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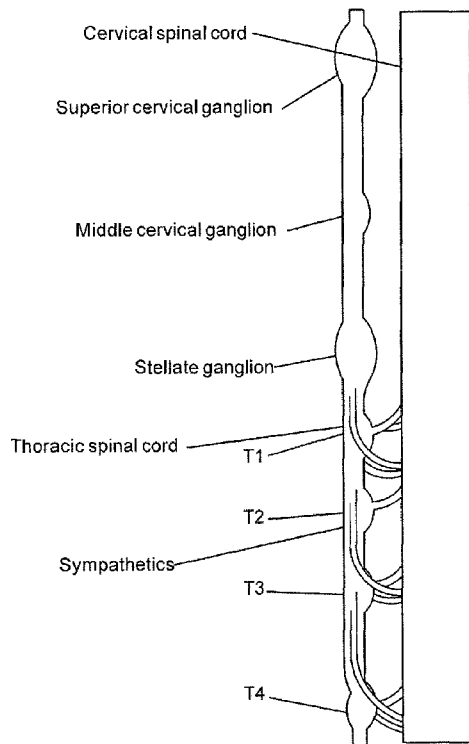


Fig. 1

(57) Abstract: One aspect of the present disclosure relates to a closed-loop therapy system for treating an anxiety or anxiety-associated disorder in a subject. The therapy delivery system can include a sensing component, a delivery component, and a controller. The sensing component can be configured to detect at least one physiological parameter associated with the anxiety or anxiety-associated disorder. The delivery component can be configured for implantation on or about an autonomic nervous tissue target or a spinal nervous tissue target. The controller can be configured to automatically coordinate operation of the sensing and delivery components. The controller can also be configured to deliver an electrical signal to the delivery component to modulate activity at the autonomic nervous tissue target or a spinal nervous tissue target and effectively treat the anxiety or anxiety-associated disorder.

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LSYSTEMS FOR TREATING ANXIETY AND ANXIETY-ASSOCIATED DISORDERS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial Nos. 61/776,072, filed March 11, 2013, and 61/896,347, filed October 28, 2013, the entirety of each of which is hereby incorporated by reference for all purposes.

TECHNICAL FIELD

[0002] The present disclosure relates generally to neuromodulatory devices, systems and methods, and more particularly to devices, systems, and methods for treating anxiety and anxiety-associated disorders.

BACKGROUND

[0003] Anxiety and depression are major psychiatric disorders of significant clinical and socioeconomic significance. Clinical depression often presents alongside anxiety disorders, and vice-versa. In the general population, these disorders affect daily performance and correlate with impulse control, financial behaviors, substance abuse and organization. Anxiety is an unpleasant state that involves a complex combination of emotions that include fear, apprehension, and worry. It is often accompanied by physical sensations, such as heart palpitations, nausea, chest pain, shortness of breath, or tension headache. "Anxiety disorder" is a blanket term covering several different forms of abnormal, pathological anxiety, fears, phobias and nervous conditions that may come on suddenly (acute anxiety) and/or gradually over a period of several years (chronic), and may impair or prevent the pursuing of normal daily routines. Anxiety disorders are often debilitating chronic conditions, which can be present from an early age or begin suddenly after a triggering event. They are prone to flare up at times of high stress.

[0004] Anxiety is often described as having cognitive, somatic, emotional, and behavioral components. The cognitive component entails expectation of a diffuse and uncertain danger. Somatically, the body prepares the organism to deal with threat (known as an emergency reaction) in the following ways: blood pressure and heart rate are increased; sweating is increased; bloodflow to the major muscle groups is increased; and immune and digestive system functions are inhibited. Externally, somatic signs of anxiety may include pale skin, sweating, trembling, and pupillary dilation. Emotionally, anxiety causes a sense of dread or panic and physically causes nausea, and chills. Behaviorally, both voluntary and involuntary behaviors may arise directed at escaping or avoiding the source of anxiety. These behaviors are frequent

and often maladaptive, being most extreme in anxiety disorders. However, anxiety is not always pathological or maladaptive — it is a common emotion along with fear, anger, sadness, and happiness, and it has a very important function in relation to survival. Conventional treatments for anxiety include behavioral therapy, lifestyle changes and/or pharmaceutical therapy (medications). Most drugs used to treat these disorders are known to have negative side effects that may limit their use, or cause habituation and dependence.

SUMMARY

[0005] The present disclosure relates generally to neuromodulatory devices, systems and methods, and more particularly to devices, systems, and methods for treating anxiety and anxiety-associated disorders.

[0006] One aspect of the present disclosure relates to a closed-loop therapy system for treating an anxiety or anxiety-associated disorder in a subject. The therapy delivery system can include a sensing component, a delivery component, and a controller. The sensing component can be configured to detect at least one physiological parameter associated with the anxiety disorder. The delivery component can be configured for implantation on or about an autonomic nervous tissue target or a spinal nervous tissue target. The controller can be configured to automatically coordinate operation of the sensing and delivery components. The controller can also be configured to deliver an electrical signal to the delivery component to modulate activity at the autonomic nervous tissue target or a spinal nervous tissue target and effectively treat the anxiety or anxiety-associated disorder.

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[0007] Another aspect of the present disclosure relates to a closed-loop therapy delivery system for treating autism in a subject. The therapy delivery system can comprise a sensing component, a delivery component, and a controller. The sensing component can be configured to detect at least one physiological parameter associated with the autism. The delivery component can be configured for implantation on or about an autonomic nervous tissue target. The controller can be configured to automatically coordinate operation of the sensing and delivery components. The controller can be configured to deliver an electrical signal to the delivery component to modulate activity of the autonomic nervous tissue target and effectively treat the autism.

[0008] Another aspect of the present disclosure relates to a method for treating an anxiety or anxiety-associated disorder in a subject. One step of the method can include placing a therapy delivery device into electrical communication with an autonomic nervous tissue target or a spinal nervous tissue target. Next, the therapy delivery device can be activated to deliver an electrical signal to the autonomic nervous tissue target or a spinal nervous tissue target to effectively treat the anxiety or anxiety-associated disorder in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The foregoing and other features of the present disclosure will become apparent to those skilled in the art to which the present disclosure relates upon reading the following description with reference to the accompanying drawings, in which:

[0010] Fig. 1 is schematic illustration showing the cervical and upper thoracic portions of the sympathetic nerve chain and the spinal cord;

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[0011] Fig. 2 is a schematic illustration of a human spinal cord and associated vertebrae;

[0012] Fig. 3 is a schematic illustration showing a closed-loop therapy delivery system for treating an anxiety or anxiety-associated disorder configured according to one aspect of the present disclosure;

[0013] Fig. 4 is a process flow diagram illustrating a method for treating an anxiety or anxiety-associated disorder according to another aspect of the present disclosure;

[0014] Fig. 5 is a schematic illustration showing the closed-loop therapy delivery system of Fig. 3 implanted in a subject;

[0015] Fig. 6 is a schematic illustration showing a transcutaneous neuromodulatory device constructed in accordance with another aspect of the present disclosure;

[0016] Figs. 7A-B are schematic illustrations showing alternative transcutaneous neuromodulatory devices constructed in accordance with other aspects of the present disclosure; and

[0017] Fig. 8 is a schematic illustration showing the closed-loop therapy delivery system in Fig. 3 implanted in a human subject.

DETAILED DESCRIPTION

[0018] Definitions

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the present disclosure pertains.

[0020] In the context of the present disclosure, the term “autonomic nervous tissue” can refer to any tissues of the sympathetic nervous system (SNS) or the parasympathetic nervous system

(PNS) including, but not limited to, neurons, axons, fibers, tracts, nerves, plexus, afferent plexus fibers, efferent plexus fibers, ganglia, pre-ganglionic fibers, post-ganglionic fibers, afferents, efferents, and combinations thereof.

[0021] As used herein, the terms “epidural space” or “spinal epidural space” can refer to an area in the interval between the dural sheath and the wall of the spinal canal. In some instances, at least a portion of a therapy delivery device or a therapy delivery system may be implanted in the epidural space.

[0022] As used herein, the term “subdural” can refer to the space between the dura mater and arachnoid membrane. In some instances, at least a portion of a therapy delivery device or a therapy delivery system may be implanted in the subdural space.

[0023] As used herein, the phrase “spinal nervous tissue” can refer to nerves, neurons, neuroglial cells, glial cells, neuronal accessory cells, nerve roots, nerve fibers, nerve rootlets, parts of nerves, nerve bundles, mixed nerves, sensory fibers, motor fibers, dorsal root, ventral root, dorsal root ganglion, spinal ganglion, ventral motor root, general somatic afferent fibers, general visceral afferent fibers, general somatic efferent fibers, general visceral efferent fibers, grey matter, white matter, the dorsal column, the lateral column, and/or the ventral column associated with the spinal cord.

[0024] As used herein, the term “subject” can be used interchangeably with the term “patient” and refer to any warm-blooded organism including, but not limited to, human beings, pigs, rats, mice, dogs, goats, sheep, horses, monkeys, apes, farm animals, livestock, rabbits, cattle, etc.

[0025] As used herein, the terms “modulate” or “modulating” with reference to an autonomic nervous tissue target or spinal nervous tissue target can refer to causing a change in neuronal activity, chemistry and/or metabolism. The change can refer to an increase, decrease, or even a change in a pattern of neuronal activity. The terms may refer to either excitatory or inhibitory stimulation, or a combination thereof, and may be at least electrical, magnetic, ultrasound, optical, chemical, or a combination of two or more of these. The terms “modulate” or “modulating” can also be used to refer to a masking, altering, overriding, or restoring of neuronal activity.

[0026] As used herein, the terms “substantially blocked” or “substantially block” when used with reference to nervous tissue activity can refer to a complete (*e.g.*, 100%) or partial inhibition (*e.g.*, less than 100%, such as about 90%, about 80%, about 70%, about 60%, or less than about 50%) of nerve conduction through the nervous tissue.

[0027] As used herein, the term “activity” when used with reference to autonomic or spinal nervous tissue can, in some instances, refer to the ability of a nerve, neuron, or fiber to conduct, propagate, and/or generate an action potential. In other instances, the term can refer to the frequency at which a nerve or neuron is conducting, propagating, and/or generating one or more action potentials at a given moment in time. In further instances, the term can refer to the frequency at which a nerve or neuron is conducting, propagating, and/or generating one or more action potentials over a given period of time (*e.g.*, seconds, minutes, hours, days, etc.).

[0028] As used herein, the term “electrical communication” can refer to the ability of an electric field generated by an electrode or electrode array to be transferred, or to have a neuromodulatory effect, within and/or on autonomic or spinal nervous tissue.

[0029] As used herein, the term “anxiety disorder” can refer to a dysfunctional state of fear and anxiety, *e.g.*, fear and anxiety that is out of proportion to a stressful situation or the anticipation of a stressful situation. In some instances, an anxiety disorder can be any one or combination of generalized anxiety disorders, such as depression, panic disorder, panic disorder with agoraphobia, agoraphobia, social anxiety disorder, a generalized stress disorder, a stress-induced anxiety disorder, addiction (*e.g.*, alcoholism), an eating disorder and obsessive-compulsive disorder.

[0030] As used herein, the term “eating disorder” can refer to any disease or condition that is characterized, at least in part, by obsession with body weight and food as well as abnormal compulsions to avoid eating or uncontrollable impulses to consume abnormally large amounts of food. Eating disorders may affect not only the social well-being, but also the physical well-being of sufferers. Eating disorders can be caused by, a symptom of, co-morbid, or otherwise associated with one or more anxiety disorders, mood disorders, neurobehavioral disorders (*e.g.*, psychotic or psychiatric disorders, such as schizophrenia), and/or abnormalities in Body Mass Index, metabolic rate, etc. Non-limiting examples of eating disorders can include anorexia nervosa, bulimia, binge or compulsive eating, obesity, cachexia and wasting syndromes.

[0031] As used herein, the term “anxiety-associated disorder” can refer to a dysfunctional or abnormal psychological and physiological state characterized by cognitive, somatic, emotional, and behavioral components that is related to, caused at least in part by, or correlated with the presence of a co-morbid disease, disorder or condition, such as an eating disorder, autism or other disorder in the autism spectrum. In some instances, these components combine to create the painful feelings typically recognized as anger, fear, apprehension or worry.

[0032] As used herein, the term “autism” can refer to any disease or disorder characterized by impaired social interaction and communication, and by restricted and repetitive behavior. In some instances, “autism” can refer to one of three recognized disorders in the autism spectrum, the other two being Asperger syndrome and pervasive developmental disorder.

[0033] As used herein, the terms “treat” or “treating” can refer to therapeutically regulating, preventing, improving, alleviating the symptoms of, and/or reducing the effects of an anxiety or anxiety-associated disorder. As such, treatment also includes situations where an anxiety or anxiety-associated disorder, or at least symptoms associated therewith, is completely inhibited, *e.g.*, prevented from happening or stopped (*e.g.*, terminated) such that the subject no longer suffers from the anxiety or anxiety-associated disorder, or at least the symptoms that characterize the anxiety or anxiety-associated disorder.

[0034] As used herein, the term “in communication” can refer to at least a portion of a therapy delivery device or therapy delivery system being adjacent, in the general vicinity, in close proximity, or directly next to and/or directly on an autonomic nervous tissue target or spinal nerve target associated with an anxiety or anxiety-associated disorder. In some instances, the term can mean that at least a portion of a therapy delivery device or therapy delivery system is “in communication” with an autonomic nervous tissue target or a spinal nervous tissue target if application of a therapy signal (*e.g.*, an electrical signal) thereto results in a modulation of neuronal activity to elicit a desired response, such as modulation of a sign or symptom associated with an anxiety or anxiety-associated disorder.

[0035] As used herein, the singular forms “a,” “an” and “the” can include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms

“comprises” and/or “comprising,” as used herein, can specify the presence of stated features, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, steps, operations, elements, components, and/or groups thereof.

[0036] As used herein, the term “and/or” can include any and all combinations of one or more of the associated listed items.

[0037] As used herein, phrases such as “between X and Y” and “between about X and Y” can be interpreted to include X and Y.

[0038] As used herein, phrases such as “between about X and Y” can mean “between about X and about Y.”

[0039] As used herein, phrases such as “from about X to Y” can mean “from about X to about Y.”

[0040] It will be understood that when an element is referred to as being “on,” “attached” to, “connected” to, “coupled” with, “contacting,” etc., another element, it can be directly on, attached to, connected to, coupled with or contacting the other element or intervening elements may also be present. In contrast, when an element is referred to as being, for example, “directly on,” “directly attached” to, “directly connected” to, “directly coupled” with or “directly contacting” another element, there are no intervening elements present. It will also be appreciated by those of skill in the art that references to a structure or feature that is disposed “directly adjacent” another feature may have portions that overlap or underlie the adjacent feature, whereas a structure or feature that is disposed “adjacent” another feature may not have portions that overlap or underlie the adjacent feature.

[0041] Spatially relative terms, such as “under,” “below,” “lower,” “over,” “upper” and the like, may be used herein for ease of description to describe one element or feature’s relationship to another element(s) or feature(s) as illustrated in the figures. It will be understood that the spatially relative terms can encompass different orientations of a device in use or operation, in addition to the orientation depicted in the figures. For example, if a device in the figures is inverted, elements described as “under” or “beneath” other elements or features would then be oriented “over” the other elements or features.

[0042] It will be understood that, although the terms “first,” “second,” etc. may be used herein to describe various elements, these elements should not be limited by these terms. These terms are only used to distinguish one element from another. Thus, a “first” element discussed below could also be termed a “second” element without departing from the teachings of the present disclosure. The sequence of operations (or steps) is not limited to the order presented in the claims or figures unless specifically indicated otherwise.

[0043] Overview

[0044] A brief discussion of the pertinent neurophysiology is provided to assist the reader with understanding certain aspects of the present disclosure.

[0045] *The autonomic nervous system (ANS)*

[0046] The nervous system is divided into the somatic nervous system and the ANS. In general, the somatic nervous system controls organs under voluntary control (*e.g.*, skeletal muscles) and the ANS controls individual organ function and homeostasis. For the most part, the ANS is not subject to voluntary control. The ANS is also commonly referred to as the visceral or automatic system.

[0047] The ANS can be viewed as a “real-time” regulator of physiological functions which extracts features from the environment and, based on that information, allocates an organism’s internal resources to perform physiological functions for the benefit of the organism, *e.g.*, responds to environment conditions in a manner that is advantageous to the organism. The ANS acts through a balance of its two components: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), which are two anatomically and functionally distinct systems. Both of these systems include myelinated preganglionic fibers which make synaptic connections with unmyelinated postganglionic fibers, and it is these fibers which then innervate the effector structure. These synapses usually occur in clusters called ganglia. Most organs are innervated by fibers from both divisions of the ANS, and the influence is usually opposing (*e.g.*, the vagus nerve slows the heart, while the sympathetic nerves increase its rate and contractility), although it may be parallel (*e.g.*, as in the case of the salivary glands). Each of these is briefly reviewed below.

[0048] The SNS is the part of the ANS comprising nerve fibers that leave the spinal cord in the thoracic and lumbar regions and supply viscera and blood vessels by way of a chain of sympathetic ganglia (also referred to as the sympathetic chain, sympathetic trunk or the gangliated cord) running on each side of the spinal column, which communicate with the central nervous system via a branch to a corresponding spinal nerve. The sympathetic trunks extend from the base of the skull to the coccyx. The cephalic end of each is continued upward through the carotid canal into the skull, and forms a plexus on the internal carotid artery; the caudal ends of the trunks converge and end in a single ganglion, the ganglion impar, placed in front of the coccyx. As partly shown in Fig. 1, the ganglia of each trunk are distinguished as cervical,

thoracic, lumbar, and sacral and, except in the neck, they closely correspond in number to the vertebrae.

[0049] The SNS controls a variety of autonomic functions including, but not limited to, control of movement and secretions from viscera and monitoring their physiological state, stimulation of the sympathetic system inducing, *e.g.*, the contraction of gut sphincters, heart muscle and the muscle of artery walls, and the relaxation of gut smooth muscle and the circular muscles of the iris. The chief neurotransmitter in the SNS is adrenaline, which is liberated in the heart, visceral muscle, glands and internal vessels, with acetylcholine acting as a neurotransmitter at ganglionic synapses and at sympathetic terminals in skin and skeletal muscles. The actions of the SNS tend to be antagonistic to those of the PNS.

[0050] The neurotransmitter released by the post-ganglionic neurons is nonadrenaline (also called norepinephrine). The action of noradrenaline on a particular structure, such as a gland or muscle, is excitatory in some cases and inhibitory in others. At excitatory terminals, ATP may be released along with noradrenaline. Activation of the SNS may be characterized as general because a single pre-ganglionic neuron usually synapses with many post-ganglionic neurons, and the release of adrenaline from the adrenal medulla into the blood ensures that all the cells of the body will be exposed to sympathetic stimulation even if no post-ganglionic neurons reach them directly.

[0051] The PNS is the part of the ANS controlling a variety of autonomic functions including, but not limited to, involuntary muscular movement of blood vessels and gut and glandular secretions from eye, salivary glands, bladder, rectum and genital organs. The vagus nerve is part of the PNS. Parasympathetic nerve fibers are contained within the last five cranial

nerves and the last three spinal nerves and terminate at parasympathetic ganglia near or in the organ they supply. The actions of the PNS are broadly antagonistic to those of the SNS — lowering blood pressure, slowing heartbeat, stimulating the process of digestion etc. The chief neurotransmitter in the PNS is acetylcholine. Neurons of the parasympathetic nervous system emerge from the brainstem as part of the Cranial nerves III, VII, IX and X (vagus nerve) and also from the sacral region of the spinal cord via Sacral nerves. Because of these origins, the PNS is often referred to as the “craniosacral outflow”.

[0052] In the PNS, both pre- and post-ganglionic neurons are cholinergic (*i.e.*, they utilize the neurotransmitter acetylcholine). Unlike adrenaline and noradrenaline, which the body takes around 90 minutes to metabolize, acetylcholine is rapidly broken down after release by the enzyme cholinesterase. As a result the effects are relatively brief in comparison to the SNS.

[0053] Each pre-ganglionic parasympathetic neuron synapses with just a few post-ganglionic neurons, which are located near, or in, the effector organ, a muscle or gland. As noted above, the primary neurotransmitter in the PNS is acetylcholine such that acetylcholine is the neurotransmitter at all the pre- and many of the post-ganglionic neurons of the PNS. Some of the post-ganglionic neurons, however, release nitric oxide as their neurotransmitter.

[0054] *The central nervous system (CNS)*

[0055] The spinal cord (Fig. 2) is part of the CNS, which extends caudally and is protected by the bony structures of the vertebral column. It is covered by the three membranes of the CNS, *i.e.*, the dura mater, arachnoid and the innermost pia mater. In most adult mammals, it occupies only the upper two-thirds of the vertebral canal as the growth of the bones composing the vertebral column is proportionally more rapid than that of the spinal cord. According to its

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rostrocaudal location, the spinal cord can be divided into four parts: cervical; thoracic; lumbar; and sacral. Two of these are marked by an upper (cervical) and a lower (lumbar) enlargement.

[0056] Alongside the median sagittal plane, the anterior and the posterior median fissures divide the cord into two symmetrical portions, which are connected by the transverse anterior and posterior commissures. On either side of the cord the anterior lateral and posterior lateral fissures represent the points where the ventral and dorsal rootlets (later roots) emerge from the cord to form the spinal nerves. Unlike the brain, in the spinal cord the grey matter is surrounded by the white matter at its circumference. The white matter is conventionally divided into the dorsal, dorsolateral, lateral, ventral and ventrolateral funiculi.

[0057] Each half of the spinal grey matter is crescent-shaped, although the arrangement of the grey matter and its proportion to the white matter varies at different rostrocaudal levels. The grey matter can be divided into the dorsal horn, intermediate grey, ventral horn, and a centromedial region surrounding the central canal (central grey matter). The white matter gradually ceases towards the end of the spinal cord and the grey matter blends into a single mass (conus terminalis) where parallel spinal roots form the so-called cauda equine.

[0058] The present disclosure relates generally to neuromodulatory devices, systems and methods, and more particularly to devices, systems, and methods for treating an anxiety or anxiety-associated disorder in a subject. The ANS, and in particular the SNS, plays a crucial role in patients with anxiety or anxiety-associated disorders. Part of the proposed pathophysiology of certain anxiety or anxiety-associated disorders is that systemic autonomic responses to certain internal external stimuli (*e.g.*, stress) feed back to increase the level of emotional arousal and anxiety. As described in detail below, the present disclosure advantageously provides, in some

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instances, devices, systems, and methods for modulating the descending nerve signals from the brain through the SNS to peripheral tissues (*e.g.*, cardiac, gastric, vascular, immunological, and other related tissues/organs), as well as ascending signals into the CNS to effectively normalize or regulate the ANS (*e.g.*, the SNS). By employing such devices, systems and methods, the present disclosure can treat anxiety or anxiety-associated disorders by, for example, replacing conventional treatment modalities, such as pharmacological treatments.

[0059] Therapy Delivery Devices and Systems

[0060] In one aspect, the present disclosure includes various therapy delivery devices (not shown) and related systems configured to treat an anxiety or anxiety-associated disorder in a subject. In some instances, therapy delivery devices that may be used to practice the present disclosure may be positioned directly on or in an autonomic nervous tissue target or spinal nervous tissue target. In other instances, therapy delivery devices that may be used to practice the present disclosure can be positioned below the skin of a subject, but not directly on or in an autonomic nervous tissue target or spinal nervous tissue target. In further instances, therapy delivery devices that may be used to practice the present disclosure can comprise external devices, *e.g.*, positioned in a lumen adjacent an autonomic nervous tissue target or spinal nervous tissue target. In still further instances, therapy delivery devices used to practice the present disclosure can comprise an external device, *e.g.*, positioned on the skin of a subject adjacent an autonomic nervous tissue target or spinal nervous tissue target. Therapy delivery devices can be temporarily or permanently implanted within, on, or otherwise associated with a subject suffering from, afflicted by, or suspected of having an anxiety or anxiety-associated disorder.

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[0061] Therapy delivery devices of the present disclosure can be configured to deliver various types of therapy signals to an autonomic nervous tissue target or spinal nervous tissue target. For example, therapy delivery devices of the present disclosure can be configured to deliver only electrical energy, only magnetic energy, only a pharmacological or biological agent, or a combination thereof. In one example, therapy delivery devices of the present disclosure can comprise at least one electrode and an integral or remote power source, which is in electrical communication with the one or more electrodes and configured to produce one or more electrical signals (or pulses). In another example, therapy delivery devices can include a pharmacological or biological agent reservoir, a pump, and a fluid dispensing mechanism. Non-limiting examples of pharmacological and biological agents can include chemical compounds, drugs (*e.g.*, prazosin, clonidine), nucleic acids, polypeptides, stem cells, toxins (*e.g.*, botulinum), as well as various energy forms, such as ultrasound, radiofrequency (continuous or pulsed), magnetic waves, cryotherapy, and the like. In yet another example, therapy delivery devices can be configured to deliver magnetic nerve stimulation with desired field focality and depth of penetration. One skilled in the art will appreciate that combinations of the therapy delivery devices above configurations are also included within the scope of the present disclosure.

[0062] In some instances, therapy delivery devices can comprise a stimulator (or inhibitor), such as an electrode, a controller or programmer, and one or more connectors (*e.g.*, leads) for connecting the stimulating (or inhibiting) device to the controller. In one example, which is described in further detail below, the present disclosure can include a closed-loop therapy delivery system 10 (Fig. 2) for treating an anxiety or anxiety-associated disorder. As shown in Fig. 2, the therapy delivery system 10 can include a sensing component 12, a delivery component

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14, a controller 16, and a power source 18. Each of the sensing component 12, delivery component 14, controller 16, and power source 18 can be in electrical communication with one another (*e.g.*, via a physical connection, such as a lead, or a wireless link). In some instances, each of the sensing and delivery components 12 and 14 can comprise an electrode. In other instances, the delivery component 14 can comprise a coil configured to deliver magnetic stimulation. In further describing representative electrodes, which are described in the singular, it will be apparent that more than one electrode may be used as part of a therapy delivery device. Accordingly, the description of a representative electrode suitable for use in the therapy delivery devices of the present disclosure is applicable to other electrodes that may be employed.

[0063] An electrode can be controllable to provide output signals that may be varied in voltage, frequency, pulse-width, current and intensity. The electrode can also provide both positive and negative current flow from the electrode and/or is capable of stopping current flow from the electrode and/or changing the direction of current flow from the electrode. In some instances, therapy delivery devices can include an electrode that is controllable, *i.e.*, in regards to producing positive and negative current flow from the electrode, stopping current flow from the electrode, changing direction of current flow from the electrode, and the like. In other instances, the electrode has the capacity for variable output, linear output and short pulse-width, as well as paired pulses and various waveforms (*e.g.*, sine wave, square wave, and the like).

[0064] The power source 18 can comprise a battery or generator, such as a pulse generator that is operatively connected to an electrode via the controller 16. The power source 18 can be configured to generate an electrical signal or signals. In one example, the power source 18 can include a battery that is rechargeable by inductive coupling. The power source 18 may be

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positioned in any suitable location, such as adjacent the electrode (*e.g.*, implanted adjacent the electrode), or a remote site in or on the subject's body or away from the subject's body in a remote location. An electrode may be connected to the remotely positioned power source 18 using wires, *e.g.*, which may be implanted at a site remote from the electrode(s) or positioned outside the subject's body. In one example, an implantable power source 18 analogous to a cardiac pacemaker may be used.

[0065] The controller 16 can be configured to control the pulse waveform, the signal pulse width, the signal pulse frequency, the signal pulse phase, the signal pulse polarity, the signal pulse amplitude, the signal pulse intensity, the signal pulse duration, and combinations thereof of an electrical signal. In other instances, the controller 16 can be configured to control delivery of magnetic energy or stimulation to the delivery component 14. The controller 16 may be used to convey a variety of currents and voltages to one or more electrodes and thereby modulate the activity of a target sympathetic nervous tissue. The controller 16 may be used to control numerous electrodes independently or in various combinations as needed to provide stimulation or inhibition of nerve activity. In some instances, an electrode may be employed that includes its own power source, *e.g.*, which is capable of obtaining sufficient power for operation from surrounding tissues in the subject's body, or which may be powered by bringing a power source 18 external to the subject's body into contact with the subject's skin, or which may include an integral power source.

[0066] The electrical signal (or signals) delivered by the controller 16 to the delivery component 14 may be constant, varying and/or modulated with respect to the current, voltage, pulse-width, cycle, frequency, amplitude, and so forth. For example, a current may range from

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about 0.001 to about 1000 microampere (mA) and, more specifically, from about 0.1 to about 100 mA. Similarly, the voltage may range from about 0.1 millivolt to about 25 volts, or about 0.5 to about 4000 Hz, with a pulse-width of about 10 to about 1000 microseconds. In one example, the electrical signal can be oscillatory. The type of stimulation may vary and involve different waveforms known to the skilled artisan. For example, the stimulation may be based on the H waveform found in nerve signals (*i.e.*, Hoffinan Reflex). In another example, different forms of interferential stimulation may be used.

[0067] To increase nerve activity in a portion of the ANS, for example, voltage or intensity may range from about 1 millivolt to about 1 volt or more, *e.g.*, 0.1 to about 50 mA or volts (*e.g.*, from about 0.2 volts to about 20 volts), and the frequency may range from about 1 Hz to about 10,000 Hz, *e.g.*, about 1 Hz to about 1000 Hz (*e.g.*, from about 2 Hz to about 100 Hz). In some instances, pure DC and/or AC voltages may be employed. The pulse-width may range from about 1 microsecond to about 10,000 microseconds or more, *e.g.*, from about 10 microseconds to about 2000 microseconds (*e.g.*, from about 15 microseconds to about 1000 microseconds). The electrical signal may be applied for at least about 1 millisecond or more, *e.g.*, about 1 second (*e.g.*, about several seconds). In some instances, stimulation may be applied for as long as about 1 minute or more, *e.g.*, about several minutes or more (*e.g.*, about 30 minutes or more).

[0068] To decrease activity in a portion of the ANS, for example, voltage or intensity may range from about 1 millivolt to about 1 volt or more, *e.g.*, 0.1 to about 50 mA or volts (*e.g.*, from about 0.2s volt to about 20 volts), and the frequency may range from about 1 Hz to about 2500 Hz, *e.g.*, about 50 Hz to about 2500 Hz. In one example, an electrical signal can have a frequency range of about 10,000 Hz or greater (*e.g.*, high frequency stimulation) to effectively

block nerve conduction. In some instances, pure DC and/or AC voltages may be employed. The pulse-width may range from about 1 microseconds to about 10,000 microseconds or more, *e.g.*, from about 10 microseconds to about 2000 microseconds (*e.g.*, from about 15 microseconds to about 1000 microseconds). The electrical signal may be applied for at least about 1 millisecond or more, *e.g.*, about 1 second (*e.g.*, about several seconds). In some instances, the electrical energy may be applied for as long as about 1 minute or more, *e.g.*, about several minutes or more (*e.g.*, about 30 minutes or more may be used).

[0069] In some instances, the controller 16 can be configured to deliver an electrical signal to the delivery component 14 so that activity of an autonomic nervous tissue target or spinal nervous tissue target is continuously and substantially blocked. Prior art methods for delivering electrical signals to sympathetic nervous tissue (*e.g.*, the stellate ganglion) include application of pulsed radiofrequency (PRF) to reduce sympathetic activity. PRF is characterized by delivery of high-intensity current in pulses; during each cycle, an active phase is followed by a silent phase. Although PRF increases the temperature of the target tissue, the silent phase allows heat to dissipate so that neurodestructive temperatures are not reached. PRF does not provide a continuous reduction or blockade of nerve activity, however, since current is not applied during the silent phase. Advantageously, one example of the present disclosure includes continuous application of an electrical signal that substantially blocks or reduces autonomic nerve activity (*e.g.*, sympathetic activity) without an increase in temperature of the target nervous tissue. As described in more detail below, application of such an electrical signal can be performed by the closed-loop system 10 of the present disclosure to effectively normalize or regulate intrinsic

autonomic activity (*e.g.*, sympathetic activity) or tone in a subject diagnosed with, or suspected of having, an anxiety or anxiety-associated disorder.

[0070] The electrode may be mono-polar, bipolar or multi-polar. To minimize the risk of an immune response triggered by the subject against the therapy delivery device, and also to minimize damage thereto (*e.g.*, corrosion from other biological fluids, etc.), the electrode (and any wires and optional housing materials) can be made of inert materials, such as silicon, metal, plastic and the like. In one example, a therapy delivery device can include a multi-polar electrode having about four exposed contacts (*e.g.*, cylindrical contacts).

[0071] As discussed above, the controller 16 (or a programmer) may be associated with a therapy delivery device. The controller 16 can include, for example, one or more microprocessors under the control of a suitable software program. Other components of a controller 16, such as an analog-to-digital converter, etc., will be apparent to those of skill in the art. In some instances, the controller 16 can be configured to record and store data indicative of the intrinsic autonomic tone or activity in the subject. Therefore, the controller 16 can be configured to apply one or more electrical signals to the delivery component 14 when the intrinsic autonomic tone or activity of a subject increases or decreases above a certain threshold value (or range of values).

[0072] Therapy delivery devices can be pre-programmed with desired stimulation parameters. Stimulation parameters can be controllable so that an electrical signal may be remotely modulated to desired settings without removal of the electrode from its target position. Remote control may be performed, *e.g.*, using conventional telemetry with an implanted power source 18, an implanted radiofrequency receiver coupled to an external transmitter, and the like.

In some instances, some or all parameters of the electrode may be controllable by the subject, *e.g.*, without supervision by a physician. In other instances, some or all parameters of the electrode may be automatically controllable by a controller 16.

[0073] In one example, the therapy delivery device can be configured for percutaneous placement or implantation. In this instance, the therapy delivery device can comprise one or more implantable electrodes shaped or configured, for example, as a wire, a rod, a filament, a ribbon, a cord, a tube, a formed wire, a flat strip, or a combination thereof. In one example, one or more of the electrodes can comprise a laminotomy electrode array. Laminotomy electrodes, for example, generally have a flat paddle configuration and typically possess a plurality of electrodes (*e.g.*, 2, 3, 4 or more) arranged on the paddle. The arrangement of electrodes on the paddle may be in rows and columns, staggered, spaced, circular, or any other arrangement that will position the electrodes for optimal delivery of electrical energy. The one or more implantable electrodes may be controlled individually, in series, in parallel, or any other manner desired. Once implanted, the implantable electrode(s) may be held in position using any method known to the skilled artisan, such as stitches, epoxy, tape, glue, sutures, or a combination thereof.

[0074] In another example, the therapy delivery device can be configured for intravascular or intraluminal placement or implantation. In some instances, a therapy delivery device configured for intravascular or intraluminal placement or implantation can be configured in an identical or similar manner as the expandable electrode disclosed in U.S. Patent Application Serial No. 11/641,331 to Greenberg *et al.* (hereinafter, "the '331 application"). In one example, the therapy delivery device can be configured for intravascular or intraluminal placement or implantation at

an implantation site that is adjacent, or directly adjacent, an autonomic nervous tissue target or spinal nervous tissue target.

[0075] In yet another example, the therapy delivery device can be configured for transcutaneous neuromodulation. In some instances, transcutaneous neuromodulation can include positioning a delivery component (*e.g.*, an electrode or magnetic coil) on a skin surface so that a therapy signal (*e.g.*, an electrical signal or magnetic field) can be delivered to an autonomic nervous tissue target or spinal nervous tissue target. Transcutaneous neuromodulation can additionally include partially transcutaneous methods (*e.g.*, using a fine, needle-like electrode to pierce the epidermis). In other instances, a surface electrode (or electrodes) or magnetic coil can be placed into electrical contact with an autonomic nervous tissue target or spinal nervous tissue target associated with an anxiety or anxiety-associated disorder. Non-limiting examples of transcutaneous neuromodulation devices that may be used for treating an anxiety or anxiety-associated disorder are discussed below.

[0076] In one example, an electrical signal used for transcutaneous neuromodulation may be constant, varying and/or modulated with respect to the current, voltage, pulse-width, cycle, frequency, amplitude, and so forth (*e.g.*, the current may be between about 1 to 100 microampere), about 10 V (average), about 1 to about 1000 Hz or more, with a pulse-width of about 250 to about 500 microseconds.

[0077] In another example, the present disclosure can include a therapy delivery device or system configured for transcutaneous neuromodulation using magnetic stimulation. A magnetic stimulation device or system can generally include a pulse generator (*e.g.*, a high current pulse generator) and a stimulating coil capable of producing magnetic pulses with desired field

strengths. Other components of a magnetic stimulation device can include transformers, capacitors, microprocessors, safety interlocks, electronic switches, and the like. In operation, the discharge current flowing through the stimulating coil can generate the desired magnetic field or lines of force. As the lines of force cut through tissue (e.g., neural tissue), a current is generated in that tissue. If the induced current is of sufficient amplitude and duration such that the cell membrane is depolarized, nervous tissue will be stimulated in the same manner as conventional electrical stimulation. It is therefore worth noting that a magnetic field is simply the means by which an electrical current is generated within the nervous tissue, and that it is the electrical current, and not the magnetic field, which causes the depolarization of the cell membrane and thus stimulation of the target nervous tissue. Thus, in some instances, advantages of magnetic over electrical stimulation can include: reduced or sometimes no pain; access to nervous tissue covered by poorly conductive structures; and stimulation of nervous tissues lying deeper in the body without requiring invasive techniques or very high energy pulses.

[0078] Therapy delivery devices can be part of an open- or closed-loop system. In an open-loop system, for example, a physician or subject may, at any time, manually or by the use of pumps, motorized elements, etc., adjust treatment parameters, such as pulse amplitude, pulse-width, pulse frequency, duty cycle, dosage amount, type of pharmacological or biological agent, etc. Alternatively, in a closed-loop system 10 (as discussed above), treatment parameters (*e.g.*, electrical signals) may be automatically adjusted in response to a sensed physiological parameter or a related symptom or sign indicative of the extent and/or presence of an anxiety or anxiety-associated disorder. In a closed-loop feedback system 10, a sensing component 12 can comprise a sensor (not shown in detail) that senses a physiological parameter associated with an anxiety or

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anxiety-associated disorder can be utilized. More detailed descriptions of sensors that may be employed in closed-loop systems, as well as other examples of sensors and feedback control techniques that may be employed as part of the present disclosure are disclosed in U.S. Patent No. 5,716,377. One or more sensing components 12 can be implanted on or in any tissue or organ of a subject. For example, a sensing component 12 can be implanted in or on a component of the ANS, such as nerves, ganglia, afferents or efferents, or the spinal cord. Alternatively or additionally, a sensing component 12 can be implanted on or in a body organ and/or an anatomical connection thereof.

[0079] It should be appreciated that implementing a therapy delivery device as part of a closed-loop system can include placing or implanting a therapy delivery device on or within a subject at an autonomic nervous tissue target or spinal nervous tissue target, sensing a physiological parameter associated with an anxiety or anxiety-associated disorder, and then activating the therapy delivery device to apply an electrical signal to adjust application of the electrical signal to the autonomic nervous tissue target or spinal nervous tissue target in response to the sensor signal. In some instances, such physiological parameters can include any characteristic, sign, symptom, or function associated with an anxiety or anxiety-associated disorder, such as a chemical moiety or nerve activity (*e.g.*, electrical activity). Examples of such chemical moieties and nerve activities can include the activity of autonomic ganglia (or an autonomic ganglion), the activity of a spinal cord segment or spinal nervous tissue associated therewith, protein concentrations, electrochemical gradients, hormones (*e.g.*, cortisol), neuroendocrine markers, such as corticosterone, norepinephrine and melatonin, electrolytes, laboratory values, vital signs (*e.g.*, blood pressure), markers of locomotor activity, cardiac

markers (*e.g.*, EKG RR intervals), or other signs and biomarkers associated with an anxiety or anxiety-associated disorder.

[0080] Methods

[0081] Another aspect of the present disclosure includes a method for treating an anxiety or anxiety-associated disorder in a subject. In general, methods of the present disclosure can include the steps of: providing a therapy delivery device; placing the therapy delivery device into electrical communication with an autonomic nervous tissue target or spinal nervous tissue target associated with the anxiety or anxiety-associated disorder; and activating the therapy delivery device to deliver a therapy signal (*e.g.*, an electrical signal or magnetic field) to the autonomic nervous tissue target or spinal nervous tissue target to effectively treat the anxiety or anxiety-associated disorder. Subjects treatable by the present disclosure can, in some instances, be diagnosed with (or suspected of having) an anxiety or anxiety-associated disorder as well as one or more related or unrelated medical conditions. Non-limiting examples of medical conditions that can be co-treated by the methods of the present disclosure can include substance abuse, sleep deprivation or sleep disorders, psychiatric disturbances or diseases, impulse control disorders, cardiovascular disease, metabolic disorders (*e.g.*, diabetes), and major depressive episodes.

[0082] In some instances, the step of placing a therapy delivery device into electrical communication with an autonomic nervous tissue target or spinal nervous tissue target can entail different surgical and/or medical techniques depending, for example, upon the target tissue. In some instances, a therapy delivery device can be surgically placed into electrical communication with an autonomic nervous tissue target or spinal nervous tissue target via a percutaneous or

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endoscopic route. In other instances, a therapy delivery device can be placed into electrical communication with an autonomic nervous tissue target or spinal nervous tissue target via an intravascular or intraluminal route. In further instances, a therapy delivery device can be placed into electrical communication with an autonomic nervous tissue target or spinal nervous tissue target via a transcutaneous approach.

[0083] Examples of autonomic nervous tissue targets into which a therapy delivery device may be placed into electrical communication with can include, but are not limited to, any tissues of the SNS or the PNS. In some instances, autonomic nervous tissue targets into which a therapy delivery device may be placed into electrical communication with can include a sympathetic chain ganglion, an efferent of a sympathetic chain ganglion, or an afferent of a sympathetic chain ganglion. In other instances, the sympathetic chain ganglion can be a cervical sympathetic ganglion, a thoracic sympathetic ganglion, or a stellate ganglion. Examples of cervical sympathetic ganglia can include an upper cervical sympathetic ganglion, a middle cervical sympathetic ganglion, or a lower cervical sympathetic ganglion. Examples of thoracic sympathetic ganglia can include a T1 sympathetic ganglia, a T2 sympathetic ganglia, a T3 sympathetic ganglia, a T4 sympathetic ganglia, a T6 sympathetic ganglia, or a T7 sympathetic ganglia.

[0084] Examples of spinal nervous tissue targets into which a therapy delivery device may be placed into electrical communication with can include, but are not limited to, a C1, C2, C3, C4, C5, C6, C7, or C8 spinal cord segment or spinal nervous tissue associated therewith, a T1, T2, T3, T4, T5, T6, T7, T8, T9, T10, T11, or T12 spinal cord segment or spinal nervous tissue associated therewith, a L1, L2, L3, L4, or L5 spinal cord segment or spinal nervous tissue

associated therewith, or a S1, S2, S3, S4, or S5 spinal cord segment or spinal nervous tissue associated therewith.

[0085] After placing the therapy delivery device, the therapy delivery device can be activated to deliver a therapy signal (*e.g.*, an electrical signal or magnetic field) to the autonomic nervous tissue target or spinal nervous tissue target. In some instances, delivery of a therapy signal to the autonomic nervous tissue target or spinal nervous tissue target can prevent a sign and/or symptom associated with an anxiety or anxiety-associated disorder from either increasing or decreasing (as compared to a control or baseline). In other instances, delivery of a therapy signal to the autonomic nervous tissue target or spinal nervous tissue target can cause a sign and/or symptom associated with an anxiety or anxiety-associated disorder to decrease (as compared to a control or baseline). The therapy delivery device can be activated at the onset of an episode (*e.g.*, the onset of a sign and/or symptom) associated with an anxiety or anxiety-associated disorder or, alternatively, the therapy delivery device can be activated continuously or intermittently to reduce or eliminate the frequency of such episode(s).

[0086] Delivery of the electrical signal to the autonomic nervous tissue target or spinal nervous tissue target can affect central motor output, nerve conduction, neurotransmitter release, synaptic transmission, and/or receptor activation at the target tissue(s). For example, the ANS may be electrically modulated to alter, shift, or change sympathetic and/or parasympathetic activity from a first state to a second state, where the second state is characterized by a decrease in sympathetic and/or parasympathetic activity relative to the first state. As discussed above, delivery of an electrical signal to the autonomic nervous tissue target or spinal nervous tissue target can, in some instances, substantially block activity of the autonomic nervous tissue target

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or spinal nervous tissue target. In other instances, delivery of an electrical signal to the autonomic nervous tissue target or spinal nervous tissue target can achieve a complete nerve conduction block of autonomic nervous tissue target or spinal nervous tissue target for a desired period of time. In other instances, delivery of an electrical signal to the autonomic nervous tissue target or spinal nervous tissue target can achieve a partial block of the autonomic nervous tissue target or spinal nervous tissue target for a period of time sufficient to decrease sympathetic and/or parasympathetic nerve activity. The degree to which sympathetic and/or parasympathetic activity is decreased or increased can be titrated by one skilled in the art depending, for example, upon the nature and severity of the anxiety or anxiety-associated disorder in the subject.

[0087] In another aspect, the present disclosure can include a method 20 (Fig. 4) for treating an anxiety disorder or an anxiety-associated disorder in a subject, such as autism. One step of the method 20 can include providing a therapy delivery device (Step 22). Alternatively, Step 22 can include providing a closed-loop therapy delivery system. Examples of suitable therapy delivery devices (and systems) are described above and further illustrated below. At Step 24, the therapy delivery device (or system) can be placed into electrical communication with an autonomic nervous tissue target or spinal nervous tissue target associated with the anxiety disorder or the anxiety-associated disorder (*e.g.*, autism). In some instances, the therapy delivery device can be placed in direct electrical contact with the autonomic nervous tissue target or spinal nervous tissue target. "Direct electrical contact" can mean that the therapy delivery device (or system) is placed on or in the autonomic nervous tissue target or spinal nervous tissue target. In other instances, "direct electrical contact" can mean that the therapy delivery device (or system) is located adjacent or directly adjacent (but not in physical contact with) the autonomic

nervous tissue target or spinal nervous tissue target such that delivery of a therapy signal (*e.g.*, an electrical signal or a magnetic field) can modulate a function, activity, and/or characteristic of the autonomic nervous tissue target or spinal nervous tissue target.

[0088] After placing the therapy delivery device (or system) into direct electrical communication with the autonomic nervous tissue target or spinal nervous tissue target, the therapy delivery device (or system) can be activated to deliver the therapy signal to the autonomic nervous tissue target or spinal nervous tissue target (Step 26). The therapy signal can be delivered in an amount and for a time sufficient to effectively treat the anxiety disorder or the anxiety-associated disorder (*e.g.*, autism). In one example, electrical energy can be delivered to the stellate ganglion by an electrode or electrode array that is placed directly on or in the stellate ganglion. In some instances, an anxiety or anxiety-associated disorder may be caused by hypersympathetic activity, which may lead to increased adrenal gland function. In such instances, it may be desirable to deliver continuous blocking stimulation to the stellate ganglion to decrease sympathetic activity in the subject and thereby cause adrenal output to decrease (*e.g.*, to a normal level).

[0089] One example of the method 20 is illustrated in Fig. 5. At Step 22, the method 20 can include providing a closed-loop therapy system 10 as described above. The closed-loop therapy system 10 can be configured for percutaneous implantation in the subject. As shown in Fig. 5, the system 10 can be implanted in the subject so that the delivery component 14 and the sensing component 12 are in direct electrical contact with the stellate ganglion and the middle cervical ganglion, respectively. Additionally, the system 10 can be implanted so that the controller 16 and the power source 18 are secured at the same or different subcutaneous locations.

[0090] Once the system 10 is implanted (Step 24), the sensing component 12 can detect electrical activity in the middle cervical ganglion, which may be indicative of intrinsic sympathetic tone in the subject. The detected level(s) of electrical activity can then be relayed to the controller 16, which determines if the detected level(s) is/are within a normal or abnormal range or level. Where the detected level(s) is/are within an abnormal range (*e.g.*, at an elevated level as compared to a control or baseline), the controller 16 can cause the power source 18 to deliver an electrical signal to the delivery component 14. The electrical signal is then delivered to the stellate ganglion to substantially block activity therein (Step 26). While the electrical signal(s) is/are being delivered to the stellate ganglion, the sensing component 12 can continue to detect the level of electrical activity within the middle cervical ganglion (Step 28). When the level of electrical activity in the middle cervical ganglion is equal, or about equal to, a normal or baseline level, the controller 16 can cease delivery of the electrical signal(s) to the delivery component 14. By continuously or intermittently monitoring the intrinsic sympathetic tone or activity of the subject, the closed-loop therapy delivery system 10 can automatically decrease or normalize hypersympathetic activity and thus effectively treat an anxiety disorder or an anxiety-associated disorder (*e.g.*, autism).

[0091] Another aspect of the present disclosure can include transvascular or transluminal delivery of an electrical energy to an autonomic nervous tissue target or spinal nervous tissue target associated with an anxiety disorder or an anxiety-associated disorder (*e.g.*, autism). Thus, in some instances, the method 20 can include providing a therapy delivery device (or system) configured for transvascular or transluminal insertion and placement within the subject. For instance, a therapy delivery device configured for intravascular or intraluminal placement in a

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subject can include an expandable electrode as disclosed in the '331 application. The therapy delivery device can be inserted into a vessel or lumen of the subject. Non-limiting examples of vessel and lumens into which the therapy delivery device can be inserted include arteries, veins, an esophagus, a trachea, a vagina, a rectum, or any other bodily orifice. The therapy delivery device can be surgically inserted into the vessel or lumen via a percutaneous, transvascular, laparoscopic, or open surgical procedure.

[0092] After inserting the therapy delivery device into the vessel or lumen, the therapy delivery device can be advanced (if needed) to an intraluminal target site so that the therapy delivery device is in electrical communication with the autonomic nervous tissue target or spinal nervous tissue target. In some instances, advancement of the therapy delivery device can be done under image guidance (*e.g.*, fluoroscopy, CT, MRI, etc.). Intraluminal target sites can include intravascular or intraluminal locations at which the therapy delivery device can be positioned. For example, an intraluminal target site can include a portion of a vessel wall that is innervated by (or in electrical communication with) the autonomic nervous tissue target or spinal nervous tissue target. Examples of intraluminal target sites can include, without limitation, vascular or luminal sites innervated by and/or in electrical communication with any nervous tissue(s) of the SNS or PNS, such as neurons, axons, fibers, tracts, nerves, plexus, afferent plexus fibers, efferent plexus fibers, ganglion, pre-ganglionic fibers, post-ganglionic fibers, cervical sympathetic ganglia/ganglion, thoracic sympathetic ganglia/ganglion, afferents thereof, efferents thereof, a sympathetic chain ganglion, a thoracic sympathetic chain ganglion, an upper cervical chain ganglion, a lower cervical ganglion, an inferior cervical ganglion, and a stellate ganglion.

[0093] After placing the therapy delivery device, a therapy signal (*e.g.*, an electrical signal or a magnetic field) can be delivered to the autonomic nervous tissue target or spinal nervous tissue target. The therapy signal can be delivered in an amount and for a time sufficient to effectively treat the anxiety disorder or the anxiety-associated disorder (*e.g.*, autism).

[0094] In another aspect, the method 20 can include providing a therapy delivery device (or system) configured for placement on the skin of the mammal. Examples of therapy delivery devices configured for transcutaneous delivery of one or more therapy signals are disclosed above and described in more detail below. In some instances, a therapy delivery device (or system) can be positioned about the subject, without penetrating the skin of the subject, so that the therapy delivery device is in electrical communication with an autonomic nervous tissue target or spinal nervous tissue target associated with an anxiety disorder or an anxiety-associated disorder (*e.g.*, autism). Non-limiting examples of an autonomic nervous tissue target or spinal nervous tissue target into which the therapy delivery device can be placed into electrical communication are described above. After placing the therapy delivery device (or system), a therapy signal can be delivered to the autonomic nervous tissue target or spinal nervous tissue target. The therapy signal can be delivered in an amount and for a time sufficient to effectively treat the anxiety disorder or anxiety-associated disorder (*e.g.*, autism).

[0095] In one example, a transcutaneous neuromodulation device can comprise a wearable accessory item, such as a necklace or collar 30 (Fig. 6). As shown in Fig. 6, a necklace or collar 30 can be configured to include at least one electrode 32 for delivering a therapy signal to a particular region of a subject's neck (*e.g.*, an anterior or posterior region thereof) depending upon the desired neuromodulatory effect. The necklace or collar 30 can additionally include an

integral power source 34 (e.g., a rechargeable battery). It will be appreciated that the electrode(s) 32 can alternatively be powered by a wireless power source (not shown). The necklace or collar 30 can be configured to obtain a pre-selected position about a subject's neck by, for example, using a positioning guide (not shown), weighting the necklace or collar, etc. Alternatively, the subject can manually adjust the necklace or collar 30 as needed to optimize delivery of the therapy signal from the electrode(s) 32 to an autonomic nervous tissue target or spinal nervous tissue target.

[0096] In another example, a transcutaneous neuromodulation device can comprise a pillow 40 (Figs. 7A-B). In some instances, the pillow 40 (Fig. 7A) can be configured as a collar for use in a reclined or upright position, such as on an airplane, in a car, on a couch, etc. The pillow 40 can include at least one electrode 42 configured to deliver a therapy signal to an autonomic nervous tissue target or spinal nervous tissue target (e.g., in a subject's head or neck). As shown in Fig. 7A, the pillow 40 includes two oppositely disposed electrodes 42. The pillow 40 can also include a power source (not shown), which may be integrally connected with the pillow or located remotely (*i.e.*, wirelessly) therefrom. In other instances, the pillow 40 (Fig. 7B) can comprise a traditional or conventional pillow for use when a subject is sleeping or lying in bed. As shown in Fig. 7B, the pillow 40 can include two oppositely disposed electrodes 42 configured to deliver a therapy signal to a target nerve when the subject neck or head is straddled between the electrodes. The pillow 40 can further include a power source 44 that is in direct electrical communication with the electrodes 42; however, it will be appreciated that the power source can be located remotely (*i.e.*, wirelessly) from the pillow.

[0097] It will be appreciated that the transcutaneous neuromodulation devices illustrated in Figs. 6 and 7A-B are illustrative only and, moreover, that such devices can include any wearable item, accessory, article of clothing, or any object, device, or apparatus that a subject can use and, during use, comes into close or direct contact with a portion of the subject's body (*e.g.*, the subject's neck). Examples of such transcutaneous neuromodulation devices can include vests, sleeves, shirts, socks, shoes, underwear, belts, scarves, wrist bands, gloves, ear pieces, band-aids, turtle neck, pendants, buttons, earrings, stickers, patches, bio-films, skin tattoos (*e.g.*, using neuro-paint), chairs, computers, beds, head rests (*e.g.*, of a chair or car seat), cell phones, and the like.

[0098] Another example of the method 20 is illustrated in Fig. 8. At Step 22, the method 20 can include providing a closed-loop therapy system 10 as described above. The closed-loop therapy system 10 can be configured for percutaneous (*e.g.*, subcutaneous) implantation in the subject. As shown in Fig. 8, the system 10 can be implanted in the subject so that the delivery component 14 and the sensing component 12 are in direct electrical contact with a spinal cord segment at the level of C8 and a spinal cord segment at the level of C6, respectively.

Additionally, the system 10 can be implanted so that the controller 16 and the power source 18 are secured at the same or different subcutaneous locations.

[0099] Once the system 10 is implanted (Step 24), the sensing component 12 can detect electrical activity in the C6 spinal cord segment, which may be indicative of intrinsic sympathetic tone in the subject. The detected level(s) of electrical activity can then be relayed to the controller 16, which determines if the detected level(s) is/are within a normal or abnormal range or level. Where the detected level(s) is/are within an abnormal range (*e.g.*, at an elevated

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level as compared to a control or baseline), the controller 16 can cause the power source 18 to deliver an electrical signal to the delivery component 14. The electrical signal is then delivered to the spinal cord segment at the level of C8 to substantially block activity therein (Step 26). While the electrical signal(s) is/are being delivered to the spinal cord segment at the level of C8, the sensing component 12 can continue to detect the level of electrical activity within the spinal cord segment at the level of C6 (Step 28). When the level of electrical activity in the spinal cord segment at the level of C6 is equal, or about equal to, a normal or baseline level, the controller 16 can cease delivery of the electrical signal(s) to the delivery component 14. By continuously or intermittently monitoring the intrinsic sympathetic tone or activity of the subject, the closed-loop therapy delivery system 10 can automatically decrease or normalize hypersympathetic activity and thus effectively treat an anxiety or an anxiety-associated disorder (*e.g.*, autism).

[00100] From the above description of the present disclosure, those skilled in the art will perceive improvements, changes and modifications. Such improvements, changes, and modifications are within the skill of those in the art and are intended to be covered by the appended claims. All patents, patent applications, and publication cited herein are incorporated by reference in their entirety.

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The following is claimed:

1. A closed-loop therapy delivery system for treating an anxiety or anxiety-associated disorder in a subject, the therapy delivery system comprising:
 - a sensing component configured to detect at least one physiological parameter associated with the anxiety or anxiety-associated disorder;
 - a delivery component configured for implantation on or about an autonomic nervous tissue target or a spinal nervous tissue target; and
 - a controller configured to automatically coordinate operation of the sensing and delivery components;wherein the controller is configured to deliver an electrical signal to the delivery component to modulate activity at the autonomic nervous tissue target or a spinal nervous tissue target and effectively treat the anxiety or anxiety-associated disorder.
2. The system of claim 1, wherein the controller is configured to deliver an electrical signal that substantially blocks activity at the autonomic nervous tissue target or a spinal nervous tissue target.
3. The system of claim 1, wherein the controller is in electrical communication with a power source.

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4. The system of claim 1, wherein all or only a portion of the system is implanted within the subject.
5. The system of claim 1, wherein the at least one physiological parameter includes a chemical moiety or an electrical activity.
6. The system of claim 1, wherein the autonomic nervous tissue target is a ganglion of the sympathetic nervous system (SNS).
7. The system of claim 6, wherein the ganglion of the SNS is a cervical ganglion, a cervicothoracic ganglion, or a thoracic ganglion.
8. The system of claim 7, wherein the cervical ganglion is an upper, middle, or lower cervical ganglion.
9. The system of claim 1, wherein the spinal nervous tissue target is one of a cervical spinal cord segment, a thoracic spinal cord segment, a lumbar spinal cord segment, a sacral spinal cord segment, or spinal nervous tissue associated therewith.
10. The system of claim 1, wherein the controller is configured to deliver an electrical signal to the delivery component without increasing the temperature of the autonomic nervous tissue target or a spinal nervous tissue target.

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11. A closed-loop therapy delivery system for treating autism in a subject, the therapy delivery system comprising:

a sensing component configured to detect at least one physiological parameter associated with the autism;

a delivery component configured for implantation on or about an autonomic nervous tissue target; and

a controller configured to automatically coordinate operation of the sensing and delivery components;

wherein the controller is configured to deliver an electrical signal to the delivery component to modulate activity of the autonomic nervous tissue target and effectively treat the autism.

12. A method for treating an anxiety or anxiety-associated disorder in a subject, the method comprising the steps of:

placing a therapy delivery device into electrical communication with an autonomic nervous tissue target or a spinal nervous tissue target associated with the anxiety or anxiety-associated disorder; and

activating the therapy delivery device to deliver an electrical signal to the autonomic nervous tissue target or a spinal nervous tissue target to effectively treat the anxiety or anxiety-associated disorder in the subject.

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13. The method of claim 12, further comprising the steps of:
sensing at least one physiological parameter associated with the anxiety or anxiety-associated disorder;
generating a sensor signal based on the at least one physiological parameter; and
activating the therapy delivery device to adjust application of the electrical signal to the autonomic nervous tissue target or a spinal nervous tissue target in response to the sensor signal to treat the anxiety or anxiety-associated disorder.
14. The method of claim 12, wherein the therapy delivery device is configured to deliver an electrical signal that substantially blocks activity at the autonomic nervous tissue target or a spinal nervous tissue target.
15. The method of claim 12, wherein the at least one physiological parameter includes a chemical moiety or an electrical activity.
16. The method of claim 12, wherein the autonomic nervous tissue target is a ganglion of the SNS.
17. The method of claim 16, wherein the ganglion of the SNS is a cervical ganglion, a cervicothoracic ganglion, or a thoracic ganglion.

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18. The method of claim 17, wherein the cervical ganglion is an upper, middle, or lower cervical ganglion.
19. The method of claim 12, wherein the spinal nervous tissue target is one of a cervical spinal cord segment, a thoracic spinal cord segment, a lumbar spinal cord segment, a sacral spinal cord segment, or spinal nervous tissue associated therewith.
20. The method of claim 16, wherein the electrical signal is delivered to the ganglion of the SNS without increasing the temperature of the ganglion.
21. The method of claim 12, wherein the anxiety-associated disorder is autism.

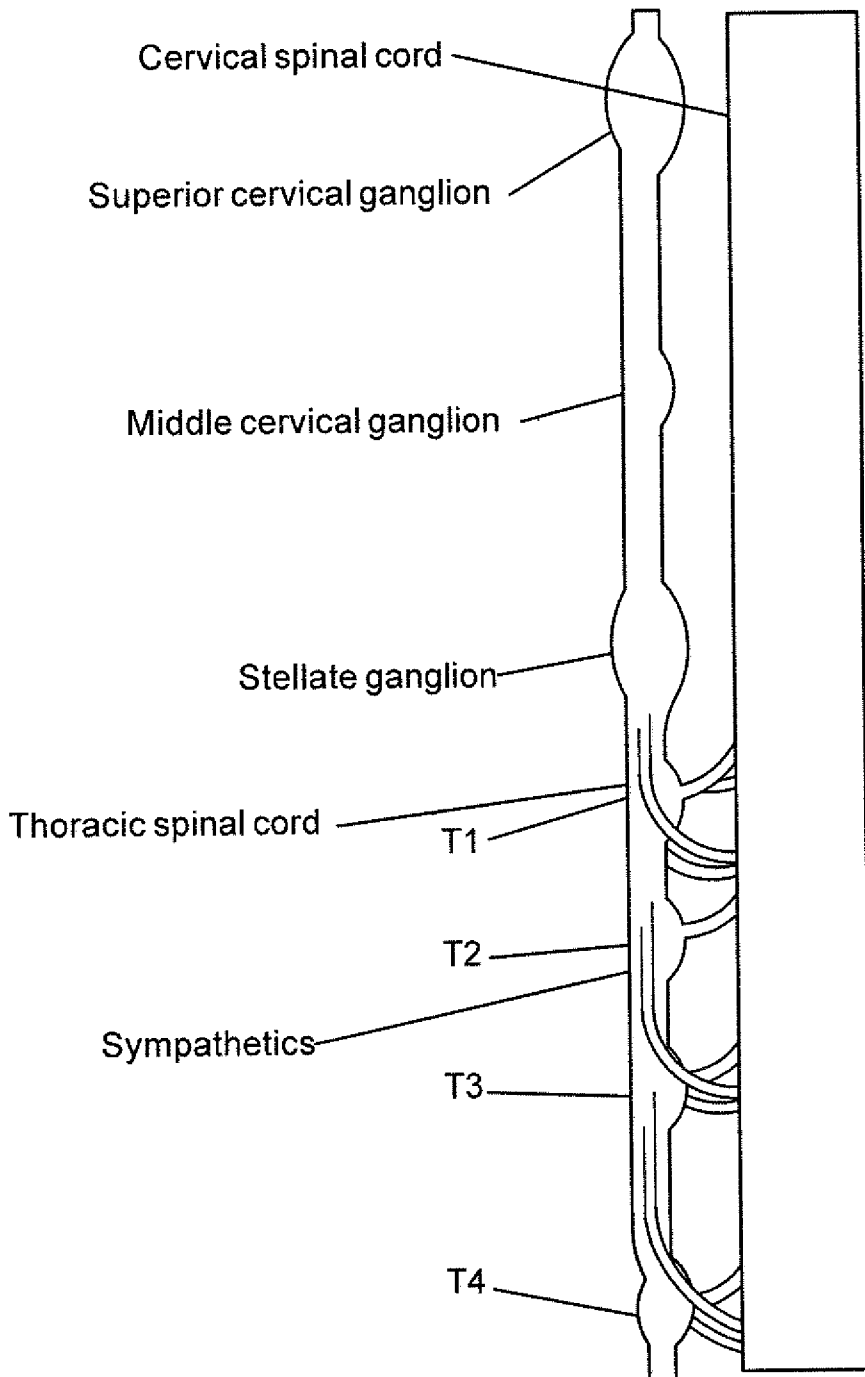


Fig. 1

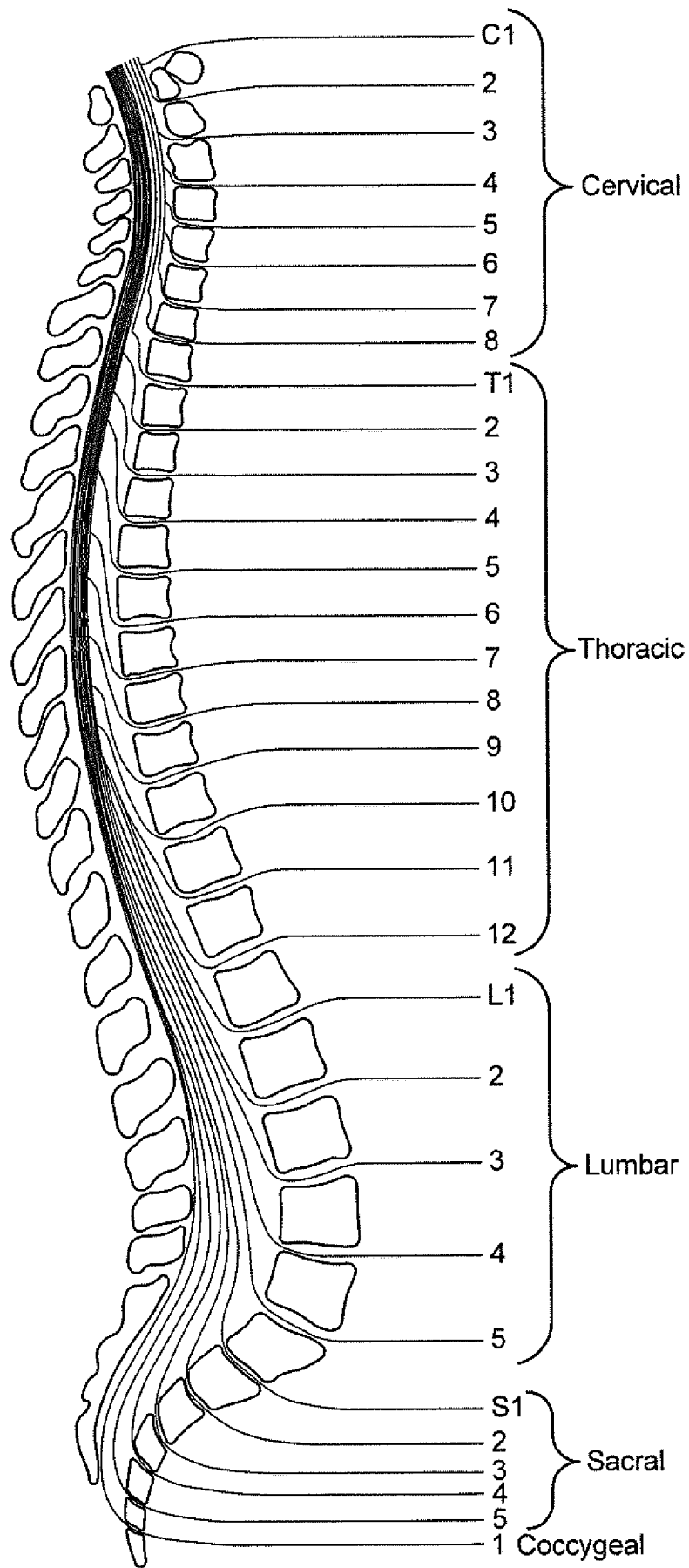


Fig. 2

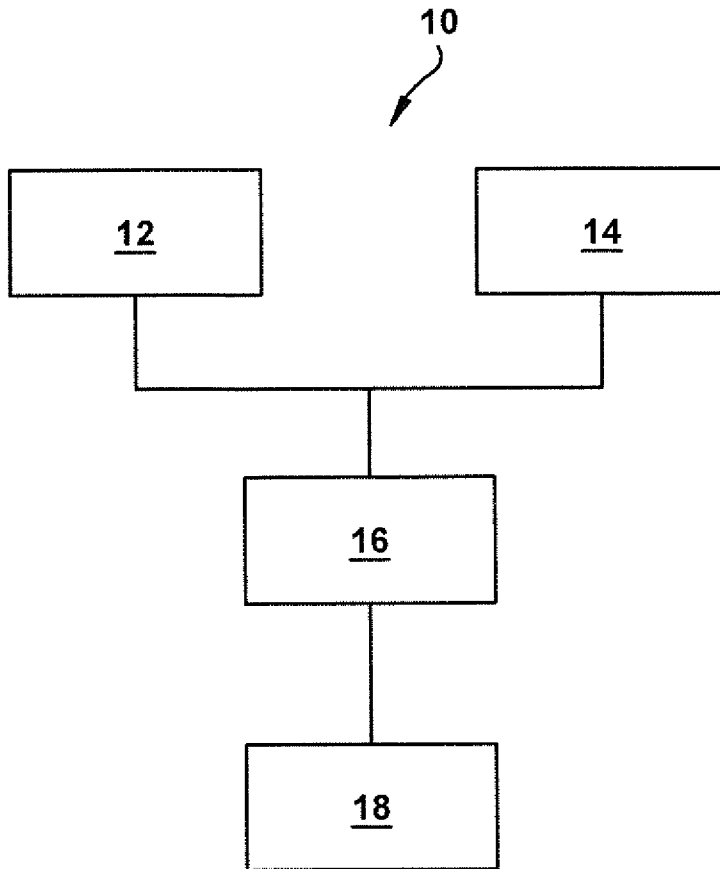
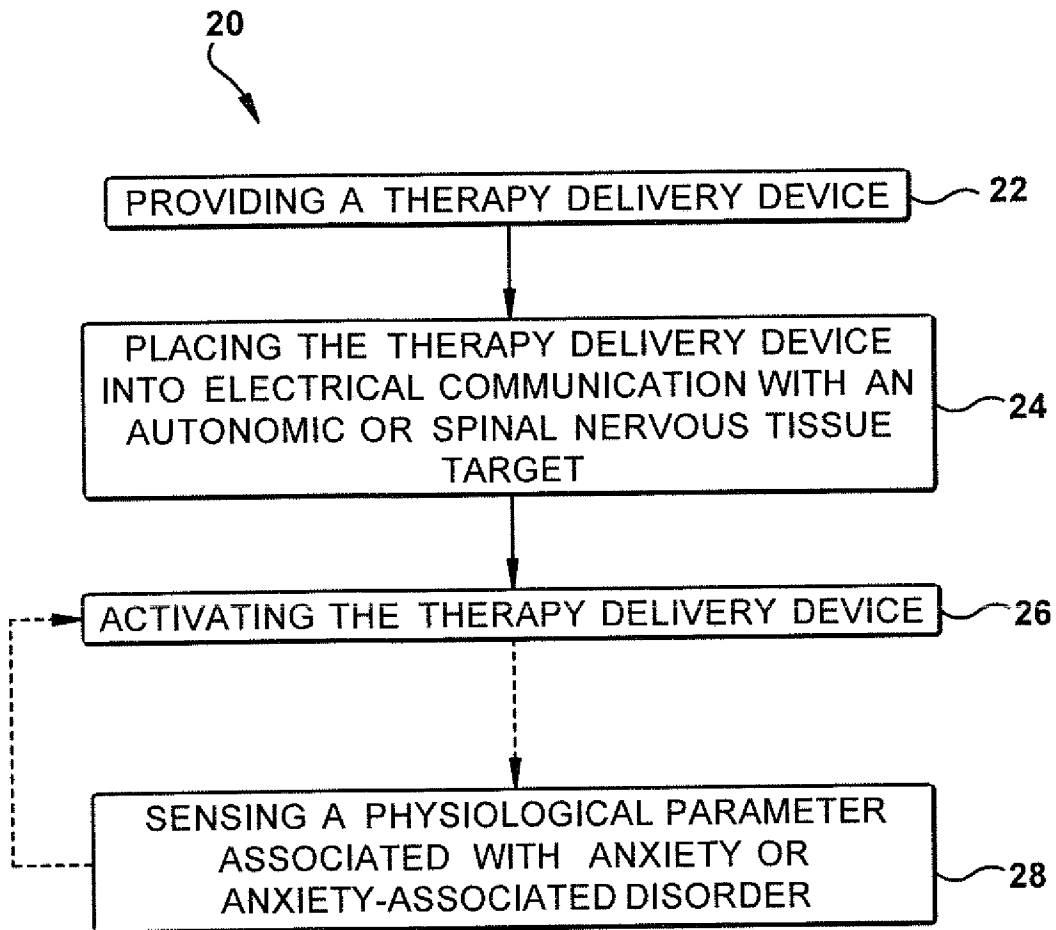


Fig. 3

**Fig. 4**

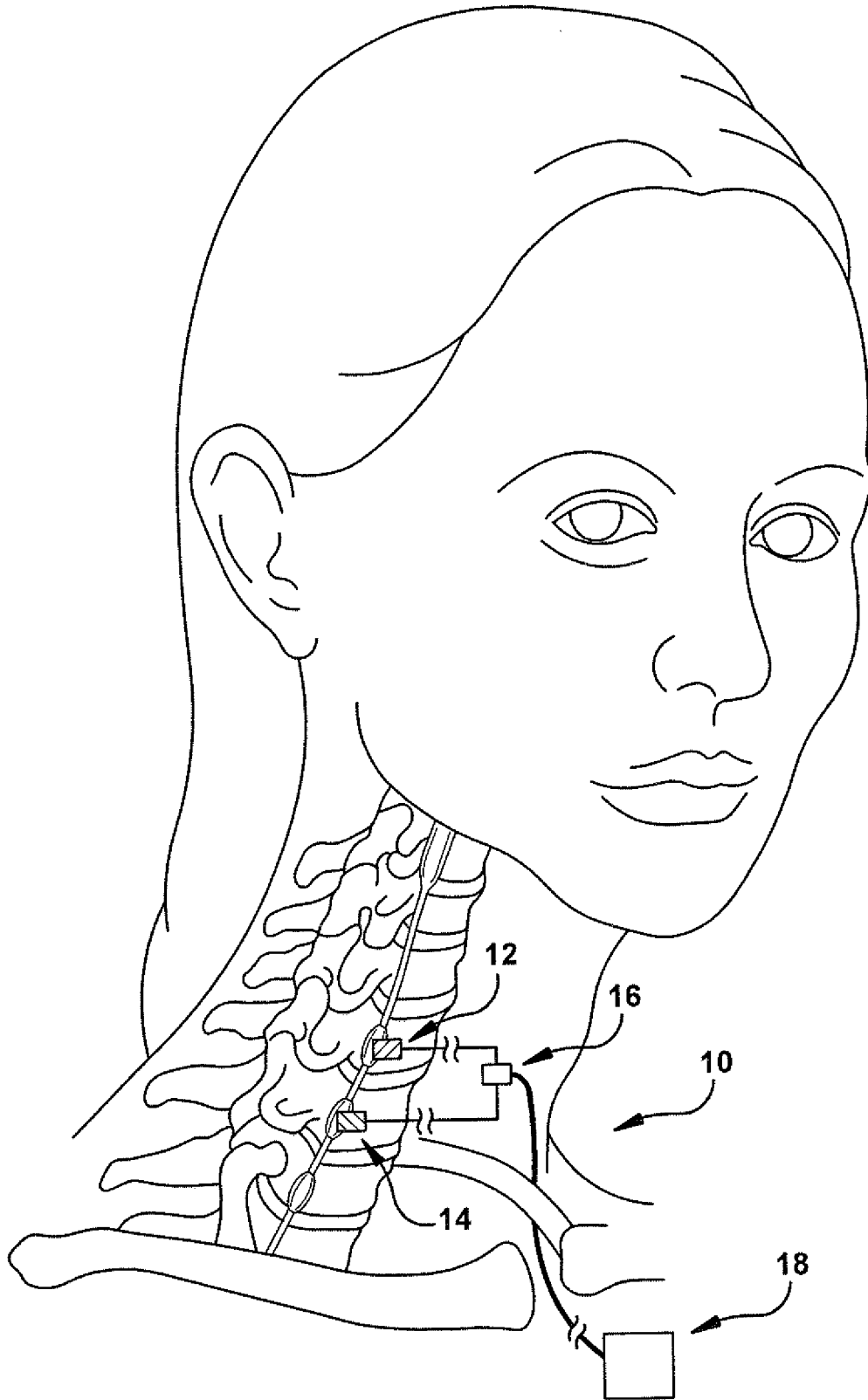


Fig. 5

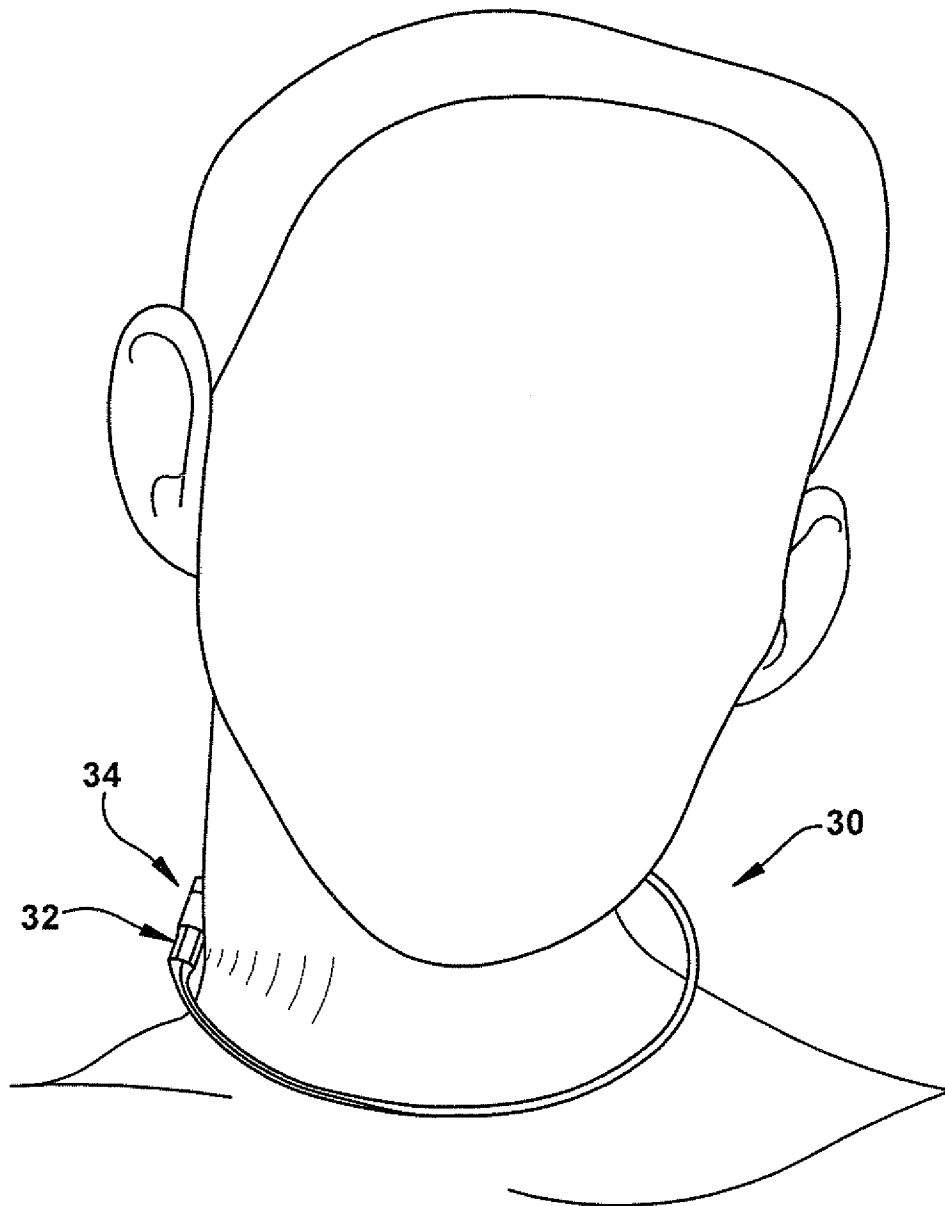


Fig. 6

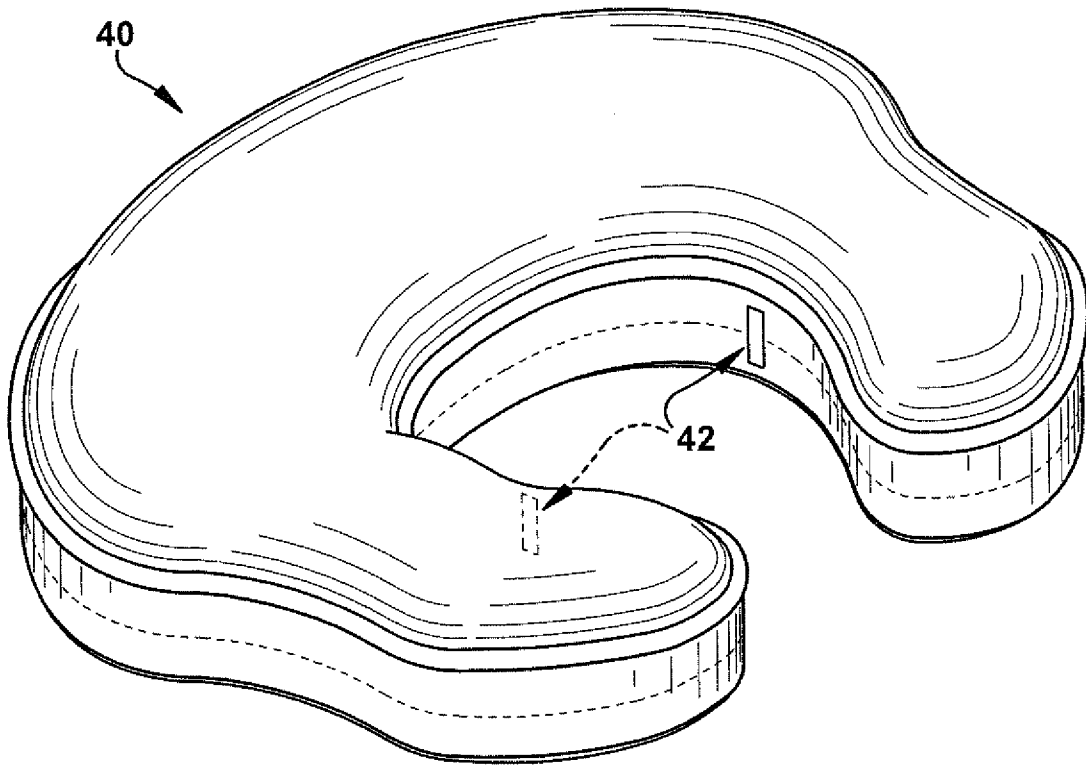


Fig. 7A

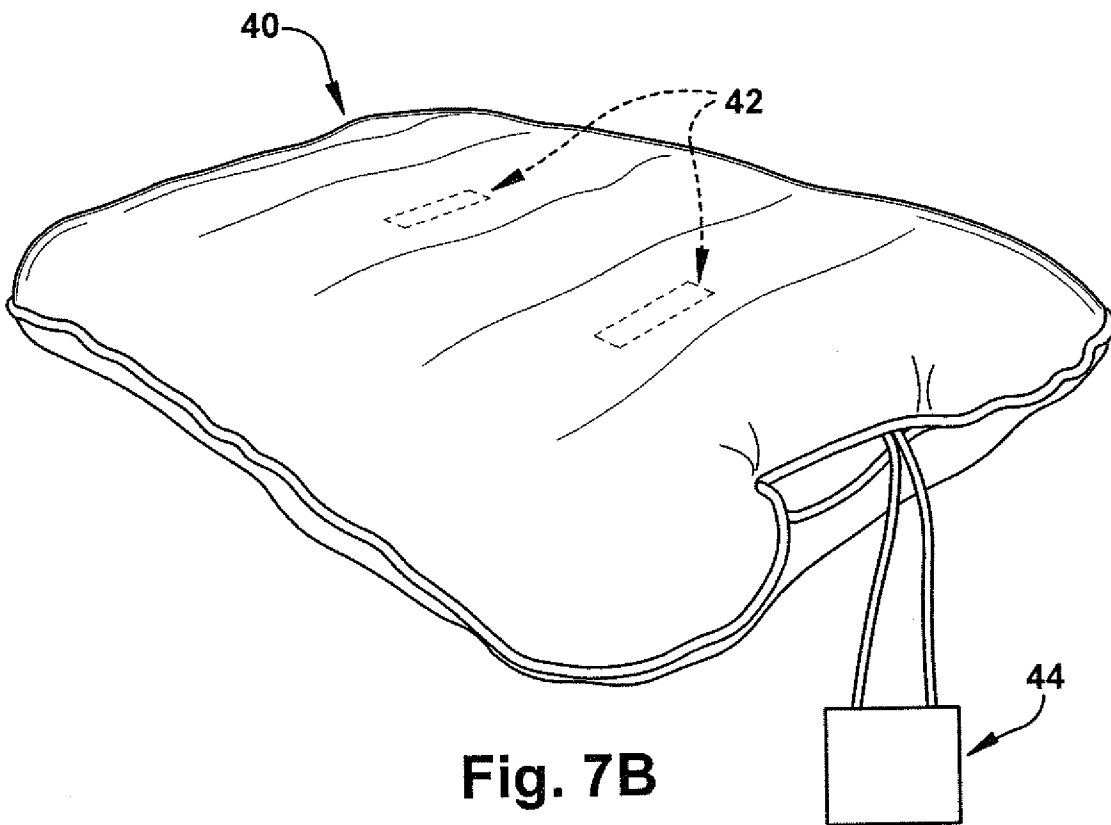


Fig. 7B

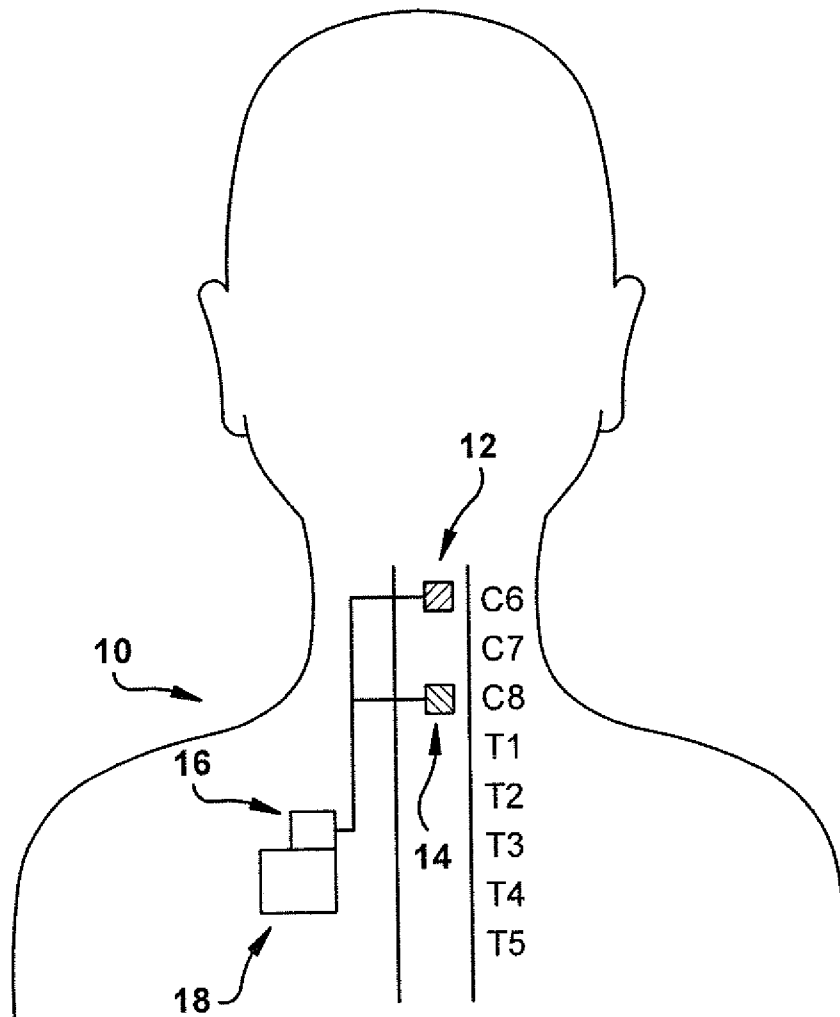


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/022419

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/05 A61N1/36
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61N
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/224749 A1 (BEN-DAVID TAMIR [IL] ET AL) 15 September 2011 (2011-09-15) abstract; figure 1 paragraphs [0007], [0203], [0214], [0456], [0457], [0469], [0524], [0525], [0534], [0557], [0654]	1-11
X	US 2010/191304 A1 (SCOTT TIMOTHY L [US]) 29 July 2010 (2010-07-29) abstract; figures 1,2 paragraphs [0003], [0031], [0049], [0050], [0053], [0054], [0060], [0066], [0086], [0087]	1,11
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 2 July 2014	Date of mailing of the international search report 08/07/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Pereda Cubián, David
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/022419

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/038264 A1 (JAAX KRISTEN N [US] ET AL) 15 February 2007 (2007-02-15) abstract; figure 8 paragraphs [0054], [0062], [0063], [0074], [0089] - [0091] -----	1,11
X	US 2003/216792 A1 (LEVIN HOWARD R [US] ET AL) 20 November 2003 (2003-11-20) abstract; figure 2 paragraphs [0033], [0060], [0061] -----	1,11
A	US 2011/270359 A1 (COLBORN JOHN C [US]) 3 November 2011 (2011-11-03) the whole document -----	1-11
A	US 2007/179557 A1 (MASCHINO STEVEN E [US] ET AL) 2 August 2007 (2007-08-02) the whole document -----	1-11
A	US 2007/100378 A1 (MASCHINO STEVEN E [US]) 3 May 2007 (2007-05-03) the whole document -----	1-11
A	US 2006/247728 A1 (FOSTER ALLISON M [US] ET AL) 2 November 2006 (2006-11-02) the whole document -----	1-11
A	US 5 716 377 A (RISE MARK T [US] ET AL) 10 February 1998 (1998-02-10) cited in the application the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/022419

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 12-21
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2014/022419

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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