatment may be 1 minute, followed by a rest interval. The rest interval may be between 1 minute and 18 hours, typically 30 minutes. In this regard, by optimising the effectiveness of signal application, this ensures the correct modulation is achieved, avoiding over or under activation of subject parameters which can lead to adverse consequences.

[0114] Accordingly, the above described arrangement provides a neuromodulation system that can be used to modulate the nerve and treat a cardiovascular disease and/or an autonomic dysfunction, which is comfortable and easy to use over prolonged periods of time, and thereby allowing users to more readily avail themselves to the benefits of neuromodulation, whilst avoiding risk, safety and efficacy issues, such as burns and/or unsafe or ineffective levels of current delivery.

[0115] An example of a process for performing neuromodulation will now be described with reference to Figure 9.

[0116] When in use, the electrodes 821, 822 are placed to be approximate to a subject at step 900. The signal generator 830 is electrically connected to the electrodes 821, 822. At step 910, the signal generator 830 is used to generate a therapy signal, which is applied to a nerve of the subject via the electrodes 821, 822. As a result, the nerve is modulated at step 920 by the therapy signal.

[0117] A number of further features will now be described.

[0118] In one example, the sequence of different types of waveforms includes a single repeating sequence of different types of waveforms. In this example, the sequence may be a sequence of a rectangular waveform followed by a ramp waveform, and this particular sequence is repeated. In another example, the sequence of different types of waveforms includes multiple different sequences of waveforms, where different sequences of different types of waveforms are applied. Additionally or alternatively, the sequence may be multiple

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repeating different sequences of waveforms, where different sequences of different types of waveforms are repeatedly applied.

[0119] In one example, the sequence of different types of waveforms can be selected and/or adjusted, for example selecting the particular waveforms used and the order in which these are applied. The selection and/or the adjustment may be performed in any appropriate manner and could be based on at least one of a condition, such as a cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback and/or user input. So for example, an initial sequence of waveforms might be selected to treat a particular condition, with the sequence being subsequently adjusted, for example by changing one or more of the waveforms, based on biofeedback and/or user input, depending on how effective the modulation proves to be.

[0120] In one example, the types of waveforms include at least one of a rectangular pulse waveform, a triangular pulse waveform, a spike waveform, a sine waveform, a ramp waveform, an exponential ramp waveform, an exponential decay waveform, and a burst waveform an arbitrary waveform; a premodulated waveform; a linear waveform; an increasing or decreasing, zeta waveform; an increasing or decreasing sawtooth waveform; a direct current waveform; a damped sine waveform; a bi-sigmoidal waveform; a complex waveform; a pulse waveform; a square waveform; a random noise waveform; a custom waveform; a differential waveform. Example waveforms will be described hereinafter in more detail and it will be appreciated that a range of different waveforms could be used.

[0121] In one example, therapy signal is triggered by at least one of a user input, a sensor input, an electrical signal, a bioelectric signal, a movement of the subject, an audio signal, a vibration, and a physiological state of the subject including respiratory cycle.

[0122] In one example, the therapy signal is at least one of symmetrical, asymmetrical, monophasic, bi-phasic, tri-phasic, and poly-phasic. The therapy signal may also include multiple phases with an interspersed dwell.

[0123] In one example, the sequence of different types of waveforms includes at least a time interval between the different types of waveforms. In one example, the time interval is variable

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or fixed, and could be any suitable time, such as 0 μ s, 0 μ s to 200000 μ s, 200 μ s to 2000 μ s, or 100 μ s to 500 μ s. Additionally, different time intervals may differ between different waveforms in the sequence, for example with the time interval between first and second waveforms being greater than or less than an interval between second and third waveforms. In one example, the time interval is selected and/or adjusted based on at least one of a condition, such as cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback, and/or user input. In the example where the time interval is adjusted based on biofeedback, the time interval may be adjusted algorithmically to mimic, synchronise or complement physiological patterns, such as the cardiac cycle and respiratory cycle.

[0124] In one example, the sequence of different types of waveforms repeats, with a dwell time between each repeat. In one example, the dwell time is at least one of variable, fixed, and 0 μ s, 1 μ s to 10000 μ s; 10000 μ s to 10000000 μ s, or around 50000 μ s. In one example, the dwell time is selected and/or adjusted based on at least one of a condition, such as cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback, and/or user input. In the example where the dwell time is adjusted based on biofeedback, the dwell time may be adjusted algorithmically to mimic, synchronise or complement physiological patterns, such as the cardiac cycle and respiratory cycle. In one example, the dwell time is stochastically determined, which has the benefit of preventing or minimising neural habituation and/or a prolonged and increased therapeutic benefit.

[0125] In one example, a magnitude of the different types of waveforms is variable and/or fixed. In one example, a magnitude is selected and/or adjusted based on at least one of a cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback, and/or user input. In one example, magnitudes of the waveforms in the sequence of different types of waveforms are controlled relative to one another. The relative magnitudes are variable and/or fixed. In one example, the relative magnitudes are selected and adjusted based on at least one of a condition such as cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback, and/or user input. For example, a first waveform in the sequence might have a lower magnitude than a second waveform, which might in turn have a greater magnitude than a third waveform. This can be used to provide greater control to the modulation, for example, priming the nerve before

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applying the modulation, or using a trailing modulation to increase the impact of the modulation. These relative magnitudes might be initially selected based on the condition being treated, and then adjusted based on biofeedback, to thereby optimise the magnitudes for the condition and subject being treated.

[0126] In one example, a duration of each waveform in the sequence of waveforms is at least one of variable or fixed, and could have a suitable duration, such as 1 μ s to 20000 μ s, or 200 μ s to 500 μ s. In one example, the duration may be depending on factors such as amplitude and frequency which influence overall charge delivery and tolerability. In one example, the duration is at least one of selected and adjusted based on at least one of a condition, such as cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback, and/or user input. In one example, durations of the waveforms in the sequence of different types of waveforms are relative to one another and these relative durations may be variable and/or fixed. Again, the relative duration can be selected and adjusted based on at least one of a condition, such as cardiovascular disease being treated, an autonomic dysfunction being treated, a responsiveness to treatment, biofeedback, and/or user input. For example, a first waveform in the sequence might have a lower duration than a second waveform, which might in turn have a greater duration than a third waveform. These durations might be initially selected based on the condition being treated, and then adjusted based on biofeedback, to thereby optimise the magnitudes for the condition and subject being treated.

[0127] In one example, the sequence of different types of waveforms includes a first waveform followed by a second waveform. In one example, the first waveform has a longer duration than the second waveform, the first waveform has a shorter duration than the second waveform, the first waveform has the same duration as the second waveform, the first waveform has a greater magnitude than the second waveform, the first waveform has a lesser magnitude than the second waveform, and/or the first waveform has the same magnitude as the second waveform.

[0128] In one example, the sequence of different types of waveforms includes a rectangular pulse waveform and an exponential ramp waveform. In one example, the sequence of different types of waveforms includes a rectangular pulse waveform at a subthreshold, a spike waveform and an exponential decay waveform.

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[0129] In one example, the rectangular pulse waveform is a pre-pulse at a subthreshold, wherein the subthreshold is a percentage of a threshold. In one example, a threshold is the limit after which nerve fibres or a substantial percentage of larger nerve fibres are excited. A subthreshold is an amplitude below the threshold, particularly, a subthreshold can be an amplitude that is larger than 0% and less than 100% of the threshold. In one example, the subthreshold is 60% of the threshold. In one example, the rectangular pulse waveform at a subthreshold is acting as a pre-pulse for depolarising nerve fibres. The sequence includes a pre-pulse at a subthreshold with the purpose of depolarising nerve fibres, so that the nerve and/or fibres are conditioned with a subthreshold current to inactivate the voltage-dependent sodium channel and increase the excitation threshold of particular fibres. This may also aide in selection of nerve fibres following the pre-pulse. A subthreshold pre-pulse may help to selectively activate or select for specific nerve fibres. This may come with limitations including potential of neural habituation. To address this, the subthreshold waveforms may be selected or delivered stochastically, such as selectively stochastic or adaptively stochastic. This allows prevention or minimising of neural habituation and prolonging treatment effect, also known as the 'memory effect' where the therapeutic benefits are experienced for longer. In one example, the parasympathetic activation may have a longer duration post signal delivery.

[0130] In one example, the neuromodulation system is configured to stimulate the nerve and thereby modulate at least one of a presence, absence or concentration of an inflammatory biomarker, an electrocardiographic biomarker, a temperature, a blood oxygen level, a heart rate, a heart rate variability, an impedance, and a galvanic skin response. In this instance, it will be appreciated that sensing of these parameters and how they respond to modulation can in turn be used to provide biofeedback and thereby control the modulation process, thereby refining the modulation to make it more effective.

[0131] In one example, the condition includes at least one of cardiovascular disease, chronic fatigue, long COVID, rheumatoid arthritis, autonomic nervous system dysfunction, dysautonomia; mental health disorders, inflammatory disorders, autoimmune disorders, cognitive dysfunction, post viral syndromes including long COVID, pain disorders, stress including acute stress and chronic stress, post-traumatic stress disorder, systemic lupus erythematosus, diabetes; and cancer. Additionally, the cardiovascular disease includes at least

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one of a cardiovascular disease with an inflammatory phenotype, a coronary heart disease, a cerebrovascular disease, a peripheral arterial disease, a rheumatic heart disease, a congenital heart disease, an ischemic heart disease; an arrhythmia, atrial fibrillation, hypertension, acute heart failure, heart failure with reduced ejection fraction, heart failure with mildly reduced ejection fraction, heart failure with preserved ejection fraction, diastolic dysfunction, postural orthostatic tachycardia syndrome, myocardial infarction and stroke.

[0132] In one example, the system enhances at least one of concomitant therapy delivery, cognition, memory, mobility, physical performance, recovery after physical activity, sleep quality, and divergent thinking.

[0133] In one example, the nerve is at least one of a vagus nerve, a central neural nerve, and a peripheral nerve. In one example, the vagus nerve includes at least one of an auricular branch, a cervical branch, and an afferent branch of the vagus nerve. In one example, the peripheral nerve includes at least one of a median nerve and a radial nerve.

[0134] In one example, the signal generator modulates the nerve including modulating at least one target of the nerve. In one example, the target of the nerve or the neural target includes an auricular branch of the nerve, a specific neural fibres, efferent fibres, afferent fibres, A-alpha ($A\alpha$) fibres, A-beta ($A\beta$) fibres, A-delta ($A\delta$) fibres, B fibres including a myelinated B fibres, and C fibres.

[0135] In one example, the electrodes may be of any non-invasive form being configured to be attached proximal to nerves of the subject. In one example, the electrodes are configured to be attached to the subject in a form of at least one of a clip, a collar, a wrist band, a headband, an earpiece, an auricular attachment, a textile attachment, a handheld attachment an ankle band, a ring, a wearable piece, a wearable jewellery, and a neckpiece. These can be used to target specific areas where the vagus nerve is more effectively modulated by external modulation applied to the skin of the subject. In one example, the attachment is at least one of directly attached to the subject, indirectly attached to the subject, directly in contact with skin of the subject, and indirectly in contact with skin of the subject

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[0136] In one example, the electrodes are configured to be attached to an ear of the subject via an attachment. The attachment includes a housing that is biased against the ear and is positioned proximate to a target nerve of the subject.

[0137] An example of a vagus nerve modulation system will now be described with reference to Figure 1A to 1D.

[0138] In this example, the nerve modulation system 100 includes an earpiece 110 having opposing arms 111, 112, with electrodes 121, 122 positioned proximate a distal end of the arms on opposing faces, which are biased towards each other. In this example, the arms are pivotally connected via a connecting hinge 113, whilst a resilient member, such as a spring, rubber stop, or the like, is provided, which is configured to bias the distal end of the arms towards each other. However, as will be described in more detail below, other configurations could be used. In this regard, it will therefore be appreciated that the term earpiece is intended to cover any arrangement in which spaced apart arms are provided that can be biased together at distal ends, and the example arrangements described herein are not intended to be limiting.

[0139] A signal generator 130 is electrically connected to the electrodes 121, 122, for example via respective connections 131, 132, with the signal generator 130 being configured to generate at least one therapy signal, which can then be applied to the subject via the electrodes 121, 122.

[0140] In use, the earpiece is configured to be attached to a tragus of a subject, and an example of this will now be described with reference to Figures 1C and 1D.

[0141] In this example, a subject's ear 100 is shown, including a tragus 101, an inferior crus 102, a superior crus 103, a helix 104, a scapha 105, an antihelix 106, a concha 107, an antitragus 108 and a lobule 109. As shown, the earpiece 110 is positioned so that the tragus 101 is provided between the electrodes 121, 122, with the electrodes 121, 122 being urged into engagement with opposing faces of the tragus by virtue of biasing of the arms 111, 112.

[0142] As a result of this configuration, therapy signals applied to the electrodes 121, 122 are applied to the tragus, which in turn results in an electric field being generated surrounding the vagus nerve within the tragus 101. This field can create or inhibit action potentials within the tragus, in turn leading to modulation of the vagus nerve.

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[0143] Accordingly, the above described nerve modulation system operates to stimulate the vagus nerve within the tragus utilising an earpiece 110 which is attached to the tragus 101 of a subject in use. The earpiece includes electrodes 121, 122 on opposing biased arms 111, 112, so that the tragus 101 can be positioned between the electrodes, with the electrodes 121, 122 being urged into engagement with the tragus 101. In this manner, the electrodes 121, 122 grip the tragus, which helps ensure good electrical contact with the tragus 101 thereby maximising the effectiveness of modulation of the vagus nerve. Additionally, having the electrodes grip the tragus also assists in securing the earpiece in place, allowing the earpiece to be worn for a prolonged period of time, thereby ensuring the stimulation signals are successfully applied to the vagus nerve throughout a stimulation session.

[0144] The configuration of the electrodes provided on opposing arms, also leads to the electrodes being provided in a substantially parallel spaced configuration, with electrodes on either side of the tragus. This configuration can allow for an increased electrode surface area, which combined with the substantially parallel positioning, maximises the field generated for a given current density at the electrode / tissue interface.

[0145] Accordingly, the above arrangement can help ensure the applied therapy signals are able to generate a therapeutic effect whilst avoiding current densities that can cause discomfort to the subject, for example by causing burns. Additionally, the above described arrangement helps maintain safety and efficacy. In this regard, by optimising the effectiveness of signal application, this ensures the correct stimulation is achieved, avoiding over or under stimulation, which can lead to adverse consequences, such as bradycardia.

[0146] Furthermore, in one example, the above described arrangement allows the earpiece 110 to be at least partially positioned within the concha 107, which provides a number of benefits. For example, this guides positioning of the earpiece 110 so that the electrodes are correctly positioned relative to the tragus and vagus nerve, thereby ensuring the nerve is effectively modulated. Additionally, this arrangement reduces the extent to which the earpiece projects outwardly from the ear, making the earpiece unobtrusive and comfortable to wear. For example, this allows the earpiece to be worn while the user is laying on their side, whilst also

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reducing the risk of the earpiece being dislodged, which can in turn affect the stimulation process.

[0147] Accordingly, the above described arrangement provides a non-invasive vagus nerve stimulation system that can be used to modulate the vagus nerve and/or improve parasympathetic activation, but which is comfortable and easy to use over prolonged periods of time, thereby allowing users to more readily avail themselves to the benefits of vagus nerve stimulation, whilst avoiding risk, safety and efficacy issues, such as burns and/or unsafe or ineffective levels of neurostimulation.

[0148] A number of further features will now be described.

[0149] In one example, the system includes a hook extending over and behind an ear of the subject, to at least partially support the earpiece. The hook can be of any appropriate form, but is typically made from an at least partially resilient material which retains its shape whilst being comfortable to wear. The hook can be attached to any part of the earpiece, but in one example is configured to extend laterally from the earpiece so that the hook can loop over and behind the ear of the subject. The hook can help distribute the weight of the earpiece across the ear, so that the weight is not solely supported by the tragus. Additionally, this provides a secondary attachment mechanism, helping reduce the likelihood of the earpiece being dislodged, and preventing the earpiece falling to the ground in the event of dislodgment, in turn helping to reduce the chance of damage to the earpiece. Furthermore, this also helps guide correct positioning of the earpiece, ensuring the electrodes are aligned with the vagus nerve, in turn optimising the effect of the applied therapy signals.

[0150] In one example, the system includes a lead extending from the earpiece, with the lead including the connections that are configured to electrically connect the electrodes to the signal generator. This allows the signal generator to be provided remotely to the earpiece and connected thereto via the connections. This can reduce the weight of the earpiece, although this is not essential and alternative embodiments could be provided, as will be described in more detail below.

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[0151] In one particular example, the lead is configured to extend laterally from the earpiece, so that the lead can loop over and behind an ear of the subject, thereby allowing the lead to help secure the earpiece in place. It will be appreciated that in this instance, the lead can act to provide the hook functionality outlined above, thereby helping to reduce weight loading on the tragus and minimising the likelihood and adverse effects of earpiece dislodgement.

[0152] In one example, the lead can be configured to extend from a distal end of an outer one of the arms. This helps secure the earpiece in place, whilst leaving a proximal end of the arms unimpeded, which can facilitate application of the earpiece to the tragus. Additionally, this further aligns the lead with the tragus and directs the lead to more easily extend behind the helix, making the earpiece more comfortable to wear and helping ensure correct positioning of the earpiece.

[0153] In one particular example, the lead includes a sheath extending at least partway along the lead, with the sheath defining the hook shape to loop over and behind an ear of the subject. In this example, the sheath can have greater resilience than unsheathed portions of the lead, which can help maintain the shape of the lead in the region of the ear, whilst allowing the lead to remain freely flexible in other regions, making this more convenient for use. This also helps protect the lead where the lead joins the earpiece, and for example reduces the chances of forces decoupling the lead from the earpiece, or damaging electrical connections between the earpiece and the lead.

[0154] As mentioned above, in one example at least one of the arms, and in particular an inner arm 111, is positioned within a concha of the user. This allows the earpiece to grip the tragus whilst allowing the tragus to remain in a substantially natural position, making the earpiece comfortable to wear. This also reduces the extent to which the earpiece extends outwardly from the ear, which can in turn reduce the likelihood of the earpiece being knocked and dislodged, whilst also making the earpiece comfortable to wear whilst the ear is resting on a pillow or other surface, making the arrangement particularly suited for long term use. Furthermore, this also helps guide correct positioning of the earpiece, ensuring the electrodes are correctly positioned on the tragus, and hence aligned with the vagus nerve, in turn optimising the effect of the applied therapy signals.

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[0155] In one example, the arms are pivotally connected about a mid-portion, although this is not essential and other arrangements could be used. For example, the arms could be made of or be interconnected by a malleable material, allowing the arms to be deformed into a desired shape, so that distal end of the arms are biased into engagement with the tragus.

[0156] The earpiece also typically includes a biasing mechanism to bias distal ends of the arms into engagement. The nature of the biasing mechanism can vary depending on the preferred implementation and could include the use of a spring or rubber member positioned between the arms. The biasing could be achieved using a malleable member interconnecting the arms or at least partially malleable arms, an at least partially elastic member interconnecting the arms or at least partially elastic arms.

[0157] In a further example, the biasing could be achieved using magnets provided in the arms. For example magnets with opposing polarities could be provided in distal ends of the arms to attract the distal ends of the arms together. It will be appreciated that this arrangement induces a magnetic field surrounding the tragus, which can be used to enhance or modulate the applied therapy signals, thereby improving safety and/or efficacy. Alternatively, magnets with like polarities could be provided in proximal ends of the arms to urge the proximal ends apart.

[0158] In one preferred example, the arms are pivotally connected and optionally biased about a mid-portion, allowing a proximal end of the arms to be biased together to urge the distal ends and hence the electrodes apart, thereby making the earpiece easy to apply. This arrangement can also help ensure the arms are approximately parallel when the tragus is positioned between the arms, which helps position the electrodes and ensure maximum surface contact between the electrodes and the tragus, in turn reducing the current density required to achieve effective stimulation and thereby improve efficacy and reduce burns.

[0159] In one example, to further facilitate this process, a proximal outer face of the arms includes a depression configured to guide positioning of a subject so that they can engage the arms and bias the arms apart, for example by grasping the proximal ends of the arms between a thumb and forefinger.

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[0160] In one example, the arms have a length that is greater than 15mm, greater than 16mm, greater than 17mm, greater than 18mm, greater than 19mm, greater than 20mm, greater than 21mm, less than 30mm, less than 28mm, less than 27mm, less than 26mm, less than 25mm, less than 24mm, less than 23mm, and more typically is about 22mm. Similarly the arms typically have a width that is greater than 5mm, greater than 6mm, greater than 7mm, greater than 8mm, greater than 9mm, greater than 10mm, less than 16mm, less than 15mm, less than 14mm, less than 13mm, less than 12mm, and more typically about 11mm. These dimensions make the arms easy to manipulate, whilst allowing the earpiece to be positioned within the concha making the earpiece comfortable to wear.

[0161] Additionally, arms dimensioned as above provide a sufficiently large surface area to accommodate the electrodes. In this regard, the electrodes are typically substantially circular, although rounded rectangular or rounded square shaped could be used. The electrodes are also optionally at least partially domed-shaped, which can help ensure that the electrodes make good electrical contact with the tragus, irrespective of a relative angle of the arms. Furthermore, the use of domed-shaped and substantially circular electrodes ensures that the electrodes do not include any sharp edges, which could cause discomfort.

[0162] Typically, the electrodes have a diameter that is greater than 4mm, greater than 5mm, greater than 6mm, greater than 7mm, less than 12mm, less than 11mm, less than 10mm, less than 9mm and more typically about 8mm. These dimensions provide a surface area that allows a sufficiently large current to be applied to induce a field that can effectively stimulate the vagus nerve, without resulting in an excessive charge or current density on the surface of the tragus, which can in turn cause discomfort or burns and/or result in ineffective treatment. The electrodes also act as a contact surface with the tragus, and including a sufficiently large electrode surface area can help ensure the earpiece effectively couples to the tragus and remains in place, even when subject to external forces.

[0163] Additionally and/or alternatively, a surface of the electrodes can be roughened, or could include grooves or ridges. The use of roughened or profiled electrode surfaces can firstly increase the friction between the electrode and the tragus, which in turn helps maintain a position of the earpiece. Additionally, roughening or including grooves or ridges on the

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electrode surface can help ensure good electrical contact between the electrode and the tragus. For example, this can help minimise disruption caused by uneven surfaces, such as bumps on the tragus, or similar. A further benefit is that surface roughness leads to an increase in the overall surface area of the electrodes, which in turn helps reduce the current density required to generate a given field within the tragus, which in turn helps ensure efficacy, whilst avoiding excessive current densities that can lead to burns.

[0164] In one example, the electrodes could also be coated, for example to improve electrical conductivity, increase surface friction and ensure biocompatibility. Any form of conductive coating could be used, and in one example, the electrodes are formed from copper electrodes coated with an inert metal, such as gold or other similar highly-conductive material.

[0165] The signal generator is typically configured to generate therapy signals having a frequency that is at least one of less than 20kHz, less than 10kHz, less than 1Hz, less than 500Hz, less than 200Hz, less than 150Hz, less than 100Hz, less than 75Hz, greater than 1Hz, greater than 2Hz, greater than 5Hz, greater than 10Hz, greater than 20Hz, about 20Hz and more typically about 50Hz. The therapy signals typically have a pulse width that is less than 5,000 μ s, less than 2,500 μ s, less than 1,000 μ s, less than 500 μ s, less than 200 μ s, less than 100 μ s, less than 75 μ s, greater than 1 μ s, greater than 2 μ s, greater than 5 μ s, greater than 10 μ s, greater than 20 μ s, and, more typically is about 50 μ s. The therapy signals typically have a voltage that is less than 50V, less than 25V, less than 10V, less than 5V, less than 2V, less than 1V, greater than 0.1V, greater than 0.2V, greater than 0.5V, and, more typically greater than 1V. The therapy signals typically have a current magnitude that is less than 50mA, greater than 1mA, greater than 0.1mA, and, between 0.1mA and 36mA.

[0166] The therapy signals can be symmetrical, asymmetrical, monophasic or biphasic. In this regard, the use of symmetrical bi-phasic signals can help reduce charge build up on a surface of the tragus, which in turn maximises the electrical fields generated within the tragus as a result of the applied therapy signal, whilst preventing charge building up to a level that can cause discomfort. This in turn helps optimise stimulation of the vagus nerve. Nevertheless, asymmetrical and/or monophasic therapy signals could be used in some circumstances, depending for example on the intended application. Additionally and/or alternatively tri-phasic

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or more broadly poly-phasic signals could be used. In one example, asymmetric tri-phasic signals can be used with negative pulses having a smaller magnitude and duration than an intervening positive pulse, which can help reduce charge build up. Signals could also include multiple phases with an intervening dwell time, allowing a charge to remain in place for a short duration, before this is discharged.

[0167] The therapy signals are typically configured to at least one of stimulate or inhibit activity within the vagus nerve, and it will be appreciated from this that the signal parameters used, such as the voltage, current, frequency and waveform can be selected depending on the intended application and the desired effect of the modulation on the vagus nerve.

[0168] In one example, one of the electrodes 121, 122 acts as ground, with the therapy signals being applied via the other electrode. However, this is not essential, and in one example, therapy signals can be applied to each of the electrodes. The therapy signals could be in phase, but more typically are out of phase, to maximise an overall field gradient across the vagus nerve, which in turn helps generate action potentials within the nerve. Additionally, this helps minimise the magnitude of the current applied via each electrode in order to generate a given electric field, which in turn helps reduce discomfort, whilst ensuring the system remains clinically effective.

[0169] In general, where a lead is used, the lead includes a respective conductor for each electrode, with the conductors being contained within an insulating layer and optionally surrounded by a braided shield. This helps ensure electrical isolation between connections, whilst providing a connecting lead that is strong and lightweight.

[0170] In one example, the system typically includes a control system having a housing containing the signal generator together with other associated electronics, such as a power supply and/or a controller. The controller is configured to control the signal generator allowing a range of different desired therapy signals to be generated. The controller may be of any appropriate form, but typically includes one or more electronic processing devices, such as a microprocessor, microchip processor, logic gate configuration, firmware optionally associated with implementing logic such as an FPGA (Field Programmable Gate Array), or any other electronic device, system or arrangement. For ease of illustration the remaining description will

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refer generally to a controller which is formed from a processing device, but it will be appreciated that multiple processing devices could be used, with processing distributed between the devices as needed, and that reference to the singular encompasses the plural arrangement and *vice versa*.

[0171] In one example, the lead extends from the earpiece to the housing so that therapy signals generated by the signal generator can be applied to the electrodes. However, as previously discussed, this is not essential, and in alternative embodiments, the signal generator can be mounted on the earpiece. In this example, the controller could be integrated into a housing forming part of the earpiece, or alternatively, the controller could communicate with the signal generator via wireless connections, allowing the signal generator to be controlled remotely using a suitable device, such as a smart phone or other client device, which then acts as the controller.

[0172] In one example, the controller is configured to determine therapy signal parameters and, control the signal generator in accordance with the therapy signal parameters. The therapy signal parameters could be determined in any one of a number of ways, including retrieving defined therapy signal parameters stored in a memory, based on signals from a sensor, based on biofeedback, based on user input commands and/or a selected therapy mode. For example, a number of different operating modes could be defined, with the user selecting a therapy mode depending on the use application, and the controller retrieving therapy signal parameters depending on the selected mode. This allows the system to be used to achieve a range of different outcomes, such as stimulating and/or inhibiting the vagus nerve, depending on requirements of the user. Additionally, this allows the controller to determine feedback, for example using signals from a sensor, and adjust the therapy signals based on the feedback, so that the therapy signals can be optimised for the subject, and in particular the response of the subject to the signals.

[0173] In one example, the system includes a sensor configured to sense at least one subject parameter. The sensor could be of any appropriate form depending on the preferred implementation and could include any one or more of an inflammatory biomarker sensor, a temperature sensor, a blood oxygen sensor, a pulse oximeter, a heart rate sensor or an

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impedance sensor. The sensor could be formed at least in part from the electrodes. For example, a heart rate sensor could utilise a voltage sensor coupled to the electrodes to detect electrical signals, such as electrocardiogram (ECG) signals, whilst an impedance sensor might include a voltage sensor coupled to the electrodes to measure voltages across the tragus resulting from current signals applied by the signal generator. Alternatively, a separate sensor could be used and may be mounted on the earpiece proximate the electrodes. For example a pulse oximeter typically includes an infrared sensor, such as a photodiode, and infrared light emitting diodes (LEDs), in which case the LEDs could be positioned on one arm, with the photodiode on the other to detect infrared radiation transmitted through the tragus. In one example, the electrodes could be transparent electrodes made from Indium Tin Oxide (ITO) or other similar materials, with the LEDs and photodiodes positioned behind the electrodes.

[0174] Irrespective of the sensor employed, the controller can be configured to determine at least one subject parameter using signals from the sensor and cause the signal generator to generate therapy signals in accordance with the at least one subject parameter. Thus, for example, the controller can determine a subject parameter such as a presence, absence or concentration of an inflammatory biomarker, a temperature, a blood oxygen level, a heart rate, a heart rate variability, an impedance or a galvanic skin response, an arrhythmia and use this as biofeedback to assess the effectiveness of an applied therapy. This can then be used to adjust the applied therapy signals, for example increasing a magnitude or altering a frequency of the therapy signals to optimise the therapy signals for the responsiveness of the respective subject. In this regard, it will be appreciated that the manner in which signals should be adjusted can be defined in memory, and could include scaling signals based on measured subject parameters.

[0175] In another example, the controller can be configured to determine feedback using user input commands and cause the signal generator to generate the therapy signals in accordance with the feedback. Thus, the user could indicate via an input whether they are perceiving any improvement, such as a reduction in anxiety or stress, with this input being used to adjust the applied therapy signals.

[0176] In one example, the controller is configured to cause the signal generator to generate therapy signals having progressively increasing magnitudes, and then select therapy signal

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magnitude in response to user input commands. This can be used to progressively increase magnitude of a current of the therapy signals up until a point at which these are noticeable to the subject, with this level then being used to select a desired therapy signal magnitude. This can be used to maximise the magnitude of the therapy signals, while preventing these creating discomfort for the user. In one example, therapy signals are increased in magnitude in steps of 1mA from 1mA to a maximum of 36mA, although other magnitudes could be used, such as 0.1mA, 0.2mA, 0.5mA, 1.5mA, 2mA, or the like.

[0177] In another example, the controller can be configured to determine selection of a mode in accordance with user input commands, and then control the signal generator in accordance with the selected mode. In this regard the system typically includes a number of therapy modes stored in a store, each therapy mode defining a sequence of therapy signals, which may be tailored for example to provide a different intervention, treat a different condition, or the like. Thus, the selected mode could be used to control the nature of the therapy signals, and could be used to stimulate or inhibit the vagus nerve, or could be used to switch between symmetric, asymmetric, monophasic and/or biphasic signals, depending upon the preferred implementation. In this instance, the controller is configured to cause the signal generator to generate the sequence of therapy signals, thereby applying the selected intervention.

[0178] In another example, a research mode can be provided, which is utilised in order to investigate the effectiveness of stimulation of the vagus nerve. In this regard, the research mode typically operates by selecting therapy signal magnitude, as described above, and then progressively decreasing the therapy signal magnitude to zero, effectively applying a null stimulation, whilst still allowing the subject to proceed with calibration so that they believe stimulation is occurring. This allows a placebo effect to be assessed, and allows a null stimulation process to be used as a control in experiments assessing the effectiveness of the stimulation process.

[0179] Whilst the system can be used to treat a wide range of different conditions, the nerve stimulation system is particularly suited for use in the treatment of heart failure or atrial fibrillation.

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[0180] A specific example of controller functionality will now be described with reference to Figure 2.

[0181] In this example, the control system 250 includes a signal generator 230, a controller 251, a memory 252, and input/output device 253, such as input buttons and a display, interconnected via a bus 255. The signal generator 250 is connected to electrodes 221, 222 via a lead 240, containing first and second connections 231, 232.

[0182] An external interface 254 can also be provided, which can be a wired or wireless interface, such as Wi-Fi, Bluetooth or another short range wireless communications interface. The external interface 254 can be used to allow an external device, such as a computer system, smart phone or table, to interface with the control system, for example to allow therapy signal parameters or operating modes to be updated, or to allow the control system to be remotely controlled. Additionally and/or alternatively the external interface 254 could be connected to a sensor 223 such as a pulse oximeter, or the like. In one example, the sensor 223 can be integrated into the earpiece 110, in which case the connection to the sensor might be integrated into the lead 240. It will also be appreciated that in other examples, a signal sensor, such as a voltage sensor (not shown) could be connected to the electrodes 221, 222, allowing signals within the body, such as ECG or impedance signals to be sensed.

[0183] In use, the controller 251 executes instructions in the form of applications software stored in the memory 252 to allow the required processes to be performed, and in particular to allow the signal generator 230 to be controlled to thereby generate therapy signals, which are then applied to electrodes 221, 222.

[0184] The applications software may include one or more software modules, and may be executed in a suitable execution environment, such as an operating system environment, or the like. The controller could be a microprocessor, microchip processor, logic gate configuration, firmware optionally associated with implementing logic such as an FPGA (Field Programmable Gate Array), or any other electronic device, system or arrangement.

[0185] The memory 252 will also typically store information necessary to generate therapy signals, such as details of therapy signal parameters, operating modes or the like, as well as

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instructions for interpreting any feedback, such as signals from sensors 223 or user input commands, allowing this feedback to be used to control the generation of therapy signals.

[0186] An example of a process for performing nerve modulation will now be described with reference to Figure 3.

[0187] In this example, the earpiece is attached to the tragus at step 300. Typically, this involves biasing arms 111, 112 apart by applying a pressure between thumb and forefinger to a proximal end of each arm 111, 112. The tragus is then positioned between the distal ends of the arms 111, 112, before the earpiece is released, allowing the electrodes 121, 122 to be urged into contact with the tragus, as shown in Figure 1D.

[0188] Next, at step 310, a therapy signal magnitude is calibrated. This process typically involves having the therapy signals generated with increasing magnitudes, until this is perceptible to the user. In this instance, the user can indicate when the signals are perceived and/or becoming uncomfortable, with this being used to set a maximum magnitude for the therapy signals.

[0189] Following this, at step 320 stimulation is performed by applying therapy signals. In this regard, the controller 251 will typically retrieve therapy signal parameters from the memory, optionally in accordance with an operating mode and/or user input commands, using these to control the signal generator 230 so that desired therapy signals are generated.

[0190] A specific example of a nerve modulation system will now be described in more detail with reference to Figures 4A to 4G.

[0191] In this example, the nerve modulation system includes a earpiece 410, having first and second arms 411, 412. The first and second arms 411, 412 are interconnected via a pivotal mounting 413, which is formed from spaced parallel upstanding members 413.1, 413.2 extending upwardly from inner surfaces of each of the first and second arms 411, 412. A pin is provided extending through the upstanding members to allow pivotal movement of the arms, whilst a spring 413.3 is mounted on the pin, so as to bias distal ends of the arms together.

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[0192] Recesses 411.1, 412.1 are provided on outer faces of proximal ends of each of the first and second arms 411, 412, with the recesses 412.1 being configured to align with a user's thumb and forefinger, so that applying pressure between the thumb and forefinger biases distal ends of the 411.1, 412.1 apart.

[0193] Electrodes 421, 422 are provided on the inner faces of the distal ends of the 411.1, 412.1. The electrodes are circular and dome shaped, so that the electrodes 421, 422 can contact a surface of the tragus when the tragus is positioned between the electrodes 421, 422. In this regard, the upstanding members 413.1, 413.2 are typically dimensioned based on an approximate thickness of the tragus, so that the arms 411, 412 and hence electrodes are substantially parallel when the earpiece is positioned on the tragus.

[0194] A lead 440 is provided, including a lead body 441 and a sheath 442, which extends partway along a distal end of the lead body 441. Specifically, the sheath 442 is formed from an overmoulded area that extends from a distal end of the outer arm 412 and has a hook shape, allowing this to be positioned behind the ear, as shown in Figure 4G. The overmoulded section typically has a length of about 100mm and is malleable, allowing this to be shaped to conform to the ear of the user. As previously described, this helps support the earpiece 410, avoiding undue strain being applied to the tragus, and preventing the earpiece 410 falling out in the event that it becomes dislodged.

[0195] A specific example of a control system form factor is shown in Figures 5A to 5C.

[0196] In this example, the control system includes a body 561, input buttons 562 and a display 563. In this example, four input buttons 562 are provided, including a power button 562.1, mode button 562.2 and up and down buttons 562.3, 562.4 are shown, allowing users to select different modes and also indicate when a desired stimulation current has been reached. The display can be of any form, and could include LED or LCD displays or similar. These can be used to display operating information, such as details of selected operating modes, therapy signal parameters, information regarding a current therapy session, such as a duration, or the like.

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[0197] The housing typically includes a connector socket, that receives a plug 543 attached to the lead 441, which extends to the earpiece 410, as previously described. The plug and socket can be of any form, but in one example are USB or other similar connectors.

[0198] It will be appreciated that in one example, the internal components of the control system are generally similar to those shown in Figure 2. An alternative example of an internal component arrangement will now be described with reference to Figure 6.

[0199] In this example, the control system 650 includes a remote device 650.1, which includes a controller 651, a memory 652, an input/output device 653 and external interface 654 interconnected via a bus 656. In this example, a second external interface 656 is provided, which provides a short range wireless connection, such as Bluetooth™ or similar, to provide connectivity to an on-earpiece device 650.2, which is mounted on the earpiece 410. In this example, the second control system portion 650.2 includes an interface system on a chip (SoC) 657 and a signal generator 650, coupled to a power supply 658. The signal generator is again connected to electrodes 621, 622, via respective connections 651, 652.

[0200] This arrangement allows control signals to be provided from the remote device 650.1, to the on-earpiece device 650.2, and hence the signal generator 650, so that the signal generator can be controlled remotely. In one example, the remote device 650.1 could have a form similar to that shown in Figures 5A to 5C. However, it will be appreciated that as the remote device need only generate control signals, this could be achieved using any suitable processing system, and could be performed using a client device, such as a tablet, smart phone, or similar.

[0201] A further example of a stimulation process will now be described.

[0202] In this example, at step 700, the earpiece 410 is attached to the tragus by having the user bias the arms apart, position the arms on either side of the tragus and release the arms, as previously described.

[0203] At step 710, the user utilises the mode input button 522.2 to select an operating mode, allowing the controller 251 to retrieve therapy signal parameters from the memory 252, which are defined for the respective operating mode selected, at step 720. The therapy signal parameters are used to control the waveform of the therapy signals that are generated, and

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include parameters such as the pulse waveform shape, pulse duration, signal magnitude, signal frequency, or the like.

[0204] A specific example of a neuromodulation approach for treating cardiovascular disease using sequences of waveforms will now be described.

[0205] In this example, a neuromodulation system and method is provided for treating or preventing a cardiovascular disease. The nerve stimulation system applies a therapy signal non-invasively via a pair of electrodes, and targets an auricular branch of a vagus nerve of a subject. The therapy may include auricular vagus neuromodulation therapy (AVNT), wherein the auricular branch of the vagus nerve is modulated and/or simulated. In one example, AVNT may be used to treat a heart rate variability. The therapy signal includes a sequence of different types of waveforms of, in this order, a pre-pulse and an exponential ramp. It should be appreciated that the system and method provided herein may also treat an autonomic dysfunction.

[0206] In one example pre-pulse is applied to depolarise neural fibres, which may be vagal neural fibres, and the subsequent waveform is targeted to activate efferent B fibres, whereby the efferent vagal signalling initiates at the brainstem, and thereby the vagal efferent B fibres are stimulated and/or modulated.

[0207] Current scientific evidence indicates that heart rate variability (HRV) is a robust, non-invasive, quantitative marker of autonomic activities. Fluctuations observed in HRV arise from the homeostatic regulation between the two branches of the autonomic nervous system: sympathetic and parasympathetic components, where the interaction of these directly affect cardiac automaticity. Parasympathetic influence is mediated via the vagus nerve and neurotransmitter acetylcholine, while the sympathetic influence is mediated by epinephrine and norepinephrine. It is clear that autonomic dysfunction plays an essential role in the manifestation of cardiovascular diseases. Abnormality in autonomic inputs, as reflected by changes in HRV indices, is associated with a higher risk for heart failure, atrial fibrillation, coronary heart diseases, and others. The advent of non-invasive techniques like HRV has provided clinicians with a great opportunity to examine the role of autonomic tones in greater

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detail, and this is a useful addition to the management of cardiovascular diseases along with existing therapy.

[0208] Referring to Figure 10, it shows the results of the above-described arrangement. In this example, patients with heart failure were positioned at rest with their resting HRV measured. Specifically, their high frequency parameter (HF) and low frequency (LF) were measured, wherein the HF is indicative of parasympathetic activity and the LF relates to sympathetic activity. The patients then engaged in the above-described arrangement of treatment/therapy for approximately 5 minutes. In this example, a sequence of a rectangular waveform, acting as a pre-pulse, followed by an exponential ramp waveform is the therapy signal. The time interval between the pre-pulse rectangular waveform and the exponential ramp waveform is 1000 μ s, and the dwell time between the sequences is 50,000 μ s. At the end of the treatment, the HRV, both HF and LF, recording was measured. It is further noted that the LF/HF is low frequency high frequency ratio, and lower ratio value indicates better autonomic balance/tone and cardiac function.

[0209] As described above, the apparatus may deliver or receive neuromodulation signals including at least one of: electrical signals; sound signals, ultrasound signal, and optical signal. In one example, the sound signals include PPG signals, which may be applied to or generated from the subject's ear, head, chest and/or limbs.

[0210] The neuromodulation signals may include different types of waveforms. In one example, the signal includes a sequence of high frequency followed by low frequency pulses. In one example, the HF may be from 1 Hz to 1000 Hz, or between 5 Hz and 50 Hz; and the low frequency may be from 0.2 Hz to 100 Hz, or between 0.5 Hz and 5 Hz. Additionally or alternatively, the signal may have a waveform with alternations to manage charges. In one example, the waveform with alternations include alternating sequence, alternating polarities, alternating shapes and intensity. Alternations as described may help initiate an action potential with limited excess residual charge, and thereby assists in electrode material longevity and reduces discomfort to the user. The above arrangement can help maximising neural recruitment and/or improving parasympathetic activation while minimising side effects, such as discomfort, or burns. Additionally, the above described arrangement increases 'memory effect'

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of the therapy, helps maintain safety and efficacy. In this regard, by optimising the effectiveness of signal application, this ensures the correct stimulation is achieved, avoiding over or under stimulation, which can lead to adverse consequences.

[0211] Accordingly, the above described arrangement provides a nerve stimulation system that can be used to stimulate the nerve and treat a cardiovascular disease and/or an autonomic dysfunction, which is comfortable and easy to use over prolonged periods of time, and thereby allowing users to more readily avail themselves to the benefits of nerve stimulation, whilst avoiding risk, safety and efficacy issues, such as burns and/or unsafe or ineffective levels of neurostimulation.

[0212] Example waveforms will now be described in more detail with reference to Figures 11A to 11R.

[0213] In the example of Figures 11A and 11B, the waveforms are generally rectangular, with the signal of Figure 8A including a ramped decay, which can arise from the discharge of capacitors used to generate the pulse waveform. The waveform is generally bi-phasic, including positive and negative components, and is symmetrical, so the magnitude of the positive and negative components are equal, thereby ensuring that the surface of the tragus is neutrally charged at the end of each pulse in the pulse sequence, which helps prevent charge build up, which can in turn mask the field generated by the applied therapy signals and hence reduce signal effectiveness, and overall efficacy. Additionally, charge build-up can also increase the risk of thermal burns or other discomfort.

[0214] It will be appreciated that different shapes could be used however, as shown in Figures 11C and 11D, which shows a ramped increase in signal magnitude in a rectangular pulse waveform, and a sine waveform respectively. The use of gradually increasing waveforms of this type can assist in avoiding a sudden application of a current to the subject, which can avoid some of the discomfort associated with electrical stimulation.

[0215] Alternative example waveforms are shown in Figures 11E and 11F. In this example, signals are again bi-phasic, but non symmetrical, meaning the magnitude of the waveform is unequal in the positive and negative phases. In this instance, this can result in generation of a

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net charge in the subject. However, this can be mitigated by having the waveform include an unequal duration in the positive and negative phases, thereby ensuring equal discharge and charging occurs, even though the signal magnitude differs.

[0216] Figure 11G shows a tri-phasic waveform, including two negative pulses and an intervening positive pulse. In this example, the sum of the negative phases is equal to the positive phase, to thereby minimise charge build-up. Furthermore, the preceding negative phase introduces a negative charge in the tissue prior to application of the positive phase, allowing the positive phase to have a greater magnitude without risk of causing thermal burns.

[0217] Figure 11H shows an arrangement in which a dwell in the form of an interphase gap is introduced between phases, which can allow for some charge to remain in place before being actively discharged, which can help efficacy. This can also be implemented with mono-phasic pulses, as shown in Figure 11I.

[0218] Figure 11J illustrates asymmetric bi-phasic signals, in which each phase has a different waveform shape, whilst Figure 11K shows a sawtooth waveform. Figure 11L illustrates a rectangular waveform with ramp, whilst Figure 11M shows a waveform similar to Figure 11L with an unequal duration in the positive and negative phases. Figure 11N illustrates bi-phasic rectangular waveform with an exponential decay.

[0219] Figures 11O to 11Q illustrate sequences of the waveform shown in Figure 11N with alternating polarity and/or shapes. Figure 11R shows a sequence of high frequency followed by low frequency pulses.

[0220] Figures 11S to 11AE each illustrates a waveform or a sequence of waveforms in combination.

[0221] It will be appreciated from the above that a wide range of different signal waveforms can be used and the above are for the purpose of example only and are not necessarily intended to be limiting.

[0222] Thus, signals can include mono-phasic, single phase, unidirectional pulse from baseline to either positive or negative. This should not be confused with Direct Current (DC), in that

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whilst one electrode is always positive and one electrode is always negative, pulsed monophasic waves have interruptions, use shorter duration pulses, and less strength than DC. As a result, monophasic waveforms do not cause the same magnitude of chemical changes as DC, and are less likely to lead to discomfort or thermal burns.

[0223] Signals can be bi-phasic, including two phases, with one positive phase and one negative phase so that the electrodes change polarity. The phases can be symmetrical so that identical phases cancel each other out, or asymmetrical, with non-identical phases either balanced with no net charge or unbalanced yielding a net charge.

[0224] Finally, more broadly, poly-phasic signals, such as tri-phasic signals could be used, with three or more phases in bursts. Again phases can be symmetrical or asymmetrical and may be separated by interphase gaps.

[0225] It will also be appreciated that therapy signal parameters may vary throughout a stimulation sequence, for example so that a magnitude, frequency and/or waveform varies during a single stimulation session, which can last for several minutes or up to or more than an hour.

[0226] Having determined the signal parameters, the controller 251 uses the therapy signal parameters to generate control signals, which are supplied to the signal generator 230 to thereby control the signal generator 230 at step 730. Initially, this will cause the signal generator 230 to generate a low magnitude therapy signal, which is applied to the subject via the electrodes 221, 222, allowing the subject to assess if they can perceive the signal and/or whether the signal is causing discomfort.

[0227] If no response is detected at step 740, the current is increased in 1mA increments at step 750, and the process repeated until a response is detected (or until a threshold signal magnitude is reached), with this being indicated by the user through activation of one of the input buttons 562.

[0228] Once a response is detected (or a threshold magnitude reached) at step 740, the therapy signal magnitude is set and stimulation sequence is performed at step 760. As previously described, the stimulation sequence is typically defined by the selected operating mode, and

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may involve applying varying therapy signals over a period of time. One example of this is if the device is operating in research mode, in which case the stimulation signals are ramped down progressively so that the stimulation session does not apply significant active stimulation, allowing this to act as a control to assess the effectiveness of a stimulation sequence applied to other subjects.

[0229] Once stimulation has commenced, the system can optionally monitor feedback at step 770, for example by having the controller 251 monitor signals from one or more sensors 223, and use this to determine a value of or changes in a subject parameter, or by monitoring user input commands received via an input button 562. The feedback can then be used to ascertain an effectiveness of the therapy signals and further alter the signals if required, for example by modifying the therapy signal parameters to alter a magnitude, waveform shape, intensity, magnitude, or the like, at step 780. The process can then return to step 760 allowing the modified therapy signals to be applied, repeating this process until the therapy is complete. This allows the system to provide a closed loop control and thereby be a closed loop system.

[0230] In one example, the system is also capable of being used to treat autonomic dysfunction.

[0231] In another example, the system is used to treat Atrial Fibrillation. An example study to assess the effectiveness of tVNS was performed using the above described arrangement to non-invasively activate the cholinergic anti-inflammatory pathway. In this study, the primary outcome of median Atrial Fibrillation burden was reduced by 85% in patients assigned to the above described device compared with those assigned a sham procedure (ratio of medians, 0.15; 95% CI, 0.03-0.65; $P = .011$). The stimulation group also had significantly altered frequency domain indices of heart rate variability ($P = .003$) and a 23% decrease in TNF-alpha ($P = .0093$) compared with the sham group, demonstrating the effectiveness of the above described apparatus.

[0232] Accordingly, the above described arrangements provide a system suitable for performing non-invasive vagus nerve stimulation utilising an earpiece that is configured to be positioned on a tragus of a subject.

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[0233] The above arrangement can provide a number of benefits, such as avoiding the risk of nerve damage as can occur with cervical VNS, avoiding the risk of stimulating carotid artery as can occur with cervical VNS & cervical nVNS or avoiding uncomfortable side effect of 'lip pull' as can arise with cervical nVNS, and avoid the chance of thermal burns.

[0234] In one example, the system employs target stimulation of the nerve via electrodes provided in a spaced substantially parallel arrangement, which provides for easier nerve excitation by allowing a greater overall electric field to be generated, whilst avoiding excessive current densities on a tissue surface.

[0235] In contrast to a number of other non-invasive techniques, the current system operates by stimulating the vagus nerve in the tragus, and specifically the inner and outer tragus, which contains longer vagal nerve fibres for greater chance of eliciting action potentials within the nerve. This improves the effectiveness of stimulation, whilst minimising the currents needed to achieve an action potential, thereby avoiding discomfort.

[0236] The above described arrangement uses an earpiece to urge the electrodes against the tissue surface. This allows for the electrodes to be urged against the tragus with an optimised pressure, which can assist in overcoming skin impedance while not causing pain or penetrating the skin. Furthermore, this helps ensure a consistency of delivery of electric current, which ensures consistent excitation to the nerve, which is important to ensure efficacy in some therapies.

[0237] The above described arrangements can use a variety of different therapy signal waveforms, which can ensure optimal nerve excitation and maximise the creation of action potentials, while avoiding the need to apply signals that cause pain to the user.

[0238] In one example, the system is configured to apply asymmetrical balanced biphasic square waveforms, which can be better tolerated by users with less chance of causing a pain response and can be more effectively focused to specific nerve fibres. Additionally and/or alternatively, symmetrical balanced biphasic square waveforms can be used to reduce charge build-up, thereby resulting in reduced skin irritation for the user.

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[0239] In one example, the above described apparatus can be used to record physiological measures for biofeedback, such as Heart Rate, Heart Rate Variability, Galvanic Skin Response, ECG, inflammatory biomarkers, or the like. This can be achieved by employing measuring apparatus on skin contacting points on or around the electrode.

[0240] Such biofeedback can then be used to deliver optimal stimulation, with therapy signal parameters, such as stimulation intensity, waveform and frequency being adjusted in real time to achieve the optimal outcome of physiological autonomic balance and/or immunological balance.

[0241] In one example, through appropriate configuration, the above described arrangement can overcome skin resistance, whilst avoiding the creation of pain. The system can effectively target vagus nerve fibres, and can sustain an electrical field around the target nerve fibre. The use of the earpiece can hold the electrodes in place during use and ensure a stable pressure and consistent electrical contact between the skin and electrode, in turn leading to more stable contact impedance and hence applied current and resulting stimulation.

[0242] In one example the system employs a lead including an overmould with soft plastic outer layer with thin wire central layer for retaining shape of ear. This section covers standard insulating cable containing anode/cathode cores, and can assist in distributing loads and helps retain the earpiece in place, allowing for the more consistent application of therapy signals.

[0243] It will be appreciated that the above described approach contrasts to traditional invasive VNS, which has to be surgically implanted, administered by a doctor and is irreversible. Specifically, the device can be administered non-invasively, without the need for surgery, and can be applied directly to the outer skin. The device can be operated by the individual without the need for assistance by a doctor and can be applied or removed from the individual at any time without any additional risks.

[0244] Other devices that target non-invasive stimulation of the vagus nerve typically need to be manually held in place to deliver stimulation and use methods of stimulating across the skin which doesn't penetrate effectively.

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[0245] In contrast the current arrangement is designed to attach to the ear to deliver effective stimulation, and furthermore, stimulates either side of the skin of the tragus to deliver a more concentrated current to the target nerve.

[0246] Other devices also typically need to be manually guided to the appropriate stimulation site, whereas the above described system guides the electrode plates to the location that will deliver stimulation to the part of the skin directly above the vagal innervation, whilst avoiding stimulation at a site that is in close proximity to the carotid artery, which can result in adverse outcomes.

[0247] The above arrangements avoid a high risk of skin irritation arising from small surface area of electrodes which yield a higher relative current density. In contrast the above arrangements using a larger surface area of electrodes which disperses current which leads to less risk of skin irritation or thermal burns.

[0248] Throughout this specification and claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers. As used herein and unless otherwise stated, the term “approximately” means $\pm 20\%$.

[0249] Persons skilled in the art will appreciate that numerous variations and modifications will become apparent. All such variations and modifications which become apparent to persons skilled in the art, should be considered to fall within the spirit and scope that the invention broadly appearing before described.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

- 1) A neuromodulation system for treating a condition, the system including:
 - a) electrodes configured to be attached to a subject; and,
 - b) a signal generator electrically connected to the electrodes, the signal generator being configured to generate at least one therapy signal that is applied to the subject via the electrodes to thereby modulate the nerve, and wherein the at least one therapy signal includes at least one sequence of different types of waveforms.
- 2) A neuromodulation system according to claim 1, wherein the at least one sequence of different types of waveforms includes:
 - a) a single repeating sequence of different types of waveforms;
 - b) multiple different sequences of waveforms; and,
 - c) multiple repeating different sequences of waveforms.
- 3) A neuromodulation system according to claim 1 or 2, wherein the at least one sequence of different types of waveforms is at least one of selected and adjusted based on at least one of:
 - a) a cardiovascular disease being treated;
 - b) an autonomic dysfunction being treated;
 - c) a responsiveness to treatment;
 - d) biofeedback; and,
 - e) user input.
- 4) A neuromodulation system according to any one of claims 1 to 3, wherein the types of waveforms include at least one of:
 - a) a rectangular pulse waveform;
 - b) a triangular pulse waveform;
 - c) a spike waveform;
 - d) a sine waveform;
 - e) a ramp waveform;
 - f) an exponential ramp waveform;
 - g) an exponential decay waveform;
 - h) a burst waveform;
 - i) an arbitrary waveform;

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- j) a premodulated waveform;
 - k) a linear waveform;
 - l) an increasing or decreasing, zeta waveform;
 - m) an increasing or decreasing sawtooth waveform;
 - n) a direct current waveform;
 - o) a damped sine waveform;
 - p) a bi-sigmoidal waveform;
 - q) a complex waveform;
 - r) a pulse waveform;
 - s) a square waveform;
 - t) a random noise waveform;
 - u) a custom waveform;
 - v) a differential waveform; and,
 - w) a rest.
- 5) A neuromodulation system according to any one of claims 1 to 4, wherein the at least one therapy signal is triggered by at least one of:
- a) a user input;
 - b) a sensor input;
 - c) an electrical signal;
 - d) a bioelectric signal;
 - e) a movement of the subject;
 - f) an audio signal;
 - g) a vibration; and,
 - h) a physiological state of the subject.
- 6) A neuromodulation system according to any one of claims 1 to 5, wherein the at least one therapy signal at least one of:
- a) are symmetrical;
 - b) are asymmetrical;
 - c) are monophasic;
 - d) are bi-phasic;
 - e) are tri-phasic;

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- f) are poly-phasic; and,
 - g) include multiple phases with at least one interspersed dwell.
- 7) A neuromodulation system according to any one of claims 1 to 6, wherein the sequence of different types of waveforms includes at least a time interval between the different types of waveforms.
- 8) A neuromodulation system according to claim 7, wherein the time interval is at least one of:
- a) variable;
 - b) fixed;
 - c) 0 μ s;
 - d) 0 μ s to 200000 μ s;
 - e) 200 μ s to 2000 μ s;
 - f) 100 μ s to 500 μ s;
 - g) at least one of selected and adjusted based on at least one of:
 - i) a cardiovascular disease being treated;
 - ii) an autonomic dysfunction being treated;
 - iii) a responsiveness to treatment;
 - iv) biofeedback; and,
 - v) user input.
- 9) A neuromodulation system according to any one of claims 1 to 8, wherein the sequence of different types of waveforms repeats, with a dwell time between each repeat.
- 10) A neuromodulation system according to claim 9, wherein the dwell time is at least one of:
- a) variable;
 - b) fixed;
 - c) 0 μ s;
 - d) 1 μ s to 10000 μ s;
 - e) 10000 μ s to 10000000 μ s;
 - f) approximately 50000 μ s; and,
 - g) at least one of selected and adjusted based on at least one of:
 - i) a cardiovascular disease being treated;
 - ii) an autonomic dysfunction being treated;

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- iii) a responsiveness to treatment;
- iv) biofeedback; and,
- v) user input.

11) A neuromodulation system according to any one of claims 1 to 10, wherein at least one of:

- a) a magnitude of at least one of the different types of waveforms is at least one of:
 - i) variable;
 - ii) fixed;
 - iii) at least one of selected and adjusted based on at least one of:
 - (1) a cardiovascular disease being treated;
 - (2) an autonomic dysfunction being treated;
 - (3) a responsiveness to treatment;
 - (4) biofeedback; and,
 - (5) user input; and,
- b) relative magnitudes of the waveforms in the sequence of different types of waveforms are at least one of:
 - i) variable;
 - ii) fixed;
 - iii) at least one of selected and adjusted based on at least one of:
 - (1) a cardiovascular disease being treated;
 - (2) an autonomic dysfunction being treated;
 - (3) a responsiveness to treatment;
 - (4) biofeedback; and,
 - (5) user input.

12) A neuromodulation system according to any one of claims 1 to 11, wherein at least one of:

- a) a duration of each waveform in the sequence of waveforms is at least one of:
 - i) variable;
 - ii) fixed;
 - iii) 1 μ s to 20000 μ s;
 - iv) 200 μ s to 500 μ s; and,
 - v) at least one of selected and adjusted based on at least one of:
 - (1) a cardiovascular disease being treated;

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- (2) an autonomic dysfunction being treated;
 - (3) a responsiveness to treatment;
 - (4) biofeedback; and,
 - (5) user input; and,
 - b) relative durations of the waveforms in the sequence of different types of waveforms are at least one of:
 - i) variable;
 - ii) fixed;
 - iii) at least one of selected and adjusted based on at least one of:
 - (1) a cardiovascular disease being treated;
 - (2) an autonomic dysfunction being treated;
 - (3) a responsiveness to treatment;
 - (4) biofeedback; and,
 - (5) user input.
- 13) A neuromodulation system according to any one of claims 1 to 12, wherein the sequence of different types of waveforms includes a first waveform followed by a second waveform.
- 14) A neuromodulation system according to claim 13, wherein at least one of:
- a) the first waveform has a longer duration than the second waveform;
 - b) the first waveform has a shorter duration than the second waveform;
 - c) the first waveform has the same duration as the second waveform;
 - d) the first waveform has a greater magnitude than the second waveform;
 - e) the first waveform has a lesser magnitude than the second waveform; and,
 - f) the first waveform has the same magnitude as the second waveform.
- 15) A neuromodulation system according to any one of claims 1 to 14, wherein the sequence of different types of waveforms includes a rectangular pulse waveform and an exponential ramp waveform.
- 16) A neuromodulation system according to any one of claims 1 to 15, wherein the sequence of different types of waveforms includes a rectangular pulse waveform at a subthreshold, a spike waveform and an exponential decay waveform.
- 17) A neuromodulation system according to claim 15 or 16, wherein the rectangular pulse waveform is a pre-pulse at a subthreshold, wherein the subthreshold is at least one of:

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- a) less than a threshold;
 - b) larger than 0% and less than 100% of a threshold;
 - c) between 50% and 70% of a threshold;
 - d) approximately 60% of a threshold; and,
 - e) approximately 50% of a threshold.
- 18) A neuromodulation system according to any one of claims 1 to 17, wherein the nerve modulation system is configured to stimulate the nerve to modulate at least one of:
- a) a presence, absence or concentration of an inflammatory biomarker;
 - b) an electrocardiographic biomarker;
 - c) a temperature;
 - d) a blood oxygen level;
 - e) a heart rate;
 - f) a heart rate variability;
 - g) an impedance; and,
 - h) a galvanic skin response.
- 19) A neuromodulation system according to any one of claims 1 to 18, wherein the condition includes at least one of:
- a) cardiovascular disease, including at least one of:
 - i) a cardiovascular disease with an inflammatory phenotype;
 - ii) a coronary heart disease;
 - iii) a cerebrovascular disease;
 - iv) a peripheral arterial disease;
 - v) a rheumatic heart disease;
 - vi) a congenital heart disease;
 - vii) an ischemic heart disease;
 - viii) an arrhythmia;
 - ix) atrial fibrillation;
 - x) hypertension;
 - xi) heart failure with reduced ejection fraction;
 - xii) acute heart failure;
 - xiii) heart failure with mildly reduced ejection fraction;

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- xiv) heart failure with preserved ejection fraction;
- xv) diastolic dysfunction;
- xvi) postural orthostatic tachycardia syndrome;
- xvii) myocardial infarction; and,
- xviii) stroke;
- b) chronic fatigue;
- c) long COVID;
- d) rheumatoid arthritis;
- e) autonomic nervous system dysfunction;
- f) dysautonomia;
- g) mental health disorders;
- h) inflammatory disorders;
- i) autoimmune disorders;
- j) cognitive dysfunction;
- k) post viral syndromes including long COVID;
- l) pain disorders;
- m) stress including acute stress and chronic stress;
- n) post traumatic stress disorder;
- o) systemic lupus erythematosus;
- p) diabetes; and,
- q) cancer.

20) A neuromodulation system according to any one of claims 1 to 19, wherein the system enhances at least one of:

- a) concomitant therapy delivery;
- b) cognition;
- c) memory;
- d) mobility;
- e) physical performance;
- f) recovery after physical activity;
- g) sleep quality; and,
- h) divergent thinking.

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- 21) A neuromodulation system according to any one of claims 1 to 20, wherein the nerve is at least one of:
- a) a cranial nerve including at least one of Cranial nerve I to XII;
 - b) a vagus nerve, including at least one of:
 - i) an auricular branch;
 - ii) a cervical branch;
 - iii) an efferent branch; and,
 - iv) an afferent branch;
 - c) a central neural nerve; and,
 - d) a peripheral nerve, including at least one of:
 - i) a median nerve; and,
 - ii) a radial nerve.
- 22) A neuromodulation system according to any one of claims 1 to 21, wherein the signal generator modulates the nerve including modulating at least one target of the nerve.
- 23) A neuromodulation system according to any one of claims 1 to 22, wherein the at least one target of the nerve includes:
- a) an auricular branch of the nerve;
 - b) a cervical branch of the nerve;
 - c) a radial branch of the nerve;
 - d) a specific neural fibres;
 - e) efferent fibres;
 - f) afferent fibres;
 - g) A-alpha ($A\alpha$) fibres;
 - h) A-beta ($A\beta$) fibres;
 - i) A-delta ($A\delta$) fibres;
 - j) B fibres including at least a myelinated B fibres; and,
 - k) C fibres.
- 24) A neuromodulation system according to any one of claims 1 to 23, wherein the electrodes are configured to be attached to the subject in a form of at least one of:
- a) a clip;
 - b) a collar;

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- c) a wrist band;
 - d) a headband;
 - e) an earpiece;
 - f) an auricular attachment;
 - g) a textile attachment;
 - h) a handheld attachment;
 - i) an ankle band;
 - j) a ring;
 - k) a wearable piece;
 - l) a wearable jewellery;
 - m) a neckpiece; and,
 - n) invasively.
- 25) A neuromodulation system according to claim 1 to 24, wherein the electrodes are configured to be attached to an ear of the subject via an attachment, wherein the attachment includes a housing biased against the ear and is positioned proximate to a target nerve of the subject.
- 26) A neuromodulation system according to claim 24 or 25, wherein the electrodes are configured to be attached to a tragus of the subject, the attachment or earpiece including:
- a) opposing arms configured so that a distal end of the arms are biased towards each other; and,
 - b) the electrodes positioned proximate a distal end of the arms on opposing faces so that the electrodes are urged into engagement with opposing faces of the tragus.
- 27) A neuromodulation system according to claim 24 or 25, wherein the system includes a hook extending over and behind an ear of the subject to at least partially support the attachment.
- 28) A neuromodulation system according to claim 27, wherein the hook is configured to extend laterally from the earpiece so that the lead can loop over and behind an ear of the subject.
- 29) A neuromodulation system according to any one of the claims 24 to 28, wherein the system includes a lead extending from the earpiece, the lead including connections configured to electrically connect the electrodes to the signal generator.
- 30) A neuromodulation system according to claim 29, wherein the lead is configured to extend laterally from the earpiece so that the lead can loop over and behind an ear of the subject.

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- 31) A neuromodulation system according to claim 29 or claim 30, wherein the lead is configured to extend from a distal end of one of the arms.
- 32) A neuromodulation system according to any one of the claims 29 to 31, wherein the lead includes a sheath extending at least part way along a length of the lead and wherein the sheath defines a hook shaped to loop over and behind an ear of the subject.
- 33) A neuromodulation system according to any one of the claims 24 to 32, wherein one of the arms is configured to be positioned within a concha of the user.
- 34) A neuromodulation system according to any one of the claims 24 to 33, wherein the arms are pivotally connected about a mid-portion.
- 35) A neuromodulation system according to any one of the claims 24 to 34, wherein a distal ends of the arms are biased together using a biasing mechanism.
- 36) A neuromodulation system according to claim 35, wherein the biasing mechanism includes at least one of:
- a) a pivot;
 - b) a spring;
 - c) a rubber member;
 - d) a malleable member interconnecting the arms;
 - e) at least partially malleable arms;
 - f) an at least partially elastic member interconnecting the arms;
 - g) at least partially elastic arms; and,
 - h) magnets provided on the arms.
- 37) A neuromodulation system according to any one of the claims 24 to 36, wherein a proximal outer face of the arms include a depression configured to allow a subject to engage the arms and bias the arms apart.
- 38) A neuromodulation system according to any one of the claims 24 to 37, wherein the arms have at least one of:
- a) a length that is at least one of:
 - i) greater than 15mm;
 - ii) greater than 16mm;
 - iii) greater than 17mm;
 - iv) greater than 18mm;

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- v) greater than 19mm;
 - vi) greater than 20mm;
 - vii) greater than 21mm;
 - viii) less than 30mm;
 - ix) less than 28mm;
 - x) less than 27mm;
 - xi) less than 26mm;
 - xii) less than 25mm;
 - xiii) less than 24mm;
 - xiv) less than 23mm; and,
 - xv) about 22mm; and,
- b) a width that is at least one of:
- i) greater than 5mm;
 - ii) greater than 6mm;
 - iii) greater than 7mm;
 - iv) greater than 8mm;
 - v) greater than 9mm;
 - vi) greater than 10mm;
 - vii) less than 16mm;
 - viii) less than 15mm;
 - ix) less than 14mm;
 - x) less than 13mm;
 - xi) less than 12mm; and,
 - xii) about 11mm.

39) A neuromodulation system according to any one of the claims 24 to 38, wherein the electrodes are:

- a) substantially circular;
- b) rounded rectangular;
- c) rounded square;
- d) at least partially dome shaped; and,
- e) have a diameter of at least one of:

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- i) greater than 4mm;
- ii) greater than 5mm;
- iii) greater than 6mm;
- iv) greater than 7mm;
- v) less than 12mm;
- vi) less than 11mm;
- vii) less than 10mm;
- viii) less than 9mm; and,
- ix) about 8mm.

40) A neuromodulation system according to any one of the claims 24 to 39, wherein a surface of the electrodes at least one of:

- a) is roughened;
- b) includes grooves;
- c) includes ridges; and,
- d) is coated.

41) A neuromodulation system according to any one of the claims 24 to 40, wherein a surface of the electrodes is coated with at least one of:

- a) an inert metal; and,
- b) gold.

42) A neuromodulation system according to any one of the claims 24 to 41, wherein therapy signals are signals having a frequency that is at least one of:

- a) less than 20kHz;
- b) less than 10kHz;
- c) less than 1Hz;
- d) less than 500Hz;
- e) less than 200Hz;
- f) less than 150Hz;
- g) less than 100Hz;
- h) less than 75Hz;
- i) greater than 1Hz;
- j) greater than 2Hz;

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- k) greater than 5Hz;
- l) greater than 10Hz;
- m) greater than 20Hz;
- n) about 20Hz; and,
- o) about 50Hz.

43) A neuromodulation system according to any one of the claims 24 to 42, wherein therapy signals are signals having a pulse width of at least one of:

- a) less than 5,000 μ s;
- b) less than 2,500 μ s;
- c) less than 1,000 μ s;
- d) less than 500 μ s;
- e) less than 200 μ s;
- f) less than 100 μ s;
- g) less than 75 μ s;
- h) greater than 1 μ s;
- i) greater than 2 μ s;
- j) greater than 5 μ s;
- k) greater than 10 μ s;
- l) greater than 20 μ s; and,
- m) about 50 μ s.

44) A neuromodulation system according to any one of the claims 24 to 43, wherein the therapy signals are signals having a voltage that is at least one of:

- a) less than 50V;
- b) less than 25V;
- c) less than 10V;
- d) less than 5V;
- e) less than 2V;
- f) less than 1V;
- g) greater than 0.1V;
- h) greater than 0.2V;
- i) greater than 0.5V; and,

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- j) greater than 1V.
- 45) A neuromodulation system according to any one of the claims 24 to 44, wherein the therapy signals are signals having a current that is at least one of:
- a) less than 50mA;
 - b) greater than 0.1mA; and,
 - c) between 0.1mA and 36mA.
- 46) A neuromodulation system according to any one of the claims 24 to 45, wherein the therapy signals at least one of:
- a) are symmetrical;
 - b) are asymmetrical;
 - c) are monophasic;
 - d) are bi-phasic;
 - e) are tri-phasic;
 - f) are poly-phasic; and,
 - g) include multiple phases with at least one interspersed dwell.
- 47) A neuromodulation system according to any one of the claims 24 to 46, wherein a respective therapy signal is applied to each of the electrodes.
- 48) A neuromodulation system according to claim 47, wherein the respective therapy signals are at least one of:
- a) in phase; and,
 - b) out of phase.
- 49) A neuromodulation system according to any of claims 24 to 48, wherein the lead includes at least one of:
- a) a respective conductor for each electrode;
 - b) at least one insulating layer; and,
 - c) a braided shield.
- 50) A neuromodulation system according to any one of the claims 24 to 49, wherein the therapy signals are configured to at least one of:
- a) stimulate activity of the vagus nerve; and,
 - b) inhibit activity of the vagus nerve.

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- 51) A neuromodulation system according to any one of the claims 24 to 50, wherein the signal generator is mounted on the earpiece.
- 52) A neuromodulation system according to any one of the claims 24 to 51, wherein the system includes a control system having a housing containing at least one of:
- a) the signal generator;
 - b) a power supply; and,
 - c) a controller.
- 53) A neuromodulation system according to claim 52, wherein a lead extends from the earpiece to the housing.
- 54) A neuromodulation system according to any of claims 24 to 53, wherein the system includes a controller configured to control the signal generator.
- 55) A nerve modulation system according to claim 54, wherein the controller is configured to:
- a) determine therapy signal parameters; and,
 - b) control the signal generator in accordance with the therapy signal parameters.
- 56) A neuromodulation system according to claim 55, wherein the controller is configured to determine the therapy signal parameters in accordance with at least one of:
- a) defined therapy signal parameters stored in a memory;
 - b) user input commands;
 - c) biofeedback;
 - d) signals from a sensor; and,
 - e) a selected therapy mode.
- 57) A neuromodulation system according to any of claims 54 to 56, wherein the system includes a sensor configured to sense at least one subject parameter and wherein the controller is configured to:
- a) determine at least one subject parameter using signals from the sensor; and,
 - b) cause the signal generator to generate therapy signals in accordance with the at least one subject parameter.
- 58) A neuromodulation system according to claim 57, wherein the sensor is at least one of:
- a) mounted on the earpiece proximate at least one electrode; and,
 - b) electrically coupled to at least one of the electrodes.

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- 59) A neuromodulation system according to claim 57 or claim 58, wherein the sensor is at least one of:
- a) an inflammatory biomarker sensor;
 - b) a temperature sensor;
 - c) a blood oxygen sensor;
 - d) a pulse oximeter;
 - e) a heart rate sensor; and,
 - f) an impedance sensor.
- 60) A neuromodulation system according to any of claims 57 to 59, wherein the at least one subject parameter includes at least one of:
- a) a presence, absence or concentration of an inflammatory biomarker;
 - b) a temperature;
 - c) a blood oxygen level;
 - d) a heart rate;
 - e) a heart rate variability;
 - f) an impedance; and,
 - g) a galvanic skin response.
- 61) A neuromodulation system according to any of claims 54 to 60, wherein the controller is configured to:
- a) determine feedback using user input commands; and,
 - b) cause the signal generator to generate the therapy signals in accordance with the feedback.
- 62) A neuromodulation system according to any of claims 54 to 61, wherein the controller is configured to:
- a) cause the signal generator to generate therapy signals having progressively increasing magnitudes; and,
 - b) selecting a therapy signal magnitude in response to user input commands.
- 63) A neuromodulation system according to claim 62, wherein the controller is configured to progressively increase the therapy signal in steps of at least one of:
- a) 0.1mA;
 - b) 0.2mA;

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- c) 0.5mA;
 - d) 0.8mA;
 - e) 1mA;
 - f) 1.5mA; and,
 - g) 2mA.
- 64) A neuromodulation system according to any of claims 54 to 63, wherein the controller is configured to:
- a) determine selection of a therapy mode in accordance with user input commands; and,
 - b) control the signal generator in accordance with the selected mode.
- 65) A neuromodulation system according to claim 64, wherein the system includes a number of therapy modes stored in a store, each therapy mode defining a sequence of therapy signals and wherein the controller is configured to cause the signal generator to generate the sequence of therapy signals.
- 66) A neuromodulation system according to any of claims 54 to 65, wherein in a research mode the controller is configured to:
- a) selecting a therapy signal magnitude in response to user input commands; and,
 - b) progressively decrease the therapy signal magnitude to zero.
- 67) A neuromodulation method for treating a condition, the method including:
- a) placing electrodes to be approximate to a subject; and,
 - b) using a signal generator electrically connected to the electrodes to generate at least one therapy signal that is applied to a nerve via the electrodes to thereby modulate the nerve, and wherein the at least one therapy signal includes at least one sequence of different types of waveforms.