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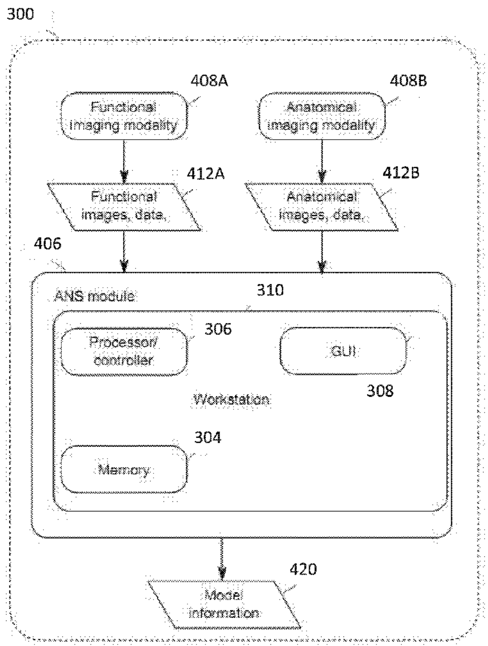

FIG. 3

(57) Abstract: A system for deciphering sensed neural activity, comprising: a memory configured to at least temporarily store at least one of a) a measured tracer radiation value from an area of interest and, b) a nerve model that interrelates measured tracer radiation and one or more parameters to neural activity; and, at least one controller extracts a value of a parameter based on the measured tracer radiation using the nerve model.

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SYSTEMS AND METHODS FOR DECIPHERING AUTONOMIC NEURAL SYSTEM FUNCTION USING MEDICAL IMAGING

PRIORITY AND RELATED APPLICATIONS

This application claims priority from U.S. Provisional Patent Application No. 62/003,108 filed May 27, 2014, PCT Patent Application No. IB2014/064316 filed Sept. 8, 2014, PCT Patent Application No. IB2014/064319 filed Sept. 8, 2014, and, PCT Patent Application No. IB2015/050148 filed January 8, 2015, and is related to:

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PCT Patent Application No. IL2014/050089 filed January 24, 2014,
PCT Patent Application No. IL2014/050090 filed January 24, 2014, and,
PCT Patent Application No. IL2014/050246 filed March 11, 2014.

The contents of the above applications are incorporated by reference as if fully set forth herein in their entirety.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to Autonomic Neural System ("ANS") sensing and, more particularly, but not exclusively, to putting sensed ANS data to practical use.

The human body has several control systems, including the hormonal system, the central nervous system and the autonomic nervous system (ANS). As traditionally depicted, the autonomic nervous system is (mostly) not under conscious control and serves to regulate various body functions, including life-sustaining functions. For example, basal heart rate, breathing and digestion are controlled by the autonomic nervous system. In some classifications, the portion of the autonomic nervous system which relates to digestion is termed the enteric nervous system (ENS).

A spinal column provides both sympathetic and parasympathetic innervation. Parasympathetic innervation may proceed directly to organs and/or to secondary ganglia. Sympathetic innervation may be modulated by the spinal ganglia and then feed into secondary ganglia or organs. In many cases, the sympathetic and parasympathetic innervations interact at the secondary ganglia (such as the ciliary, celiac, and other ganglia). Secondary ganglia may be connected directly to nerve endings at an organ. In some cases, an intermediary network or chain of ganglia exists as well.

The ANS is generally considered to include two main functional layers, the sympathetic nervous system (SNS), generally (but not exclusively) in charge of excitatory and increased responsiveness and control, and the parasympathetic nervous system (PNS), generally (but not exclusively) in charge of damping responsiveness and control. For example, heart rate is increased by increased activity of the SNS and decreased by increased activity of the PNS. In some organs, such as the heart, the nerve fibers of the SNS and nerve fibers of the PNS meet at certain ganglia. Ganglia which include both SNS fibers and PNS fibers utilize a balance between the excitations of the SNS and PNS to determine their behavior.

In general, ANS functions can be divided into sensory ("afferent") and motor ("efferent") subsystems. Another way of characterizing afferent and efferent is that afferent is information received (leading towards the innervated tissue) and efferent is information transmitted (leading away from the innervated tissue).

Specifically, the ANS controls the operation of a specific organ by receiving information about the function of the controlled organ (and possibly other organs also), comparing the afferent information with "normal operational" values retained within the body and responding by generating certain output transmission signals to the controlled organ, as well as to other organs possibly.

SUMMARY OF THE INVENTION

The present invention, in some embodiments thereof, relates to methods and systems for deciphering neural activity from imaging signals of the ANS.

According to an aspect of some embodiments of the present invention there is provided a method for deciphering sensed neural activity by correlating it to medical imaging of the ANS.

In some embodiments of the invention, the correlation is ascertained by using sensing for at least one of the afferent and/or the efferent signals. Optionally, sensed afferent and/or efferent signals are compared to a stored reference value.

In some embodiments of the invention, the correlation (may also referred to as comparison) is used to detect diseased states in a body. In some embodiments of the invention, the correlation is used to treat diseased states in the body. In some embodiments of the invention, the correlation is used to effectuate behavior and/or performance changes in the body.

According to an aspect of some embodiments of the present invention there is provided a system for deciphering sensed neural activity by correlating it to medical imaging of the ANS, direct sensing of activity in the ANS and/or by measuring performance characteristics of at least a portion of the body. In some embodiments of the invention, medical imaging of the ANS is used for deciphering neural activity.

According to an aspect of some embodiments of the present invention there is provided a method for deciphering sensed neural activity, comprising: placing at least one sensor near an area of interest; measuring neural activity at the area of interest using the sensor to get a measured neural activity value; comparing the measured neural activity value to an expected reference value stored in a database; and, analyzing a result of the comparing for differences between the measured neural activity and the expected reference value using a processor.

In some embodiments of the invention, the method further comprises diagnosing a dysfunctional state of the area of interest at least partly based on the differences between the measured neural activity value and the expected reference value.

In some embodiments of the invention, the method further comprises treating the area of interest at least partly based on the differences between the measured neural activity value and the expected reference value.

In some embodiments of the invention measuring is performed using medical imaging.

In some embodiments of the invention, the method further comprises administering a tracer, where the amount of uptake of the tracer indicates neural activity in the area of interest.

In some embodiment of the invention, the method further comprises measuring organ performance to get a measured performance value to be compared to an expected performance value.

In some embodiments of the invention, measuring includes determining the concentration of the tracer in a presynaptic nerve to give an indication of neural activity.

There is provided in accordance with an exemplary embodiment of the invention, a system for deciphering sensed neural activity, comprising: a memory configured to at least temporarily store at least one of a) a measured tracer radiation value from an area of interest and, b) a nerve model that interrelates measured tracer radiation and one or more parameters to neural activity; and, at least one controller extracts a value of a parameter based on the measured tracer radiation using the nerve model.

In an embodiment of the invention, the system is configured to correlate the nerve model to an expected reference value model to generate a neural activity status of the area of interest.

In an embodiment of the invention, the memory is further configured to at least temporarily store at least one of a measured a) ANS function, and, b) parameter.

In an embodiment of the invention, the controller is further configured to perform at least one of a) updating the expected reference value model based on measurements of the at least one parameter, b) updating the nerve model based on measurements of the tracer radiation in combination with the at least one parameter, c) correlating the nerve model to at least one of the expected reference value model and an ANS function, and, d) creating an ANS model based on measurements of at least one of the tracer radiation and an ANS function.

In an embodiment of the invention, the ANS function is at least one of afferent signal and efferent signal.

In an embodiment of the invention, the system further comprises at least one sensor configured to sense at least one of a) an ANS function, b) tracer radiation indicative of at least one of tracer uptake and tracer release, and c) at least one parameter, in an area of interest.

In an embodiment of the invention, at least one sensor is a direct biometric sensor.

In an embodiment of the invention, the at least one sensor is at least one of a functional imaging modality and an anatomical imaging modality.

In an embodiment of the invention, the functional imaging modality is at least one of a PET, CT, MRI and SPECT imager.

In an embodiment of the invention, the anatomical imaging modality is at least one of a CT, MRI, X-ay and ultrasound imager.

In an embodiment of the invention, the controller is configured to create an ANS model of the area of interest including at least one of nerve locations, interconnections and activity levels.

In an embodiment of the invention, the system further comprises a GUI associated with the at least one controller and configured to effectuate user control of the system.

In an embodiment of the invention, measured tracer radiation is correlated to neural activity using at least one of a) a number of NA transmissions in a presynaptic nerve, b) NE quanta discharged per transmission, c) NE concentration in blood of a patient, d) tracer degradation rate, e) re-uptake I for NE, f) tracer concentration in the blood of the patient, g) time elapsed between a tracer injection and a medical imaging time, and, h) synaptic effective distribution volume.

In an embodiment of the invention, the system further comprises a tool configured to perform at least one of ablation, freezing, stimulation, and anesthesia.

In an embodiment of the invention, there is provided a system for planning based on sensed neural activity, comprising: a sub-system for deciphering sensed neural activity; and, a sub-system for utilizing the generated neural activity status, comprising, a diagnosis subsystem configured to generate a personalized diagnosis, and, a planning subsystem configured to create a plan based on the personalized diagnosis for modifying the neural activity status.

In an embodiment of the invention, the diagnosis subsystem is configured to receive at least one of the model of an area of interest, patient information and diagnosis database information from a diagnosis database.

In an embodiment of the invention, the planning subsystem is configured to receive at least one of the personalized diagnosis and treatment database information from a treatment database.

In an embodiment of the invention, at least one of the memory and the at least one controller are remotely located from the at least one sensor.

In an embodiment of the invention, at least one component of the sub-system for deciphering sensed neural activity or the sub-system for utilizing a model of an area of interest is located remotely from the at least one sensor.

There is further provided in accordance with an exemplary embodiment of the invention, a method for deciphering sensed neural activity, comprising: placing at least one sensor configured to sense tracer radiation in an area of interest; measuring tracer radiation in the area of interest; comparing the measured tracer radiation to an expected reference value model to determine a neural activity status.

In an embodiment of the invention, the method further comprises analyzing the neural activity status to create a plan for modifying the neural activity status based on the analyzing.

In an embodiment of the invention, the method further comprises creating an ANS model of the area of interest at least partially based on the measuring.

In an embodiment of the invention, the method further comprises diagnosing a dysfunctional state of the area of interest at least partly based on the differences between the measured neural activity value and the expected reference value.

In an embodiment of the invention, the method further comprises treating the area of interest at least partly based on the differences between the measured neural activity value and the expected reference value.

In an embodiment of the invention, measuring is performed using medical imaging.

In an embodiment of the invention, medical imaging is at least one of PET, CT, MRI, SPECT, CT, MRI, X-ay and ultrasound.

In an embodiment of the invention, measuring is performed using a direct biometric sensor.

In an embodiment of the invention, a direct biometric sensor is at least one of an implantable CMOS biosensor, an electrical sensor, a blood pressure sensor and a blood flow sensor.

In an embodiment of the invention, measured tracer radiation is correlated to neural activity using at least one of a) a number of NA transmissions in a presynaptic nerve, b) NE quanta discharged per transmission, c) NE concentration in blood of a patient, d) tracer degradation rate, e) re-uptake I for NE, f) tracer concentration in the blood of the patient, g) time elapsed between a tracer injection and a medical imaging time, and, h) synaptic effective distribution volume

There is further provided in accordance with an exemplary embodiment of the invention, A system for deciphering sensed neural activity, comprising: a memory configured to at least temporarily store at least one of a) a measured tracer radiation value from an area of interest and, b) an expected reference value model that interrelates measured tracer radiation and one or more parameters to neural activity; and, at least one controller extracts a value of a parameter based on the measured tracer radiation using the expected reference value model.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

As will be appreciated by one skilled in the art, aspects of the present invention may be embodied as a system, method or computer program product. Accordingly, aspects of the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment (including firmware, resident software, micro-code, etc.) or an embodiment combining software and hardware aspects that may all generally be referred to herein as a “circuit,” “module” or “system.” Furthermore, aspects of the present invention may take the form of a computer program product embodied in one or more computer readable medium(s) having computer readable program code embodied thereon. Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof.

For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

Any combination of one or more computer readable medium(s) may be utilized. The computer readable medium may be a computer readable signal medium or a computer readable storage medium. A computer readable storage medium may be, for example, but not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, or device, or any suitable combination of the foregoing. More specific examples (a non-exhaustive list) of the computer readable storage medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a hard disk, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, a portable compact disc read-only memory (CD-ROM), an optical storage device, a magnetic storage device, or any suitable combination of the foregoing. In the context of this document, a computer readable storage medium may be any tangible medium that can contain, or store a program for use by or in connection with an instruction execution system, apparatus, or device.

A computer readable signal medium may include a propagated data signal with computer readable program code embodied therein, for example, in baseband or as part of a carrier wave. Such a propagated signal may take any of a variety of forms, including, but not limited to, electro-magnetic, optical, or any suitable combination thereof. A computer readable signal medium may be any computer readable medium that is not a computer readable storage medium and that can communicate, propagate, or transport a program for use by or in connection with an instruction execution system, apparatus, or device.

Program code embodied on a computer readable medium may be transmitted using any appropriate medium, including but not limited to wireless, wireline, optical fiber cable, RF, etc., or any suitable combination of the foregoing.

Computer program code for carrying out operations for aspects of the present invention may be written in any combination of one or more programming languages, including an object oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the "C" programming language or similar programming languages. The program code may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote computer or server. In the latter scenario, the remote computer may be connected to the user's computer through any type of network, including a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider).

Aspects of the present invention are described below with reference to flowchart illustrations and/or block diagrams of methods, apparatus (systems) and computer program products according to embodiments of the invention. It will be understood that each block of the flowchart illustrations and/or block diagrams, and combinations of blocks in the flowchart illustrations and/or block diagrams, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

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

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

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example, are not necessarily to scale, and are for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is a method for deciphering sensed neural activity by correlating it to medical imaging of the ANS, in accordance with exemplary embodiments of the invention;

FIG. 2 is a system for deciphering sensed neural activity by correlating it to medical imaging of the ANS, in accordance with exemplary embodiments of the invention;

FIG. 3 is a block diagram of a model ANS modeling and/or pattern evaluation system/unit, in accordance with some exemplary embodiments of the invention;

FIG. 4 is a block diagram of a model and/or pattern analysis and treatment planning system/unit, in accordance with some exemplary embodiments of the invention; and,

FIG. 5 is a block diagram which shows at least an area or portion of interest of the body connected to at least a portion of the system of FIGS. 2, 3 or 4 for performing at least a portion of the method of FIG. 1, in accordance with an exemplary embodiment of the invention.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to ANS sensing and, more particularly, but not exclusively, to putting sensed ANS data to practical use.

Generally, in some embodiments of the invention, medical imaging is used to gather information (*e.g.*, dynamic information) about an area of interest or a portion of a body of a patient, for example tracer radiation which can be linked to tracer uptake and/or release by at least a portion of the body (*e.g.* the nerves around an organ) is measured/sensed and then the information is used to effectuate a practical course of action with respect to the patient. In some embodiments of the invention, ANS factors such as afferent and/or efferent signal values are measured. In some embodiments of the invention, a model of expected reference values or expected changes in values is used to interpret the gathered information. In an embodiment of the invention, creation of the model of expected reference values depends on one or more factors/parameters, including some physiological, some procedural, and/or some inherent to the materials being used. In some embodiments of the invention, a result of comparing the model of expected values to actual measurements is used to provide possible guidance for diagnosing/assessing the area of interest in order to determine healthy or diseased states and/or treatment options for the portion of the body being measured.

In some embodiments of the invention, concentration of the tracer in the presynaptic nerve (in order to determine level of neural activity) is calculated by evaluating the concentrations in the blood of adrenaline vs. the tracer, factoring in a at least one additional variable such as time, re-uptake rate of adrenaline or other neurotransmitter, number of nerve signal transmissions, amount of adrenaline discharge per nerve signal transmission, and the like. In some embodiments of the invention, measurements are made of body organ performance and are compared to a value of expected performance for that organ (e.g. comparing measured tracer uptake to expected uptake). In some embodiments of the invention, the expected values are based on the patient (*e.g.* from a healthy part of the patient's body), optionally in different situations or times (*e.g.*, data obtained few years ago). In some embodiments of the invention, at least a portion of the expected values are derived from at least one third party (*e.g.*, a healthy body at the same gender, age etc.). In some embodiments of the invention, the reference value is estimated. The comparison/analysis data is then used to diagnose and/or render treatment to the body, e.g., in order to bring measured values closer to the model/expected values.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Referring now to the drawings, FIG. 1 illustrates a method 100 for deciphering sensed neural activity by correlating it to medical imaging of the ANS, in accordance with exemplary embodiments of the invention. Description of the method 100 will be in conjunction with a generalized system 200, portrayed in FIG. 2, for efficiency. System 200 is an exemplary system for deciphering sensed neural activity, according to some embodiments of the invention.

In some embodiments of the invention, sensing or measuring is performed using medical imaging only. In some embodiments of the invention, different types of sensing can be performed, for example by direct nerve sensing, using implantable CMOS biosensors or electrical sensors (*e.g.* EMG, ENoG), and/or using other types of sensing, for example using biometric sensors, such as blood pressure or blood flow sensors, as examples.

In some embodiments of the invention, sensing is performed using a combination of medical imaging and direct nerve signal sensing. In some embodiments of the invention, sensing weighs additionally, optionally, and/or alternatively to the above methodologies, performance characteristics of an organ and/or body portion being observed, for example blood-flow throughput of a heart, blood pressure achieved in a cardiovascular system or Heart Rate Variability reflecting autonomic cardiac innervation.

Generally, the nervous control system has afferent and efferent arms, one arm going into an organ (the afferent arm) and one going out (the efferent arm). In some embodiments of the invention, an area of interest or portion of a patient or subject is placed in operational proximity to and/or attached to (102) at least one sensor 202 – for example: to medical imaging sensor 202a (*e.g.* SPECT, PET, CT, MRI), wherein the at least one imaging sensor 202a is placed near and/or attached to the afferent and/or the efferent arms in order to measure (104) neural activity and/or generate an ANS model 420 for analysis (*e.g.* as described in more detail below). In some embodiments of the invention, a neural activity/nerve model is generated in advance, whose parameters (*e.g.* NE concentration in blood) may be altered later based on real time measurements of factors or parameters (described below). In some embodiments of the invention, an afferent sensor 202b is placed (102) near the afferent arm and a second, efferent sensor 202c is placed (102) near the efferent arm. Optionally, sensors 202b, 202c are the same type, but are merely used in different locations in the body.

In some embodiments of the invention, a tracer is used (106) in combination with the medical imaging sensor 202a, where the tracer interacts with the ANS to either have an uptake or release by or from the ANS which is recordable by the sensor (*e.g.*, sensor 202a). Optionally, ^{123}I-mIBG is used as the tracer. In some embodiments of the invention, the activity, temporal and spatial distribution of the sympathetic component of the ANS is measured (104). While the emitted radiation from the tracer can be affected by multiple body mechanisms, in an embodiment of the invention the focus is on neural activity related to the emitted radiation. In some embodiments of the invention, a value of expected tracer uptake is compared to the actually measured tracer uptake (exemplary comparison (108) described in more detail below), where the tracer uptake which is measured is based on nerve activity. In some embodiments of the invention, medical imaging is used at a time when the expected uptake is less than 100% and/or the image is updated multiple times (or even continuously) in order to measure uptake rate.

In some embodiment of the invention, measuring (104) is performed directly, possibly in a relatively minimally invasive nature, for example by attaching (102) at least one direct sensor 202d to a nerve such as a peroneal nerve. In some embodiments of the invention, the information generated by such measuring (104) is limited to the sampled nerve or ganglia activity. In some embodiments of the invention, measuring (104) is as a function of time (or before steady state time).

In some embodiments of the invention, measurement (104) is applied to specific neurotransmitters, for example to specifically focus on afferent or efferent behavior.

It is believed that measured (104) tracer uptake that has a large differential from the expected reference value may indicate at least some form of dysfunction in the body portion being examined, however it may be due to a change in one or more of the factors described herein. In some embodiments of the invention, the expected reference values are optionally recalculated using contemporaneous measurements to establish more accurate references values. In some embodiments of the invention, the bigger the differential the more likely and/or the more pronounced the diseased state. In some embodiments of the invention, the expected reference value is determined by: measuring patient characteristics under different conditions, for example while under stress, while eating, after eating, stimulation with a known effect on the body or a known portion of the body (e.g. a specific organ, body state, and/or organ behavior); from other patients; or from a different time in the patient's life; or before or after treatment.

While in a diseased state, the response of the ANS to the disease-altered state of the body and/or the function of a controlled organ has a major role on the ability of the body to recover from the disease or the path for recovery.

Certain ANS activities can ameliorate the disease process while other types of ANS responses can exacerbate the course of the disease and prevent recovery. Thus the knowledge of the activity of the ANS components (e.g. CNS, ganglia, nerves and/or end organ – neuro junctions) is valuable for the diagnosis and treatment of disease.

In some embodiments of the invention, the measured (104) activity (for example the amount of tracer taken up by the measured body portion) is compared (108) by a processor or controller 204 to an expected reference value. The expected reference value is comprised of a number of factors/parameters, for example: a) number of NA (neural activity) transmissions in a presynaptic nerve, b) NE (adrenaline) quanta discharged per transmission, c) NE concentration in blood of a patient, d) tracer degradation rate, e) re-uptake I for NE, f) tracer concentration in the blood of the patient, g) time elapsed between a tracer injection and a medical imaging time, and/or h) synaptic effective distribution volume. In some embodiments, where the greater the differential between the two, the more likely that there is some sort of medical dysfunction or diseased state. In some embodiments of the invention, measured tracer uptake or release is correlated to some value of afferent or efferent signal which is indicative of a level of neural activity. The expected reference value varies in relation to varying activity rates in some embodiments of the invention, for example the reference value for uptake/release should be higher at a higher neural activity rate. In some embodiments of the invention, the expected reference value is stored in a database 206. Optionally, the expected reference value is a baseline value established through earlier measuring of the patient's neural activity. Optionally, the expected reference value is determined through experimental studies involving third party patients to determine what is "normal". In some embodiments of the invention, the expected reference value is updated and/or changed occasionally.

In some embodiment of the invention, characteristic quantitative cardiac innervation, as measured by a single tracer like ^{123}I-mIBG on SPECT (*e.g.*, D-SPECT, a product of Spectrum Dynamics Medical, Ltd.) fused with CT/MR or ^{123}I-mIBG on CT-SPECT or ^{124}I-mIBG on CT-PET, representing both epicardial ganglionated plexi as well as atrial wall neural activity, may differentiate between different clinical states on the spectrum of Atrial Fibrillation (paroxysmal, persistent, chronic persistent and permanent AF). Optionally, a catheter based detector is used to measure the tracer. The measured values may first be compared to normal cardiac innervation in healthy, age and gender matched, volunteers. Furthermore, it may then be correlated with a known database, serving as an atlas, of such characteristic innervations representing all different AF states.

Similarly, an atlas/database of expected innervation values and typical pattern successful or failed post intervention, e.g. post-surgery, post cardiac ablation (surgical or catheter-based), post cardiac neuromodulation (ablation or block) may be used as reference for decision making, in some embodiments of the invention.

In some embodiments of the invention, myocardial innervation is measured in a more complex PET imaging protocol using multiple radiolabeled Catecholamines like ^{11}C-Epinephrine (neuronal uptake and vesicular storage) + ^{11}C-Hydroxy-Ephedrine (neuronal uptake) + ^{11}C-Phenylephrine (neuronal uptake and protection from metabolic degradation) and/or coupled with perfusion measured by ^{13}N-Amonia. Using such a special protocol, perfusion/innervation match or mismatch may be depicted highlighting territories of viable but denervated myocardial tissue which are relevant to arrhythmia generation. Moreover, an intermediate state between normal innervation and complete denervation may also be identified this way, thereby enabling targeting only the truly denervated tissue.

In some embodiments of the invention, measuring (104) includes penetrating a bipolar electrode needle at the vicinity of an area of interest (*e.g.*, measured body portion), for example an epicardial ganglionated plexus.

In some embodiments of the invention, measuring (104) may include non-invasively measuring whole-body systemic sympathetic neural activity via devices like EndoPAT™ (from Itamar Medical) measuring peripheral arterial tone. Such measurement can be performed at baseline and/or during neuromodulation therapy and/or immediately post-therapy and/or during long term follow-up, for example to monitor and validate the therapeutic effect.

Similarly, using a minimally-invasive approach, the sympathetic neural discharges may be monitored by a sensor or electrode implanted in the stellate ganglia to measure the stellate ganglia nerve activity (SGNA) of the patient from the left stellate ganglion (LSG), the right stellate ganglion (RSG), or both. Such measurement can be performed at baseline to accurately diagnose neural activity state, during neuromodulation therapy and immediately post-therapy to monitor and validate the therapeutic effect. *See* U.S. Pat. App. Pub. No. 2010268289. This is an example of a minimally-invasive approach, simultaneous recording of sympathetic nerve activity and electrocardiogram using electrodes on the skin. In some embodiments of the invention, neuECG may be used for real time monitoring of a catheter-based epicardial GP ablation or GP block, for example, administered pursuant to creating (112) a treatment plan 432 (described in more detail below) for modifying the neural activity value result. In some embodiments of the invention, ENoG is used to calibrate the model that links tracer measurements to neural activity.

In some embodiments of the invention, measured (104) values are calibrated to time and/or for the amount of tracer material before comparing (108). In some embodiments of the invention, neural activity can be estimated based on measured (104) tracer uptake using the formula:

$$C_{pn} = [C_0+(N*Q*t)/V_s+ NE_B]* K_2 *[C_0 / C_0+ (N*Q*t)/V_s+ NE_B]- K_1*(C_0*K2) *[C_0 / C_0+ (N*Q*t)/V_s+ NE_B].$$

Where the following parameters/factors are:

N = Number of NA (Neural Activity) transmissions in the presynaptic nerve
Q = NE quanta discharged per transmission
NE_B = NE (adrenaline) concentration in the blood
K_1 = tracer degradation rate
K_2 = Reuptake I for NE
C_0 = Concentration in blood of tracer at time immediate after injection to blood
t = Time elapsed between injection and imaging time
C_{pn} = Concentration of tracer in the presynaptic neuron (*i.e.* measured tracer uptake/release)
V_s = Synaptic effective distribution volume

and, by measuring C_{pn}, C_0, t, NE_B, and making assumptions regarding Q, V_s, K_1, and K_2, one can solve for N (generating the nerve model and subsequently a neural activity result). In some embodiments of the invention, some of the variables are estimated based on a biopsy and/or lab results from the patient. Optionally, K_1 and K_2 may be estimated based on experiments. As an example of the flexibility of the formula or invention, instead of measuring C_{pn} and solving for N, in some embodiments of the invention C_{pn} is estimated or assumed and another neural parameter, like K_2 is measured. In some embodiments of the invention, only one or some of the factors shown above are used in correlating measured tracer uptake to neural activity. For example, if the particular tracer being used degrades over a very long time, K_1 can be optionally ignored since the degradation rate will not substantially affect the result of the formula when solving for N. Additionally, alternatively and/or optionally, different factors are used. In some embodiments of the invention, a different way of correlating C_{pn} to N is used, for example a table correlating C_{pn} to N is used (where the other factors are assumed or estimated) in order to determine a neural activity based on measured tracer uptake/release.

In some embodiment of the invention, a multi-compartmental model, useful for isolating analysis/diagnosis and/or treatment, is used for analysis of ANS functioning, wherein representative compartments include at least one of a presynaptic nerve, a synaptic cleft and the blood. Optionally, each of the compartments has its own estimated or measured variable and/or parameter values. In some embodiments of the invention, activity is measured across compartments.

In some embodiment of the invention, analysis (110) is performed on the differential between the measured neural activity and the expected value of activity, if any, and the extent of the differential in order to attempt to explain and/or diagnose the discrepancy and/or dysfunction and/or diseased state of the body portion being examined and/or to determine an overall level of functionality of the area of interest. In some embodiments of the invention, and as noted elsewhere, analysis (110) includes comparing measured values to model values (*e.g.* expected reference values).

In some embodiments of the invention, measurement (104), comparison (108) and/or analysis (110) are cycled (114) in order to give values for different conditions of the body portion being examined. Optionally, the body portion being examined is subjected to various conditions whereupon measurement (104), comparison (108) and/or analysis (110) are performed in order gauge and/or record the body portion's reaction to those various conditions.

In some embodiments of the invention, creating (112) a plan for modifying the neural activity value result of the dysfunctional body portion is performed at least partly based on the differential. For example, by selectively stimulating nerves (and thus propagating neural activity), performance characteristics of portions of the body can be altered. In some embodiments of the invention, the stimulating is based on at least one of expected reference values and the measured (104) neural activity of the body portion. In some embodiment of the invention, neural activity of the body is stimulated in order to reduce or increase the differential. In some embodiments of the invention, treatment (112) factors in node distance from a point in the body (e.g. an organ), for example by calculating how many ganglions away from the organ intervention should be performed. In some embodiments of the invention, distance away affects expected neural activity/body behavior and/or indicates treatment actions which could or should be performed. In some embodiments of the invention, at least one of measurement (104), comparison (108) and/or analysis (110) are cycled (114), optionally more than once, in order to gauge the effectiveness of treatment (112) and/or the effect of the stimulating on the body.

In some embodiment of the invention, some or all of the system 200 components 202, 204, 206 are remote with respect to each other and/or are connected to a communications network 208, such as the Internet or a WAN or a LAN. In some embodiments of the invention, at least a portion of the system is located remotely, for example the database. In some embodiment of the invention, at least some action of the methodologies described herein happens remotely from other actions, for example, the patient is measured in location A, but the analysis happens in location B.

Reference is now made to FIG. 3, which is a more specific block diagram (in relation to system 200 of FIG. 2) of a system 300 including an ANS modeling system/unit 406, in accordance with some exemplary embodiments of the invention.

It should be understood that while "ANS modeling" system/unit terminology is used to describe component 406, in some embodiments of the invention, this component is also capable of generating a nerve model using, for example, the formula described above and/or is capable of determining a differential between the nerve model and expected values and/or is capable of comparing the ANS model to the nerve model and/or to the expected values. In some embodiments of the invention, systems 300, 400 can be used to set a baseline for neural activity and/or generate an ANS model which can optionally be factored into the nerve model and/or expected reference value model.

In some embodiments, ANS modeling system/unit 406 is provided as a part of a system 300 including functionalities with which ANS modeling system/unit coordinates in series or in parallel. For example, a system 300 includes a functional imaging modality 408A (such as a SPECT imager), and/or an anatomical imaging modality 408B. Anatomical image modality data comprises data obtained, for example, from a CT (X-ray or gamma-ray, for instance), MRI, 3-D ultrasound, 2-D ultrasound, or by another modality. Optionally, an ANS modeling system/unit is comprised in part of another system configuration, such as a system 400, as described in relation to FIG. 4 hereinbelow.

In some embodiments of the invention, ANS module 406 receives functional images and/or imaging data 412A (for example, as produced by functional imaging modality 408A) from an area or patient body part of interest; and anatomical images and/or imaging data 412B (for example, as produced by anatomical imaging modality 408B) from a patient body part of interest.

The ANS module itself produces ANS model information 420 comprising information about a patient body part of interest, for example, Ganglion Plexus ("GP") locations, interconnections and/or activity levels. In some embodiments, image data within GP locations resolves one or more distinct and/or identifiable GP regions. Production of an ANS model comprises, for example, one or more of the blocks described in relation to FIG. 8 of related application PCT Patent Application No. IB2014/064319. It should be understood that a GP is just one example of a body part of interest, and that it could be virtually any component of the ANS which is measured, scanned, sensed, diagnosed, observed, and/or treated.

In some embodiments of the invention, ANS module 406 comprises processor/ controller 306. Processor/controller carries out computational tasks of ANS model generation, for example, computational tasks described in relation to FIG. 8 of related application PCT Patent Application No. IB2014/064319, and/or nerve model generation which uses the exemplary formula described above. In some embodiments of the invention, the nerve model is compared by the processor 306 to at least one expected value to gauge a neural activity status of the area of interest. In an embodiment of the invention, status is a measure of neural activity. Optionally, status is a measure of change of neural activity. In some embodiments of the invention, ANS module 406 is provided with a GUI 308. In some embodiments, ANS module 406 (or any of the databases and/or controllers described herein) comprises memory 304, used, for example to receive and at least temporarily store images, associated data, model information, and/or process/controller instructions. Optionally, GUI 308 is configured to effectuate user control of the system, for example, for the selection of image sources, images, and/or regions of data for analysis. Optionally or alternatively, GUI 308 is used, for example, to show model results; for example: regions of tissue health or disease, regions of innervation or lack of innervation, regions of nervous system activity/inactivity, and/or any of these regions in relation to one another. In some embodiments, ANS module 406 comprises a workstation 310. The workstation itself, in some embodiments, optionally comprises the processor/controller 306 and/or the GUI

308. In some embodiments, functions of workstation 310 are distributed; for example, at least a part of ANS and/or nerve and/or expected value modeling carried out by processor/controller 306 is calculated remotely, for example, as a provided service.

In some embodiments, system 300 includes one or more tools for a treatment (112) option such as ablation, freezing, stimulation, anesthesia, or another neuromodulatory intervention. In some embodiments, system 300 is operable for guidance of a probe for treatment (112) based on real-time display of a probe and ANS map in registration, direct (for example, robotic) guidance of probe position, or another method of ANS map-guided treatment and/or treatment probe placement.

FIG. 4 is a block diagram of a model and/or pattern analysis and treatment planning system/unit 400, in accordance with some exemplary embodiments of the invention.

In some embodiments, once an ANS model and/or a nerve model is available, it is used for diagnosis/analysis (110) and/or planning a treatment (112) for example as described elsewhere herein. For example, analysis (110) can include comparison of the nerve model to expected values to determine a differential and possibly a treatment plan. Groups of elements comprising a system/unit 400 include, for example, blocks within the boundaries delineating system configurations 400A, 400B, 400C, 400D, and/or another system configuration comprising blocks of FIG. 4.

In some embodiments, unit 400 carries out functions of various model analyses described herein (*e.g.* ANS, nerve, expected value), for example, in relation to FIG. 3. For example, it includes analysis/modeling subsystem 406, as in configuration 400C. In some embodiments, unit 400 is integral to and/or co-located with imaging and/or treatment systems (for example, it includes imaging subsystem(s) 408, as in configuration 400D). In some embodiments (for example, including analysis/modeling subsystem 406), images and imaging data 412 are received by the system/unit 400. In some embodiments (for example, including imaging subsystem(s) 408), images and imaging data 412 are generated by the system/unit 400. In some embodiments, imaging subsystems 408 include an imaging modality described in relation to FIG. 3, for example, a functioning imaging modality 408A, and/or an anatomical imaging modality 408B.

In some embodiments, unit 400 (for example, configurations 400A and/or 400B) is remotely located relative to other subsystems, and/or is distributed. Optionally, the functions of, for example, subsystem 400A are provided as a service. In exemplary embodiments of the invention, rather than provide a user with a model of the ANS, the nerve model and/or the expected value model 420, what is provided is a combination of one or more of these models 420 and a treatment (112) plan 432 (for example, a combination comprising the information of model information 420 and treatment plan 432) or possibly just a treatment plan 432. Some exemplary treatment plans 432 are described below. In some embodiments, the ANS and/or its activity are described as a pattern (which is not necessarily a model as such), and the pattern becomes the basis for classification with respect to the identification of diagnosis and/or planning of treatment.

In some embodiments of the invention, model information 420 and patient information 422 are provided to a diagnosis subsystem 402. In some embodiment, estimated neural activity (the expected values) and/or differences between the measured neural activity (the nerve model) and the expected reference value are provided to a diagnosis subsystem 402 as a part of the model information 420. In some embodiments of the invention, the diagnosis subsystem 402 performs at least a part of the analyzing (110). ANS model information 420 includes, for example, GP locations, interconnection and/or activity level. Patient information 422 includes, for example, patient demographics, history and/or previous response to therapy. Optionally, diagnosis subsystem 402 uses a diagnosis database 424 to assist in providing a diagnosis. Diagnosis database 424 includes, for example, rules, example diagnoses, and/or machine learning data. Optionally or alternatively, diagnosis subsystem 402 includes one or more modules which apply processing on the model to extract diagnoses. In some exemplary embodiments of the invention, the diagnosis database 424 is updatable and/or parts thereof are available at different and/or additional cost.

Exemplary rules for diagnosis/analysis help direct operation of the system 200, 300, 400 with respect to measured values and/or the differentials between measured and expected values. For example, if the amount of measured tracer in an area of interest is low, but an expected value for tracer in the same area of interest is significantly lower, then what this really means according to a possible rule (where the rule sets an actionable “high” level) is that the amount of measured tracer is higher than what was expected and that some treatment plan may be called for. As another example, instead of a difference in value, a rule could be created which is linked to change in value over time. In such an example, a rule could be created which may call for the creation of a treatment plan if the expected reference value was supposed to show an increase of tracer amount over time, but instead the actual nerve model showed a decrease. Optionally, it is not an increase vs. decrease but a slower/faster increase or slower/faster decrease than expected (where the rule defines a specific rate of increase or decrease, above or below which calls for treatment).

The output of diagnosis system 402, in some embodiments, is a personalized diagnosis 430. In some exemplary embodiments of the invention, the diagnosis database 424 includes a plurality of templates, each one optionally associated with one or more possible diagnoses and/or including instruction for missing data to assist in diagnosis. Optionally or alternatively, at least one dynamic template is used. Such a template is potentially useful, for example, if a disease is characterized by a temporal pattern of behavior. Such a template includes, for example, multiple snapshots with a time indicator, and/or defines a function of change over time and/or in response to a trigger.

In some exemplary embodiments of the invention, personalized diagnosis 430 is provided to a planning subsystem 404. In some embodiments, planning subsystem 404 generates a treatment plan suitable for the patient, based on the diagnosis and/or best practices. Optionally, a treatment database 426 is used to aid in treatment planning. The treatment database 426 includes, for example, exemplary treatments, and/or rules for applying them.

Optionally or alternatively, planning subsystem 404 uses modules to plan various parts of the treatment and/or to determine if parts of the treatment are reasonable and/or safe. Optionally, model information 420 and/or patient information 422 also serve as input for the treatment planning. For example, the information 420, 422 is used to help determine what effect a treatment may have on a patient. In some embodiments, the result is a treatment plan 432.

In some exemplary embodiments of the invention, treatment plan 432 includes one or more of: a plurality of locations to be treated, an expected measurement for the effect of treatment of a location, treatment parameters for one or more of the location treatments and/or alternatives for one or more of the locations. Optionally, the plan 432 includes a time line indicating the order of treatment and/or delay times between treatment locations.

In some exemplary embodiments of the invention, a treatment is defined with a time scale of several minutes, hours or days; for example, defining a wait of between 1 and 1010 minutes or between 1 and 20 hours between treatment locations.

It should be noted that analysis (110) and/or modeling is potentially improved, in some embodiments, by taking into account the effect of treatment. In some exemplary embodiments of the invention, a treatment plan 432 includes a suggestion to recalculate model 420 (*e.g.* the nerve model) and/or analysis (110) and/or treatment (112) plan 432, for example, in response to a measurement exceeding a certain threshold or matching a certain pattern, and/or otherwise to fulfill a rule. In some embodiments of the invention, a measurement exceeding a certain threshold includes, for example, a marked increase in uptake and/or release of tracer in the area of interest, which would potentially indicate an enhancement of neural activity.

FIG. 5 is a block diagram 500 which shows at least a portion of the body 502 of interest connected to at least a portion of the systems 200, 300 or 400 for performing at least a portion of the method 100 of FIG. 1, in accordance with some exemplary embodiments of the invention. As described elsewhere herein, a portion of the body 502, besides being a part of the ANS (like a GP), is optionally an organ, such as the heart. In some embodiments of the invention, at least one sensor 202 is used to measure (104) neural activity (to create a nerve model), physiological factors and/or at least a portion of the ANS. The at least one sensor 202 is any of those described herein or known in the art, in some embodiments of the invention. In an embodiment of the invention, neural activity is measured (104) by sensing at and/or near one, some and/or all nerves 504, 508 and/or at one, some and/or all nerve nodes 506a, 506b, 510. In some embodiments of the invention, at least one afferent nerve 504 is measured. Additionally, alternatively and/or optionally, at least one efferent nerve 508 is measured (104). Optionally, measuring (104) is of tracer uptake. Optionally, measuring (104) is of portion of interest of the body 502 performance. In some embodiment of the invention, at least one sensor 202 is operationally connected to system 200, 300 or 400. In an embodiment of the invention, sensor 202 directs measurements to a controller/processor of systems 200, 300, 400 where comparing (108) and/or analyzing (110) are performed. It should be understood that this block diagram is by of example only, and that any actual configuration and/or anatomical features being examined is determined by patient anatomy and/or information gathering, diagnosis, and/or treatment objectives.

The terms "comprises", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to".

The term “consisting of” means “including and limited to”.

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases “ranging/ranges between” a first indicate number and a second indicate number and “ranging/ranges from” a first indicate number “to” a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term “treating” includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A system for deciphering sensed neural activity, comprising:

a memory configured to at least temporarily store at least one of a) a measured tracer radiation value from an area of interest and, b) a nerve model that interrelates measured tracer radiation and one or more parameters to neural activity; and,

at least one controller extracts a value of a parameter based on the measured tracer radiation using the nerve model.

2. A system according to claim 1, configured to correlate the nerve model to an expected reference value model to generate a neural activity status of the area of interest.

3. A system according to claim 1, where the memory is further configured to at least temporarily store at least one of a measured a) ANS function, and, b) parameter.

4. A system according to claim 3, where the controller is further configured to perform at least one of a) updating the expected reference value model based on measurements of the at least one parameter, b) updating the nerve model based on measurements of the tracer radiation in combination with the at least one parameter, c) correlating the nerve model to at least one of the expected reference value model and an ANS function, and, d) creating an ANS model based on measurements of at least one of the tracer radiation and an ANS function.

5. A system according to claim 3, where the ANS function is at least one of afferent signal and efferent signal.

6. A system according to claim 1, further comprising at least one sensor configured to sense at least one of a) an ANS function, b) tracer radiation indicative of at least one of tracer uptake and tracer release, and c) at least one parameter, in an area of interest.

7. A system according to claim 6, wherein the at least one sensor is a direct biometric sensor.

8. A system according claim 6, the at least one sensor is at least one of a functional imaging modality and an anatomical imaging modality.

9. A system according to claim 8, where the functional imaging modality is at least one of a PET, CT, MRI and SPECT imager.

10. A system according to claim 8, where the anatomical imaging modality is at least one of a CT, MRI, X-ay and ultrasound imager.

11. A system according to claim 1, where the controller is configured to create an ANS model of the area of interest including at least one of nerve locations, interconnections and activity levels.

12. A system according to claim 1, further comprising a GUI associated with the at least one controller and configured to effectuate user control of the system.

13. A system according to claim 1, where measured tracer radiation is correlated to neural activity using at least one of a) a number of NA transmissions in a presynaptic nerve, b) NE quanta discharged per transmission, c) NE concentration in blood of a patient, d) tracer degradation rate, e) re-uptake I for NE, f) tracer concentration in the blood of the patient, g) time elapsed between a tracer injection and a medical imaging time, and, h) synaptic effective distribution volume.

14. A system according to claim 1, further comprising a tool configured to perform at least one of ablation, freezing, stimulation, and anesthesia.

15. A system for planning based on sensed neural activity, comprising:

a sub-system for deciphering sensed neural activity according to any of claims 1-14; and,

a sub-system for utilizing the generated neural activity status, comprising,

a diagnosis subsystem configured to generate a personalized diagnosis, and, a planning subsystem configured to create a plan based on the personalized diagnosis for modifying the neural activity status.

16. A system for planning based on sensed neural activity according claim 15, where the diagnosis subsystem is configured to receive at least one of the model of an area of interest, patient information and diagnosis database information from a diagnosis database.

17. A system for planning based on sensed neural activity according claim 15, where the planning subsystem is configured to receive at least one of the personalized diagnosis and treatment database information from a treatment database.

18. A system according to claim 1, where at least one of the memory and the at least one controller are remotely located from the at least one sensor.

19. A system according to claim 15, where at least one component of the sub-system for deciphering sensed neural activity or the sub-system for utilizing a model of an area of interest is located remotely from the at least one sensor.

20. A method for deciphering sensed neural activity, comprising:

placing at least one sensor configured to sense tracer radiation in an area of interest;

measuring tracer radiation in the area of interest;

comparing the measured tracer radiation to an expected reference value model to determine a neural activity status.

21. A method according to claim 20, further comprising analyzing the neural activity status to create a plan for modifying the neural activity status based on the analyzing.

22. A method according to claim 20, further comprising creating an ANS model of the area of interest at least partially based on the measuring.

23. A method according to claim 20, further comprising diagnosing a dysfunctional state of the area of interest at least partly based on the differences between the measured neural activity value and the expected reference value.

24. A method according to claim 20, further comprising treating the area of interest at least partly based on the differences between the measured neural activity value and the expected reference value.

25. A method according to claim 20, wherein measuring is performed using medical imaging.

26. A method according to claim 25, where medical imaging is at least one of PET, CT, MRI, SPECT, CT, MRI, X-ay and ultrasound.

27. A method according to claim 20, wherein measuring is performed using a direct biometric sensor.

28. A method according to claim 27, where a direct biometric sensor is at least one of an implantable CMOS biosensor, an electrical sensor, a blood pressure sensor and a blood flow sensor.

29. A method according to claim 20, where measured tracer radiation is correlated to neural activity using at least one of a) a number of NA transmissions in a presynaptic nerve, b) NE quanta discharged per transmission, c) NE concentration in blood of a patient, d) tracer degradation rate, e) re-uptake I for NE, f) tracer concentration in the blood of the patient, g) time elapsed between a tracer injection and a medical imaging time, and, h) synaptic effective distribution volume.

30. A system for deciphering sensed neural activity, comprising:

a memory configured to at least temporarily store at least one of a) a measured tracer radiation value from an area of interest and, b) an expected reference value model that interrelates measured tracer radiation and one or more parameters to neural activity; and,

at least one controller extracts a value of a parameter based on the measured tracer radiation using the expected reference value model.

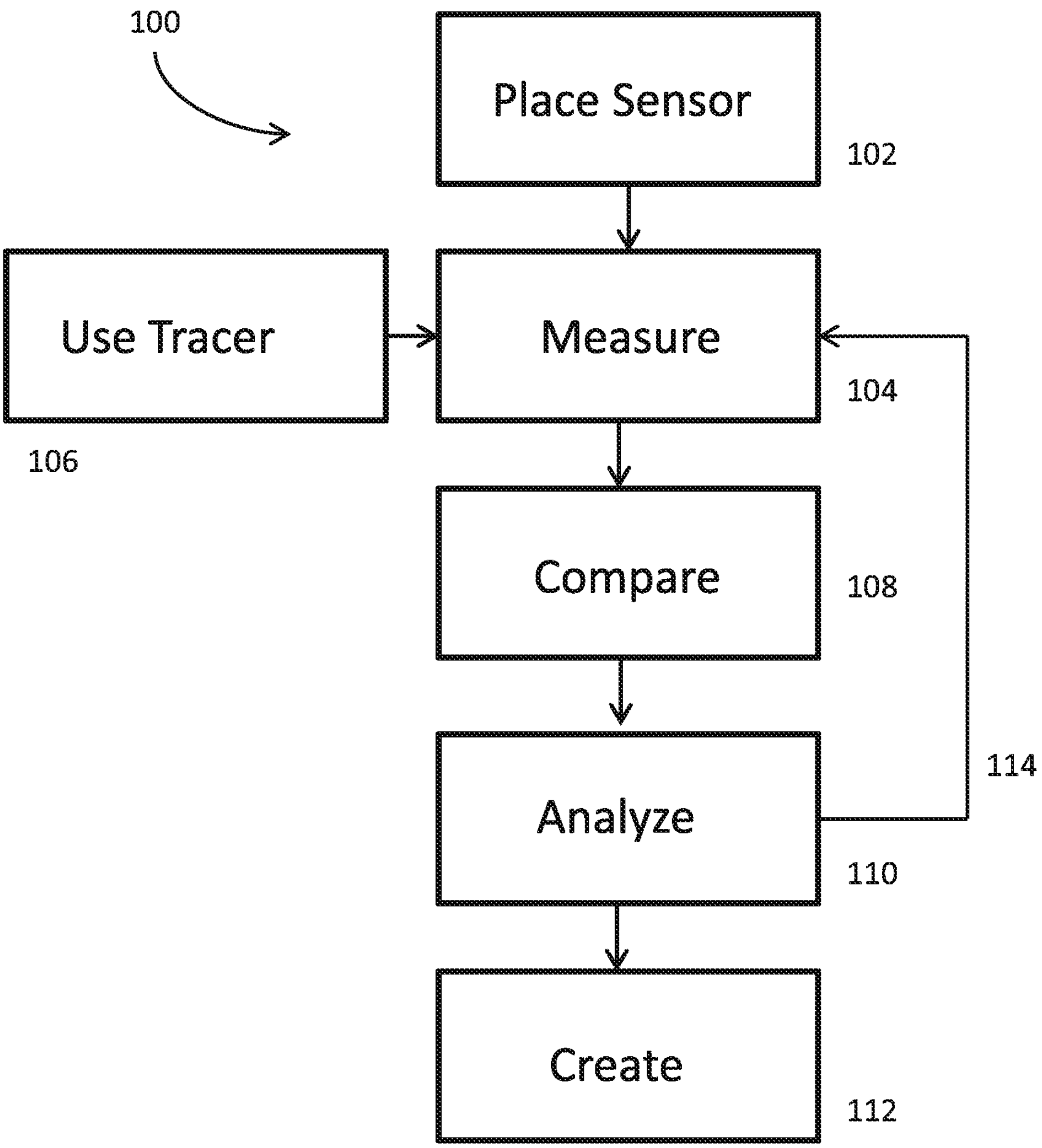

100
Place Sensor
102
Use Tracer
Measure
104
106
Compare
108
114
Analyze
110
Create
112

FIG. 1

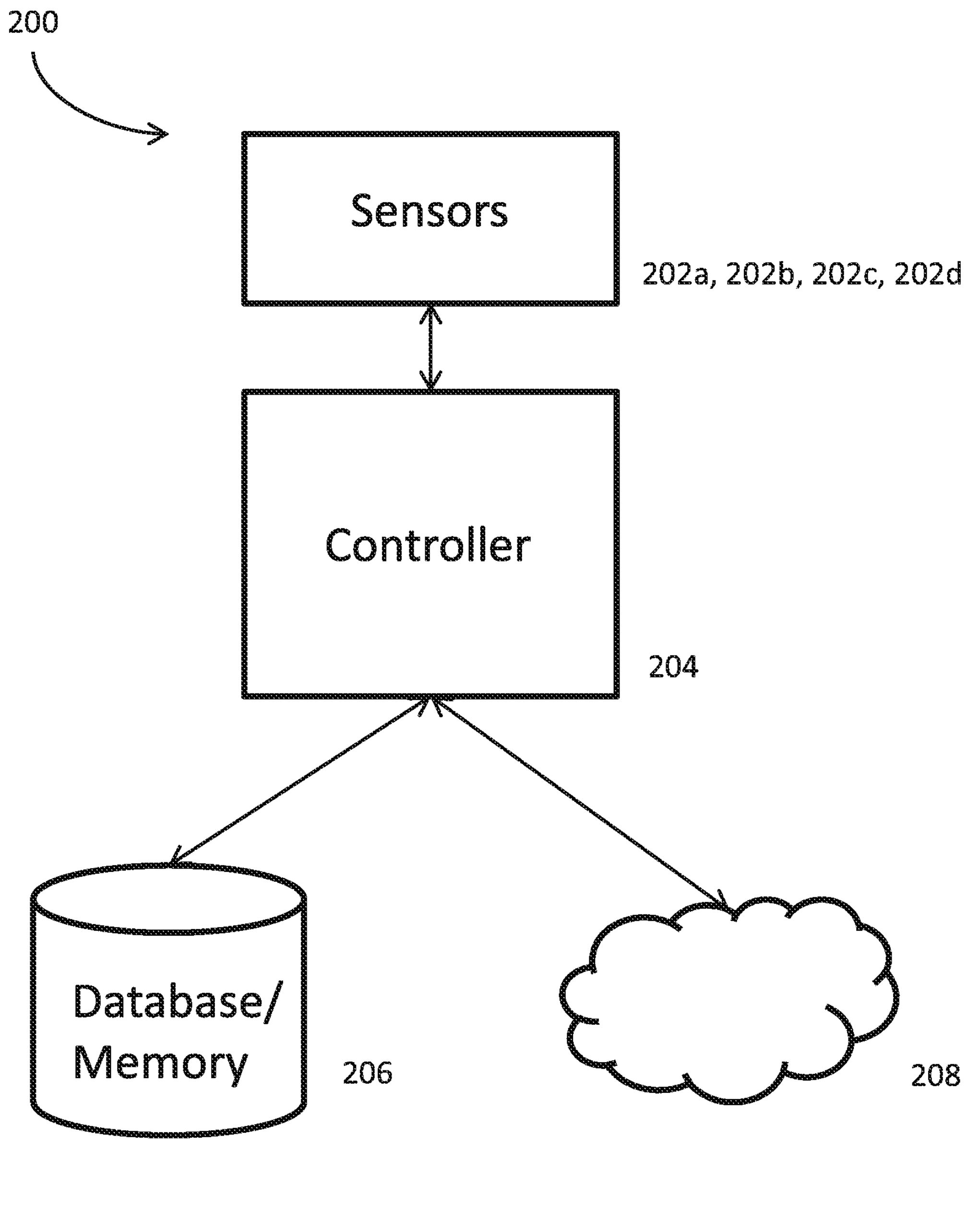

200
Sensors
202a, 202b, 202c, 202d
Controller
204
Database/
Memory
206
208

FIG. 2

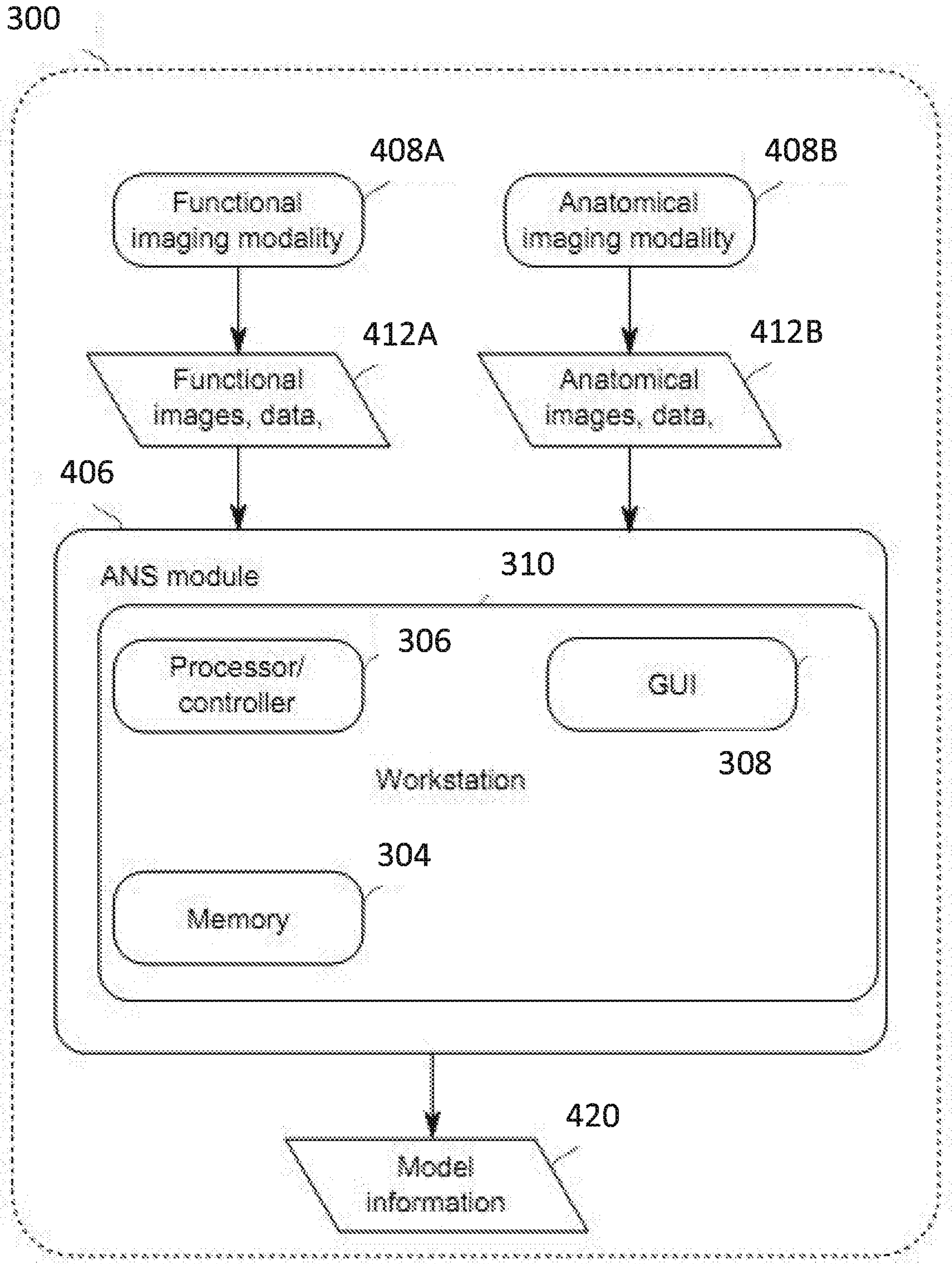
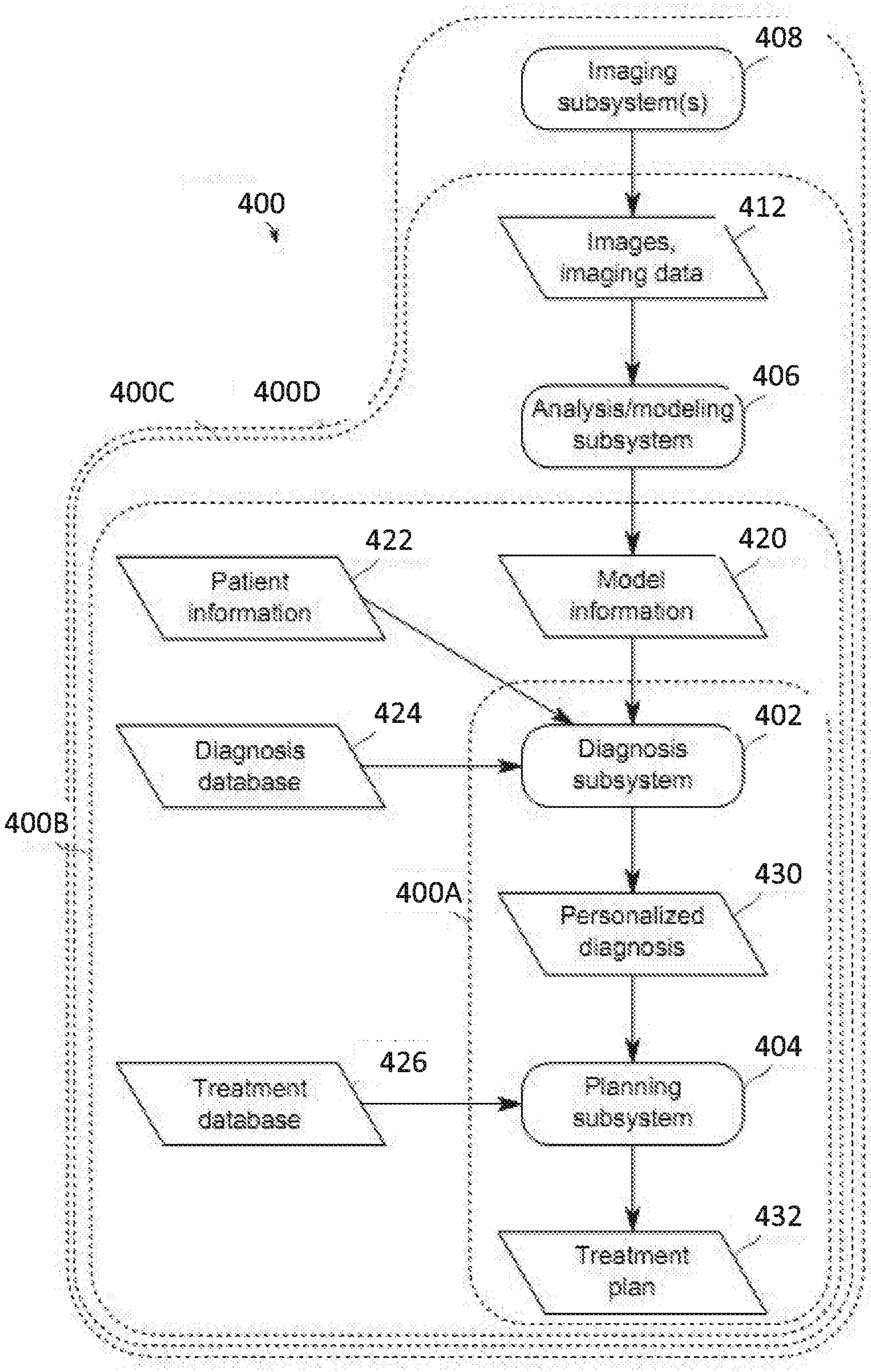

300
408A
Functional
imaging modality
408B
Anatomical
imaging modality
412A
Functional
images, data,
412B
Anatomical
images, data,
406
ANS module
310
306
Processor/
controller
GUI
308
Workstation
304
Memory
420
Model
information

FIG. 3



400
408
Imaging subsystem(s)
412
Images, imaging data
400C
400D
406
Analysis/modeling subsystem
422
Patient information
420
Model information
424
Diagnosis database
402
Diagnosis subsystem
400B
400A
430
Personalized diagnosis
426
Treatment database
404
Planning subsystem
432
Treatment plan

FIG. 4

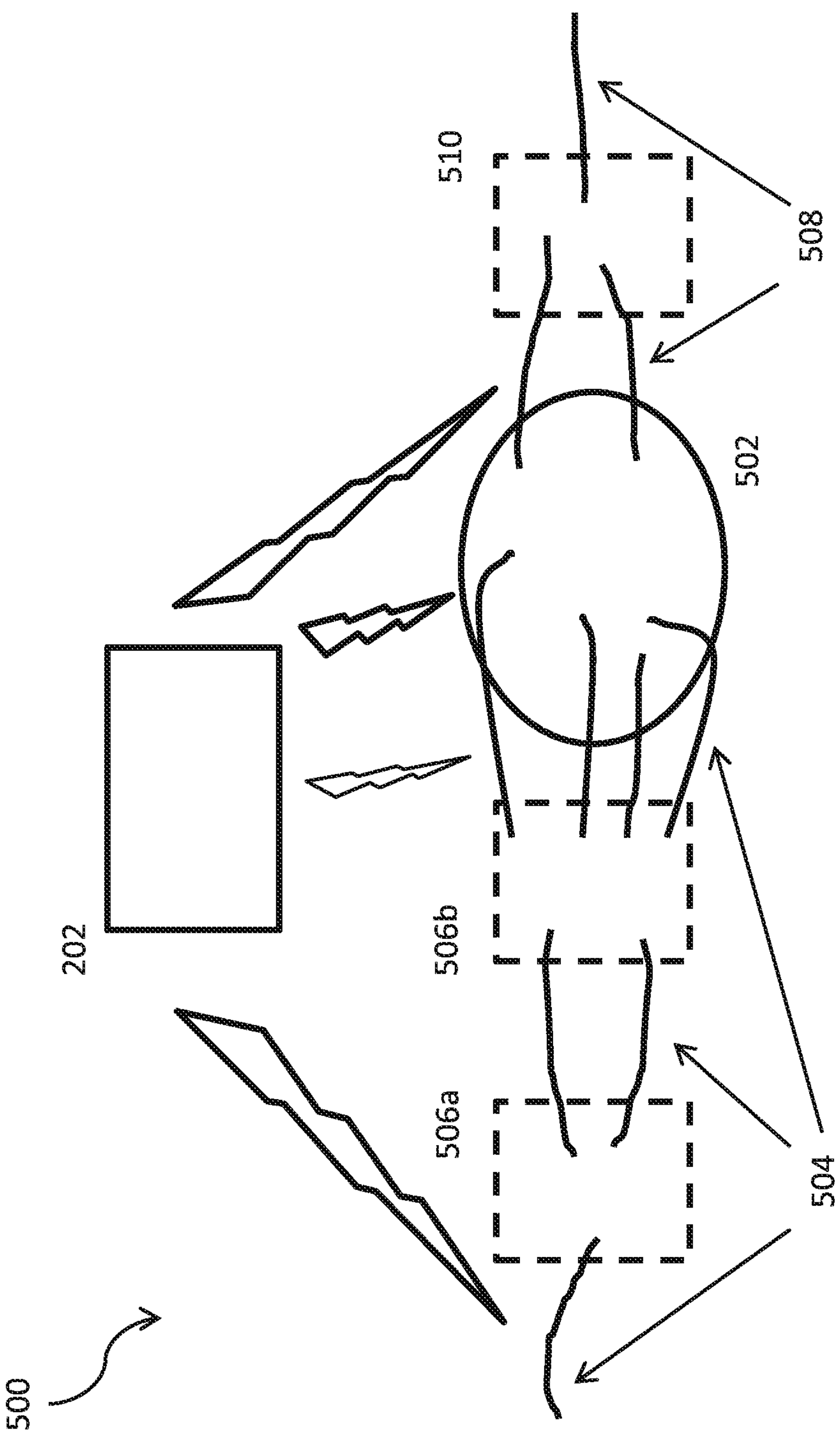


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/053984

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B6/00 A61B6/03 A61B5/04 A61B5/00 A61B18/14
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)
A61B G06T

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	Mark A Rabinovitch ET AL: "A Method of Dynamic Analysis of Iodine-123-Metaiodobenzylguanidine Scintigrams in Cardiac Mechanical Overload Hypertrophy and Failure", J Nucl Med, 1 April 1993 (1993-04-01), pages 589-600, XP055214626, Retrieved from the Internet: URL:http://jnm.snmjournals.org/content/34/4/589.long [retrieved on 2015-09-18]	1-13,20, 23,25, 26,29,30
Y	page 589, column 1 - page 593, column 2 page 598, column 2 - page 599, column 1	14-19, 21,22, 24,27,28

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2015	01/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Martinez Möller, A

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RISPLER SHMUEL ET AL: "Quantitative 123I-MIBG SPECT/CT assessment of cardiac sympathetic innervation - A new diagnostic tool for heart fai", INTERNATIONAL JOURNAL OF CARDIOLOGY, vol. 168, no. 2, 17 January 2013 (2013-01-17), pages 1556-1558, XP028740607, ISSN: 0167-5273, DOI: 10.1016/J.IJCARD.2012.12.077 page 1556, column 1 - page 1558, column 1 -----	1-6, 8-13,20, 22,23, 25,26, 29,30
X	ANTONELLA STEFANELLI ET AL: "I-MIBG Scintigraphy as a Powerful Tool to Plan an Implantable Cardioverter Defibrillator and to Assess Cardiac Resynchronization Therapy in Heart Failure Patients", INTERNATIONAL JOURNAL OF MOLECULAR IMAGING, vol. 7, no. 5, 1 January 2012 (2012-01-01) , pages 398-6, XP055214933, ISSN: 2090-1712, DOI: 10.1007/s00259-008-0971-2 abstract page 1, column 1 - page 2, column 1 -----	1-6, 8-13, 15-26, 29,30
X	Jicun Hu ET AL: "Dynamic molecular imaging of cardiac innervation using a dual head pinhole SPECT system", , 23 May 2008 (2008-05-23), pages 1-54, XP055214624, Retrieved from the Internet: URL:http://escholarship.org/uc/item/45f1m763 [retrieved on 2015-09-18] Abstract page 16, paragraph 3 - page 20, paragraph 2; figures 9,10; table 2 -----	1-6, 8-13,20, 22,23, 25,26,29
X	D. M. RAFFEL ET AL: "Quantification of Cardiac Sympathetic Nerve Density with N-11C-Guanyl-meta-Octopamine and Tracer Kinetic Analysis", THE JOURNAL OF NUCLEAR MEDICINE, vol. 54, no. 9, 25 July 2013 (2013-07-25), pages 1645-1652, XP055214628, ISSN: 0161-5505, DOI: 10.2967/jnumed.113.120659 page 1645, column 1 - page 1647, column 1; figures 1,2 -----	1-6, 8-13,20, 22,23, 25,26,29

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/053984

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/123773 A1 (SCHWARTZ YITZHACK [IL]) 16 May 2013 (2013-05-16) paragraph [0046] - paragraph [0053]; claim 1; figure 3 -----	14-19, 21,22, 24,27,28
A	Anonymous: "NCT02071680 on 2014_02_25: ClinicalTrials.gov Archive", , 25 February 2014 (2014-02-25), XP055214861, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT02071680/2014_02_25 [retrieved on 2015-09-21] page 1 - page 3 -----	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/053984

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2794791 A1	14-05-2013
		CN 103099671 A	15-05-2013
		EP 2591722 A1	15-05-2013
		JP 2013103134 A	30-05-2013
		US 2013123773 A1	16-05-2013