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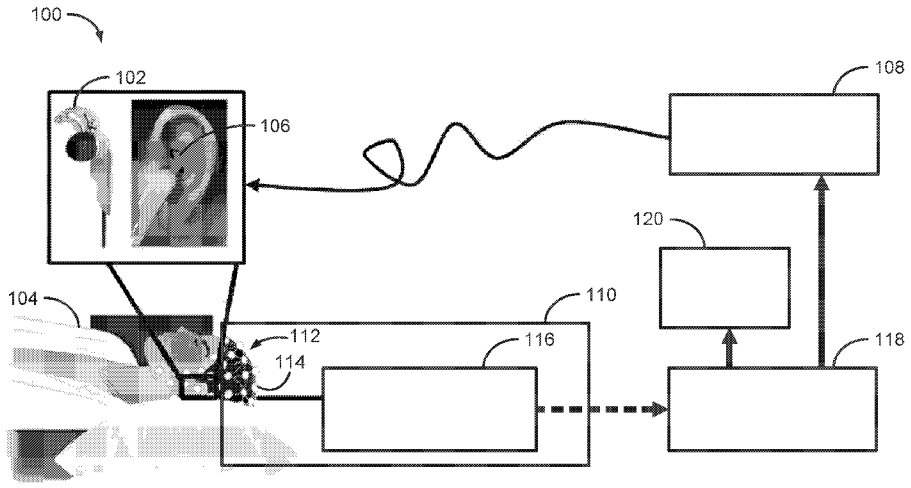


FIG. 1

(57) Abstract: Systems and methods are described for neurostimulation to provide therapeutic outcomes, such as the treatment of delirium, disorders of consciousness, narcolepsy, and inflammatory disorders, with signals that are adjusted based on electroencephalographic (EEG) signals. The neurostimulation may target the vagus nerve or its branches. The systems and methods use a detecting device to detect EEG characteristics where central autonomic nuclei may be more receptive to afferent input from the vagus nerve. A stimulator is controlled to provide neurostimulation to the auricular branch of a vagus nerve of the subject.

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SYSTEM AND METHOD TO MODULATE AROUSAL OR REDUCE DELIRIUM SEVERITY

Cross Reference to Related Applications

[0001] The present application is based on, claims priority to, and incorporates herein by reference in its entirety for all purposes, US Provisional Application Serial No. 63/486,259, filed February 22, 2023.

Background

[0002] Delirium is a serious form of brain dysfunction characterized by acute deficits in awareness, attention, and cognition. Delirium arises from an altered state of consciousness and is the most common neuropsychiatric disorder observed in hospitalized patients, especially the elderly. Delirium has been linked to specific disturbances in electroencephalography (EEG) rhythms. Delirium is marked by the presence of delta waves on EEG, a typical feature of non-rapid eye movement (NREM) sleep, that normally do not occur during the wakeful state. The presence of these delta waves reflects a periodic alternation between *Up* states, where underlying neural circuits are more active, and sustained *Down* states, where neuronal activity is suppressed. Current clinical approaches for delirium involve the adjustment of medications and dosage, physical restraint, and use of antipsychotic or sedative pharmacotherapy. These approaches do not directly address the underlying neural pathophysiology of delirium and have shown minimal impact on delirium-associated morbidity – e.g. institutionalization, dementia, or death.

Summary

[0003] The present disclosure provides systems and methods that overcome the aforementioned drawbacks by providing systems and methods of non-invasive EEG-gated auricular vagal afferent nerve stimulation (EAVANS) to modulate arousal and/or reduce delirium severity. The stimulation may be coordinated by a controller designed to modulate

arousal as well as markers of impaired arousal such as delta power, by providing auricular vagal afferent nerve stimulation in a manner phase-locked to the delta or slow wave. Since cognitive impairment and neurocognitive disorders such as delirium can occur in part due to an impairment of arousal, this modulation of arousal can serve to prevent or ameliorate or counteract delirium.

[0004] In one aspect, a neuromodulation system for modulating delta power is described. The system comprises an electrode configured to be electrically coupled to an auricular branch of a vagus nerve of a subject, a stimulation circuit connected to the electrode to deliver a stimulation signal to the electrode to stimulate the auricular branch of the vagus nerve, an EEG sensor configured to acquire an EEG signal of the subject. The system further comprise a controller configured to receive the EEG signal from the EEG sensor, wherein the controller extracts one or more EEG characteristics of interest and sends control signals to the stimulation circuit to deliver the stimulation signal based on the one or more EEG characteristics to modulate arousal or reduce delirium severity.

[0005] In another aspect, a method for modulating delta power is described. The method comprises positioning on a subject an electrode configured to be electrically coupled to an auricular branch of a vagus nerve of the subject, delivering, by a stimulation circuit connected to the electrode, a stimulation signal to the electrode, thereby stimulating the auricular branch of the vagus nerve, acquiring, via an electroencephalography (EEG) sensor, an EEG signal of the subject, and receiving, via a controller, the EEG signal from the EEG sensor. The method further comprises extracting, via the controller, one or more EEG characteristics of interest, sending, via the controller, control signals to the stimulation circuit, and delivering, via the stimulation circuit, a stimulation signal based on the one or more EEG characteristics, wherein the stimulation signal is delivered to modulate arousal or reduce delirium sensitivity.

[0006] These aspects are nonlimiting. Other aspects and features of the systems and methods described herein will be provided below.

Brief Description of the Drawings

[0007] The foregoing features of embodiments will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

[0008] FIG. 1 is a schematic of the neuromodulation system, according to aspects of the present disclosure.

[0009] FIG. 2 is a schematic of an example neuromodulation system, according to aspects of the present disclosure.

[0010] FIG. 3 is a schematic of example components that can implement the neuromodulation system of FIG. 2.

[0011] FIG. 4 is a flow chart of the method for modulation of delta power, according to aspects of the present disclosure.

[0012] FIG. 5 is an illustration of the neuromodulation system, according to another aspect of the disclosure.

[0013] FIG. 6. Is a diagram showing that oscillator states can be viewed as Phasor, undergoing rotation (1), scaling (2), and addition of noise (3) at every time point, while the real coordinate is observed via a noisy measurement.

[0014] FIG. 7A shows scalp maps reporting the names and locations of the recording EEG electrodes, according to aspects of the present disclosure. The color codes for the difference in delta power between different experimental conditions: active control versus absence of stimulation (GANctrl – No-Stim), active vagus nerve stimulation versus absence of stimulation

(EAVANS – No-Stim), active vagus nerve stimulation versus active control (EAVANS – GANctrl).

[0015] FIG. 7B shows a box plot and violin plot reporting delta power distribution (averaged across electrodes) in experimental conditions No-Stim, GANctrl and EAVANS.

[0016] FIG. 7C is a plot of the delta power distribution during EAVANS and GANctrl while stimulating during either *Up* or *Down* delta phases states.

[0017] FIG. 8 is a plot of 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) total score reported for three subjects for three time points.

[0018] FIG. 9 is a plot of the percentage of correct answers (CA%) reported for three subject for three time points.

Detailed Description

[0019] The present disclosure provides systems and methods for EEG-gated vagus nerve stimulation (VNS) that enhances therapeutic outcomes, including for the treatment of delirium. Specifically, transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive method achieved by applying an electrical current to the cutaneous receptive field formed by the auricular branch of the vagus nerve (outer ear). Promising clinical outcomes have been shown for a range of disorders including depression, epilepsy and migraine. As disclosed herein, a combination of taVNS with EEG is presented to modulate arousal as well as markers of impaired arousal such as delta power.

[0020] The system and method described herein employ EEG-gated auricular vagal afferent nerve stimulation (EAVANS), which may be an enhanced approach to taVNS to disrupt the delta waves (0.5 to 4 Hz) that are markers of impaired arousal and prevent or ameliorate states of delirium. In particular, taVNS could be imparted during a specific phase of the delta wave, thereby increasing arousal and activating ascending noradrenergic pathways via the nucleus tractus solitarius and potentially disrupting the cycle of *Up/Down* states that

characterize periods of reduced or impaired arousal. Furthermore, periodically gated stimulation paradigms circumvent the habituation that is commonly observed with more sustained, continuous peripheral nerve stimulation. Additionally, taVNS has been proposed to also modulate neuroinflammation, another key contributing factor to delirium and other neurocognitive disorders, by the cholinergic anti-inflammatory pathway and efferent feedback connections to the vagal innervation of the spleen.

[0021] In a non-limiting example, an EAVANS neuromodulation system 100 is shown in FIG. 1. The system may include an electrode 102 configured to be electrically coupled to an auricular branch of the vagus nerve of a subject 104. In a non-limiting example, the electrode 102 is configured to engage within the cymba conchae of the ear 106. Alternatively, the electrode 102 may be electrically coupled to an afferent nerve fiber of a vagus nerve of a subject 104.

[0022] The system 100 further includes a stimulation circuit 108 operably connected to the electrode 102 to deliver a stimulation signal to the auricular branch of the vagus nerve. In a non-limiting example, the stimulation signal may be provided by a current-constant stimulator (e.g., Urostim, schwa-medico GmbH, Ehringshausen, Germany). In one aspect, the stimulation signal comprises, but is not limited to, a monophasic rectangular pulse burst train. Further, the stimulation signal may have a frequency of 100 Hz and a pulse width of 300 μs. In one non-limiting embodiment, the stimulation signal consists of biphasic rectangular pulse trains 1 to 1.5 seconds in duration with 100 to 600 μs pulse width, delivered at a frequency 1 to 200 Hz, initiated 0.1 to 1 seconds following peak inspiration by the subject 104. In a non-limiting example, the stimulation signal causes a reduction of neuroinflammation coordinated via the activation of cholinergic anti-inflammatory pathways and efferent feedback connections to the vagal innervation of the spleen. In a non-limiting example, the stimulation signal can modulate delta oscillations (0.5 to 4 Hz) in order to increase arousal or reverse

impaired arousal. In another non-limiting example, the stimulation signal can modulate delta oscillations (0.5 to 4 Hz) in order to increase arousal or reverse impaired arousal and in turn improve cognitive function.

[0023] In a non-limiting example, the stimulation signal delivered by the stimulation circuit 108 can be based on an EEG signal obtained from the subject 104 using an EEG system 110. The EEG system 110 includes an EEG sensor 112 configured to acquire EEG signal from the subject 104 to determine and extract one or more EEG characteristics. In a non-limiting example, an EEG characteristic may be related to the delta wave (0.5 to 4 Hz) phase. In another non-limiting example, the one or more EEG characteristic includes a phased of a delta wave embedded in the EEG signal.

[0024] In one aspect, the EEG system 110 may be wireless and receive EEG signal from the EEG sensor 112. Alternatively, the EEG sensor 112 may be electrically connected to the EEG system 110 by wires. The EEG system 110 may further include an amplifier 116 configured to amplify the EEG signal.

[0025] In a non-limiting example, the EEG sensor 112 includes a plurality of sensor electrodes 114. The plurality of sensor electrodes 114 may be configured to be placed on the subject's scalp for detecting the EEG characteristic. In a non-limiting example, the EEG sensor 112 may include one to 64 channels. In a preferred embodiment, the EEG sensor 112 includes at least eight channels. The EEG sensor 112 may by arranged in a net or on a cap configured to be placed on the subject's scalp. In a non-limiting example, the EEG sensor 112 may include two to 128 sensor electrodes 114. In one embodiment, the EEG sensor 112 include eight sensor electrodes 114. The eight sensor electrodes 114 may be frontal electrodes Fpz, Fp1, Fp2, AF3, AF4, F7, F8 and Cz to facilitate Laplacian referencing of the signal recorded by the Fpz electrode.

[0026] In a non-limiting example, the system 100 further comprises a controller 118 for receiving the EEG signal from the EEG sensor 112 and sends control signals to the stimulation circuit 108 to the electrode 102 based on the one or more EEG characteristics. In another aspect, the controller 118 is configured to estimate instantaneous phase or power of the delta wave as EEG characteristics and determine control signals based on that EEG characteristics.

[0027] In a non-limiting example, the stimulation signal is delivered during a selected phase of a delta wave to modulate arousal or reduce neuroinflammation associated with delirium. In one embodiment, the controller 118 is configured to cause the stimulation circuit 108 to deliver the stimulation signal during a rising phase of the delta wave. Further, the controller 118 is configured to cause the stimulation circuit 108 to deliver the stimulation signal in the range of $-\pi/2$, 0 radians. In one aspect, the controller 118 is configured to control the stimulation circuit 108 to reduce delta power in the subject experiencing or at risk of delirium. In another aspect, the controller 118 is configured to control the stimulation circuit to reduce delta power during non-rapid eye movement (NREM) sleep in the subject. In another example, the controller 118 is configured to control delirium severity in the subject during at least one of pre-operative and post-operative conditions.

[0028] In a non-limiting example, the system 100 further includes a display 120. In a non-limiting aspect, the controller 118 includes integrated algorithm configured to provide real-time display of the acquired EEG signal and its spectral properties. In a non-limiting example, EEG-based features are estimated such as Power Spectral Density (PSD) and phase synchronization-based Phase Locking Value (PLV) in δ, θ, and α frequency bands. In another aspect, the integrated algorithm may detect in real-time *Up* and *Down* states, based on an adaptive threshold detection algorithm.

[0029] Referring now to FIG. 2, an example of a system 200 for neuromodulation of delta power in accordance with some embodiments of the systems and methods described in the present disclosure is shown. As shown in FIG. 2, a computing device 250 can receive EEG data from data source 202. In some embodiments, computing device 250 can execute at least a portion of the EEG system 204 to extract one or more EEG characteristics from data received from the data source 202.

[0030] Additionally or alternatively, in some embodiments, the computing device 250 can communicate information about data received from the data source 202 to a server 252 over a communication network 254, which can execute at least a portion of the EEG system 204. In such embodiments, the server 252 can return information to the computing device 250 (and/or any other suitable computing device) indicative of an output of the EEG system 204.

[0031] In some embodiments, computing device 250 and/or server 252 can be any suitable computing device or combination of devices, such as a desktop computer, a laptop computer, a smartphone, a tablet computer, a wearable computer, a server computer, a virtual machine being executed by a physical computing device, and so on. The computing device 250 and/or server 252 can also construct scalp maps from the data.

[0032] In some embodiments, data source 202 can be any suitable EEG data source such as EEG sensor 112, another computing device (e.g., a server storing previously acquired EEG data), and so on. In a non-limiting embodiment, the data source 202 may additionally include an electrocardiogram (ECG) data source, a galvanic skin response (GSR) data source, and/or a respiration data source. In some embodiments, data source 202 can be local to computing device 250. For example, data source 202 can be incorporated with computing device 250 (e.g., computing device 250 can be configured as part of a device for measuring, recording, estimating, acquiring, or otherwise collecting or storing data). As another example, data source 202 can be connected to computing device 250 by a cable, a direct wireless link, and so on.

Additionally or alternatively, in some embodiments, data source 202 can be placed locally and/or remotely from computing device 250 and can communicate data to computing device 250 (and/or server 252) via a communication network (e.g., communication network 254).

[0033] In some embodiments, communication network 254 can be any suitable communication network or combination of communication networks. For example, communication network 254 can include a Wi-Fi network (which can include one or more wireless routers, one or more switches, etc.), a peer-to-peer network (e.g., a Bluetooth network), a cellular network (e.g., a 3G network, a 4G network, etc., complying with any suitable standard, such as CDMA, GSM, LTE, LTE Advanced, WiMAX, etc.), other types of wireless network, a wired network, and so on. In some embodiments, communication network 254 can be a local area network, a wide area network, a public network (e.g., the Internet), a private or semi-private network (e.g., a corporate or university intranet), any other suitable type of network, or any suitable combination of networks. Communications links shown in FIG. 2 can each be any suitable communications link or combination of communications links, such as wired links, fiber optic links, Wi-Fi links, Bluetooth links, cellular links, and so on.

[0034] Referring now to FIG. 3, an example of hardware 300 that can be used to implement data source 202, computing device 250, and server 252 in accordance with some embodiments of the systems and methods described in the present disclosure is shown.

[0035] As shown in FIG. 3, in some embodiments, computing device 250 can include a controller 302, a display 304, one or more inputs 306, one or more communication systems 308, and/or memory 310. In some embodiments, controller 302 can be any suitable hardware processor or combination of processors, such as a central processing unit ("CPU"), a graphics processing unit ("GPU"), and so on. In some embodiments, display 304 can include any suitable display devices, such as a liquid crystal display ("LCD") screen, a light-emitting diode ("LED") display, an organic LED ("OLED") display, an electrophoretic display (e.g., an "e-

ink" display), a computer monitor, a touchscreen, a television, and so on. In some embodiments, inputs 306 can include any suitable input devices and/or sensors that can be used to receive user input, such as a keyboard, a mouse, a touchscreen, a microphone, and so on.

[0036] In some embodiments, communications systems 308 can include any suitable hardware, firmware, and/or software for communicating information over communication network 254 and/or any other suitable communication networks. For example, communications systems 308 can include one or more transceivers, one or more communication chips and/or chip sets, and so on. In a more particular example, communications systems 308 can include hardware, firmware, and/or software that can be used to establish a Wi-Fi connection, a Bluetooth connection, a cellular connection, an Ethernet connection, and so on.

[0037] In some embodiments, memory 310 can include any suitable storage device or devices that can be used to store instructions, values, data, or the like, that can be used, for example, by processor 302 to present content using display 304, to communicate with server 252 via communications system(s) 308, and so on. Memory 310 can include any suitable volatile memory, non-volatile memory, storage, or any suitable combination thereof. For example, memory 310 can include random-access memory ("RAM"), read-only memory ("ROM"), electrically programmable ROM ("EPROM"), electrically erasable ROM ("EEPROM"), other forms of volatile memory, other forms of non-volatile memory, one or more forms of semi-volatile memory, one or more flash drives, one or more hard disks, one or more solid state drives, one or more optical drives, and so on. In some embodiments, memory 310 can have encoded thereon, or otherwise stored therein, a computer program for controlling operation of computing device 250. In such embodiments, processor 602 can execute at least a portion of the computer program to present content (e.g., images, user interfaces, graphics, tables), receive content from server 252, transmit information to server 252, and so on. For example, the

controller 302 and the memory 310 can be configured to perform the methods described herein (e.g., the method of FIG. 4).

[0038] In some embodiments, server 252 can include a processor 312, a display 314, one or more inputs 316, one or more communications systems 318, and/or memory 320. In some embodiments, processor 312 can be any suitable hardware processor or combination of processors, such as a CPU, a GPU, and so on. In some embodiments, display 314 can include any suitable display devices, such as an LCD screen, LED display, OLED display, electrophoretic display, a computer monitor, a touchscreen, a television, and so on. In some embodiments, input 316 can include any suitable input devices and/or sensors that can be used to receive user input, such as a keyboard, a mouse, a touchscreen, a microphone, and so on.

[0039] In some embodiments, communications systems 318 can include any suitable hardware, firmware, and/or software for communicating information over communication network 254 and/or any other suitable communication networks. For example, communications systems 318 can include one or more transceivers, one or more communication chips and/or chip sets, and so on. In a more particular example, communications systems 318 can include hardware, firmware, and/or software that can be used to establish a Wi-Fi connection, a Bluetooth connection, a cellular connection, an Ethernet connection, and so on.

[0040] In some embodiments, memory 320 can include any suitable storage device or devices that can be used to store instructions, values, data, or the like, that can be used, for example, by processor 312 to present content using display 314, to communicate with one or more computing devices 250, and so on. Memory 320 can include any suitable volatile memory, non-volatile memory, storage, or any suitable combination thereof. For example, memory 320 can include RAM, ROM, EPROM, EEPROM, other types of volatile memory, other types of non-volatile memory, one or more types of semi-volatile memory, one or more flash drives, one or more hard disks, one or more solid state drives, one or more optical drives, and so on.

In some embodiments, memory 320 can have encoded thereon a server program for controlling operation of server 252. In such embodiments, processor 312 can execute at least a portion of the server program to transmit information and/or content (e.g., data, a user interface) to one or more computing devices 250, receive information and/or content from one or more computing devices 250, receive instructions from one or more devices (e.g., a personal computer, a laptop computer, a tablet computer, a smartphone), and so on.

[0041] In some embodiments, the server 252 is configured to perform the methods described in the present disclosure. For example, processor 312 and memory 320 can be configured to perform the methods described herein (e.g., the method of FIG. 4).

[0042] In some embodiments, data source 202 can include a controller 322, one or more data acquisition systems 324, one or more communications systems 326, and/or memory 328. In some embodiments, controller 322 can be any suitable hardware processor or combination of processors, such as a CPU, a GPU, and so on. In some embodiments, the one or more data acquisition systems 324 are generally configured to acquire data and can include EEG data. Additionally or alternatively, in some embodiments, the one or more data acquisition systems 324 can include any suitable hardware, firmware, and/or software for coupling to and/or controlling operations of EEG sensor 112. In some embodiments, one or more portions of the data acquisition system(s) 324 can be removable and/or replaceable.

[0043] Note that, although not shown, data source 202 can include any suitable inputs and/or outputs. For example, data source 202 can include input devices and/or sensors that can be used to receive user input, such as a keyboard, a mouse, a touchscreen, a microphone, a trackpad, a trackball, and so on. As another example, data source 202 can include any suitable display devices, such as an LCD screen, an LED display, an OLED display, an electrophoretic display, a computer monitor, a touchscreen, a television, etc., one or more speakers, and so on.

[0044] In some embodiments, communications systems 326 can include any suitable hardware, firmware, and/or software for communicating information to computing device 250 (and, in some embodiments, over communication network 254 and/or any other suitable communication networks). For example, communications systems 326 can include one or more transceivers, one or more communication chips and/or chip sets, and so on. In a more particular example, communications systems 326 can include hardware, firmware, and/or software that can be used to establish a wired connection using any suitable port and/or communication standard (e.g., VGA, DVI video, USB, RS-232, etc.), Wi-Fi connection, a Bluetooth connection, a cellular connection, an Ethernet connection, and so on.

[0045] In some embodiments, memory 328 can include any suitable storage device or devices that can be used to store instructions, values, data, or the like, that can be used, for example, by controller 322 to control the one or more data acquisition systems 324, and/or receive data from the one or more data acquisition systems 324; to present content (e.g., data, images, a user interface) using a display; communicate with one or more computing devices 250; and so on. Memory 328 can include any suitable volatile memory, non-volatile memory, storage, or any suitable combination thereof. For example, memory 328 can include RAM, ROM, EPROM, EEPROM, other types of volatile memory, other types of non-volatile memory, one or more types of semi-volatile memory, one or more flash drives, one or more hard disks, one or more solid state drives, one or more optical drives, and so on. In some embodiments, memory 328 can have encoded thereon, or otherwise stored therein, a program for controlling operation of data source 202. In such embodiments, controller 322 can execute at least a portion of the program to generate images, transmit information and/or content (e.g., data, images, a user interface) to one or more computing devices 250, receive information and/or content from one or more computing devices 250, receive instructions from one or more devices (e.g., a personal computer, a laptop computer, a tablet computer, a smartphone, etc.), and so on.

[0046] In some embodiments, any suitable computer-readable media can be used for storing instructions for performing the functions and/or processes described herein. For example, in some embodiments, computer-readable media can be transitory or non-transitory. For example, non-transitory computer-readable media can include media such as magnetic media (e.g., hard disks, floppy disks), optical media (e.g., compact discs, digital video discs, Blu-ray discs), semiconductor media (e.g., RAM, flash memory, EPROM, EEPROM), any suitable media that is not fleeting or devoid of any semblance of permanence during transmission, and/or any suitable tangible media. As another example, transitory computer-readable media can include signals on networks, in wires, conductors, optical fibers, circuits, or any suitable media that is fleeting and devoid of any semblance of permanence during transmission, and/or any suitable intangible media.

[0047] As used herein in the context of computer implementation, unless otherwise specified or limited, the terms "component," "system," "module," "framework," and the like are intended to encompass part or all of the computer-related systems that include hardware, software, a combination of hardware and software, or software in execution. For example, a component may be, but is not limited to being, a processor device, a process being executed (or executable) by a processor device, an object, an executable, a thread of execution, a computer program, or a computer. By way of illustration, both an application running on a computer and the computer can be a component. One or more components (or system, module, and so on) may reside within a process or thread of execution, may be localized on one computer, may be distributed between two or more computers or other processor devices, or may be included within another component (or system, module, and so on).

[0048] In some implementations, devices or systems disclosed herein can be utilized or installed using methods embodying aspects of the disclosure. Correspondingly, description herein of particular features, capabilities, or intended purposes of a device or system is

generally intended to inherently include disclosure of a method of using such features for the intended purposes, a method of implementing such capabilities, and a method of installing disclosed (or otherwise known) components to support these purposes or capabilities. Similarly, unless otherwise indicated or limited, discussion herein of any method of manufacturing or using a particular device or system, including installing the device or system, is intended to inherently include disclosure, as embodiments of the disclosure, of the utilized features and implemented capabilities of such device or system.

[0049] Referring to FIG. 4, a method for neuromodulation is described. In a non-limiting example, the method 400 implements the system described in FIG. 1. The method includes positioning an electrode on a subject at step 402. In a non-limiting example, the electrode is positioned such that it is electrically coupled to the auricular branch of the vagus nerve of the subject. At 404, a stimulation signal is delivered to the electrode thereby stimulating the auricular branch of the vagus nerve. The stimulation signal is delivered by a stimulation circuit connected to the electrode. At step 406, the method 400 includes acquiring, via an EEG sensor, an EEG signal of the subject. The controller receives the acquired EEG signal and one or more EEG characteristics are extracted from the EEG signal at step 408. At step 410 the controller sends a control signal to the stimulation circuit based on the extracted characteristic(s). In a non-limiting example, the method 400 operates as a feedback loop and returns to step 404 to control the stimulation circuit to deliver the stimulation signal based on the EEG characteristic at step 408. As will be understood by one skilled in the art, the method 400 may be initiated at any of the steps 402-410 and need not be in the exact order depicted in FIG. 4. For example, the first step may be acquiring the EEG signal via the EEG sensor at step 406.

[0050] Another non-limiting embodiment of a neuromodulation system is shown in FIG. 5. The device components include an EEG amplifier (Neuroelectrics), an EEG network having

10 to 64 channels, EEG software for data monitoring and quality assessment, a System for data streaming and evaluation of the feedback in real time (LSL), a Stimulator (Grass Instruments, Astro-Med), an ergonomically shaped electrode to be placed on the left ear, a laptop-controlled device (National Instruments DAQ) to generate analogue outputs, a high-frequency relay (G6Z-1P-DC5, Omron Electronics Components), an AD Instruments setup for physio data acquisition and monitoring ECG, GSR, and respiration. The brain gating is implemented by measuring electrical signals from the subjects' scalp using a wireless EEG system including an amplifier and nets with 2 to 128 electrodes. An integrated software displays in real time the acquired signals and their main spectral properties enabling monitoring and quality assessment. Inhouse developed MATLAB (MATLAB R2020b) code is used to estimate EEG-based features such us Power Spectral Density (PSD) and phase synchronization--based Phase Locking Value (PLV) in δ, θ, and α frequency bands. The same code detects in real-time *Up* and *Down* states, based on an adaptive threshold detection algorithm, and a laptop-controlled device (National Instruments USB DAQCard 6009, 14-bit i/o) is used to generate a 5 Volt analogue output, to be sent to a miniature high-frequency relay (G6Z-1P-DC5, Omron Electronics Components, Schaumburg, IL, USA), thereby controlling the onset and offset of stimulation.

[0051] In the following examples, the results of a study investigating EAVANS for real-time stimulation imparted during a specific delta phase are presented.

Example 1

[0052] *Clinical Relevance*— Given the serious health consequences and costs associated with delirium, and the absence of effective non-pharmacological treatments, the disclosed neuromodulatory system and method are a promising option for reducing delirium and other disorders of consciousness. The EAVANS system has been tested on healthy volunteers during a NREM sleep state, acknowledging the rationale that reduced arousal marked by

delta (0.5 to 4 Hz) waves in the EEG are a shared feature of sleep as well as impaired neurocognitive states such as delirium. This novel non-pharmacological and non-invasive closed-loop neuromodulatory device could be used peri-operatively and in inpatient hospital settings to treat patients at risk of developing delirium. For instance, in a pre-operative setting, this technology may provide an effective preventative "pre-habilitation" approach for patients at high risk of developing delirium. Post-operatively, the technology may help rescue patients from delirium.

[0053] *Materials and Methods*

[0054] A. Subjects

[0055] Seven healthy volunteers (3 female, age: 35.8 ± 14 years, mean ± SD) were enrolled. All study procedures were approved by the local Institutional Review Board, and written informed consent was provided by all subjects. Prior to the sleeping phase, participants were familiarized with the stimulation and a calibration procedure was performed. Specifically, the sensory threshold for both left and right ears was determined using the method of limits, a procedure based on gradually increasing and decreasing the magnitude of the stimulus in discrete steps. The current amplitude (mA) corresponding to the participants' sensory threshold was employed for all active stimulation blocks.

[0056] B. EEG-gated neurostimulation

[0057] EAVANS is a closed-loop neuromodulatory device-based approach (FIG. 1) which targets a particular phase of the EEG-acquired delta wave (0.5 to 4 Hz). The EEG gating was implemented by measuring electrical signals from subjects' scalp using a wireless EEG system (Neuroelectrics Instrument Controller, NIC, Enobio 8). An 8-channel montage was selected containing 7 frontal electrodes (Fpz, Fp1, Fp2, AF3, AF4, F7, F8) and Cz to facilitate Laplacian referencing of the signal recorded by the Fpz electrode. An integrated software displayed in real-time the acquired signals and their main spectral properties

enabling monitoring and online quality assessment. Raw EEG signals were received from LabStreamingLayer (LSL). An in-house developed MATLAB code was used for online preprocessing (band-pass filtering between 0.5 and 40 Hz, and down-sampling from 500 to 250 Hz) as well as to compute instantaneous phase and power.

[0058] Specifically, state space models were used to estimate the instantaneous phase. Given a single-channel neural signal recording **y**, represented as a univariate time-series, it may be determined which neural oscillations are present in the data and characterize the phases and amplitudes of these oscillations. For this purpose, it would be achieved in real-time, i.e., causally, as opposed to the existing data analysis technique that applies non-causal band-pass filtering and Hilbert transform. These tasks are accomplished based on a novel parametric representation of stochastic oscillators (Matsuda & Komaki, 2017):

$$\begin{bmatrix} x_{t,1} \\ x_{t,2} \end{bmatrix} = a \begin{bmatrix} \cos\frac{2\pi f}{f_s} & -\sin\frac{2\pi f}{f_s} \\ \sin\frac{2\pi f}{f_s} & \cos\frac{2\pi f}{f_s} \end{bmatrix} \begin{bmatrix} x_{t-1,1} \\ x_{t-1,2} \end{bmatrix} + \begin{bmatrix} v_{t,1} \\ v_{t,2} \end{bmatrix}, \quad \begin{bmatrix} v_{t,1} \\ v_{t,2} \end{bmatrix} \sim \mathcal{N}\left(\mathbf{0}, \begin{bmatrix} \sigma^2 & 0 \\ 0 & \sigma^2 \end{bmatrix}\right), \quad \text{Eq. 1a}$$

$$y_t = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} x_{t,1} \\ x_{t,2} \end{bmatrix} + \epsilon_t, \quad \epsilon_t \sim \mathcal{N}(0, \tau^2) \quad \text{Eq. 1b}$$

where three positive parameters f, a, σ^2 fully characterizes the oscillation through specifying the center frequency, damping factor, and the process noise variance that is driving the oscillation. Briefly, the current state of oscillator, $x_t = \left[x_{t,1}, x_{t,2}\right]^T$ is determined by rotating x_{t-1} counterclockwise through an angle of $2\pi f/f_s$ ($f < f_s$, f_s: sampling frequency) about the origin, scaling by a (< 1), and lastly adding system noise, ϵ_t. At every time point, a noisy observation of the first coordinate is made. In other words, x_t can be seen as a generalization of phasor (with $x_{t,1}$ and $x_{t,2}$ are the real and imaginary components respectively) rotating in time, while a noisy version of its projection on the real line is

observed (FIG. 6). Clearly, this a Gaussian linear state space representation of stochastic oscillators, developed based on Wiener's random frequency modulation. Naturally, the instantaneous phase of the oscillator is defined as:

$$\phi_t = arctan(x_{t,2}/x_{t,1}) \quad \text{Eq 2.}$$

The model can be easily generalized for multiple oscillation components by treating oscillation components independently and the observation time series as a noisy superposition of the first coordinates of all the oscillators.

[0059] The oscillator parameters (f, a, σ^2) and the observation noise variance τ^2 are learned using an instance of Expectation Maximization (EM) algorithm. EM alternates between optimizing the distribution over the hidden oscillator states given the current parameters (the E-step) and updating the parameters given the distribution of hidden states (the M-step). The E-step can be implemented efficiently using an instance of Kalman filter (KF) and fixed-interval smoothing (FIS). KF provides the one-step-ahead prediction for the oscillation states, and time-series, thus is causal. On the contrary, FIS is non-causal since it estimates the oscillation state, given the above mentioned one-step-ahead state prediction, and future observations within the given interval. The M-step utilizes the results of FIS, to update the oscillator state-space model parameters by maximizing the Q-function, defined as the expectation of complete log-likelihood with respect to the FIS output. The updates are stopped when the value of the likelihood of the observation stabilize. In summary, the iterative algorithm identifies a set of oscillations that explicitly characterizes the underlying neural oscillations with stationary parameters that are present in EEG data, in an unsupervised manner. These parameters could be learned from scout or baseline data from a patient prior to stimulation, or could be learned from a representative data set and applied to patients in general.

[0060] Now that the oscillations that are present in a given time-series can be identified, and their stationary properties characterized, the next step would be to decompose the EEG data into the constituent oscillation time-series. It turns out that can be accomplished by the abovementioned E-step. In fact, the result of the FIS run with the identified model parameters is the best linear unbiased estimate of the oscillation states, and the real indices of the oscillation states are the constituent oscillation time series that are present in the EEG data. The instantaneous phase estimate can then be defined for the oscillations as Eq. 2, with the quantities replaced by the FIS estimates. However, running FIS requires time series recorded within an interval (i.e., in batches), so it is not useful in real-time applications.

[0061] A fixed lag smoother (FLS) with lag 1 is used to identify the phase of the slow oscillation in real-time. This involves first running the Kalman filter update for the oscillation state, to obtain the best linear unbiased estimate of the oscillation states at present, given the past observations. Then the present observation is utilized to compute the one step ahead prediction error and update the estimate of the oscillation states to incorporate the information from the most recent time-point observed. It is noted that this smoothing horizon can be extended beyond lag 1 to any arbitrary horizon. Then these FLS output in Eq. 2 are used to estimate phase in real time.

[0062] In a similar fashion, the Kalman filter outputs could also be used, i.e., one step ahead forecast as the oscillation state estimate to estimate phase in a causal manner. Again, this can be generalized to multiple-step-ahead state forecast. However, this should be used with caution since the estimation performance degrades exponentially with the forecasting lead.

[0063] In the real-world stimulation hardware, (1) the EEG recording is acquired in batches and sent to the computing node in packets of several milliseconds of recording. (2) The computing node then runs the Kalman filtering, followed by either, FIS within the entire batch or, FLS with the lag l. FIS is the most computationally demanding, i.e., requires more

clock cycles, while FLS with the lag l=1 is least computationally demanding, i.e., requires least number of clock cycles.

[0064] Further, the controller then can decide the status of the relay, i.e., if the relay will be ON or OFF, and sends that signal via COM port.

[0065] These three steps incur respective delays, so that the relay box state conforms to the controller signal Δ milliseconds after the last time-point of EEG recording. Note that, the EEG device is sampling the voltage measurements without any pause, so the EEG sampling/ data acquisition does not contribute to the delay. For example, in the current hardware implementation, the following delays are incurred: Wifi communication delay (~ 3 ms), computation delay (~ 5 ms), and Com port delay for relay box (~ 1 ms) so that $\Delta \sim 9$. To make the stimulation system synchronized to a given range of slow phase, this anticipated delay in signaling is taken into account in the computation node. To do so, the 'smoothed' slow/delta phase in the last k (=11, for example) samples of the current data packet is estimated, and further averaged to find a robust estimate of the slow/delta phase at the $\lfloor k/2 \rfloor^{\text{th}}$ sample from the end of the current data packet. This estimated phase is then extrapolated by the anticipated processing delay, i.e., by

$$\left({}^{\lfloor k/2 \rfloor}/_{f_s} \times 10^3 + \Delta \right) \text{ ms} \qquad \text{Eq. 3}$$

to make the decision-making close to real-time. For the above example, the phase will be extrapolated by 19 ms, considering typical sampling rate of 500 samples/s.

[0066] With a slow/delta wave with center frequency 1.2Hz, this will translate to adding $\frac{2 \times 19 \times 12}{1000}\pi \sim 0.05\pi$ rad to the abovementioned robust estimate of phase. Here the following observations are made: For slow/delta oscillation the interpolation/correction term is small. However, as the frequency of the oscillation of interest increases, or as the delay increases, the interpolation/correction term becomes large, and may result in incorrect synchronization if the delay is not accounted for appropriately.

[0067] The delta phase for each streamed "chunk" of data (1s), and delivered the stimulation when it was rising in the interval between -π/2 and 0 radians (Up state), for the active condition. A MATLAB-controlled device (National Instruments USB DAQCard 6009, 14-bit i/o) was used to generate a 5 Volt analog output, to be sent to a miniature high-frequency relay (G6Z-1P-DC5, Omron Electronics Components, Schaumburg, IL, USA), thereby controlling the onset and offset of stimulation. EAVANS taVNS stimuli consisted of monophasic rectangular pulse burst trains at 100Hz and with 300μs pulse width, provided by a constant-current electrostimulation unit (UROstim, schwa-medico GmbH, Ehringshausen, Germany). Stimuli to the auricle were delivered using custom built, ergonomic electrodes (Bionik Medical Devices, Bucaramanga, Colombia) placed within the cymba conchae of the left ear. The stimulus frequency of 100 Hz was chosen based on previous work.

[0068] C. Experimental Protocol

[0069] After EEG montage setup and taVNS calibration, each subject underwent a single sleep session. The sleep duration varied from 70 to 180 minutes across subjects. Participant were instructed to press/move a button at peak inhalation of every breath in order to track the onset of sleep and awakening. The sleep session consisted of a passive control run (i.e., electrode placed within cymba conchae, but no electrical current passed, *No-Stim*) and four 5-minute EEG-gated stimulation runs including two active stimulation runs, and two active control runs. Specifically, during the active stimulation runs (EAVANS), taVNS stimulation was delivered to the auricular territory innervated by the auricular branch of the vagus nerve on the left ear during either the rising (*Up*) or the descending (*Down*) phase of the delta wave. During active control stimulation runs (GANctrl) the EEG-gated stimulation was delivered to the territory innervated by the greater auricular nerve (GAN) on the right earlobe, also targeting either the rising or descending delta phase. The order of the passive control and the 4 active stimulation runs was counterbalanced across subjects.

[0070] D. EEG Data Analysis

[0071] Preprocessing. EEG scalp data were band-pass filtered between 0.5 and 45 Hz and re-referenced (average). Independent Component Analysis (ICA) was employed to remove artifacts associated with the presence of the stimulation. For each run, time series were segmented in 2-second epochs (number of trials per condition: 61.0 ± 14, mean ± SD). Residual artifacts were removed using a semi-automatic procedure based on a threshold criterion (±80 μV).

[0072] delta power estimate. Power spectra were extracted from each 2-second epoch and averaged together using the multi-taper method with 3 Slepian tapers. For each run, spectral power was averaged across frequencies in the delta band (0.5 – 4 Hz) for comparison across stimulation conditions and subjects.

[0073] Statistical analysis. Given the small sample available, the following statistical tests were employed: i) Friedman test (α=0.05) as a non-parametric alternative to the one-way ANOVA with repeated measures to test the hypothesis of decreased delta power during EAVANS compared to GANctrl and *Non-Stim* conditions; ii) non-parametric statistical tests for pairwise comparisons of delta Power between conditions EAVANS/GANctrl (factor "SITE") and *Up/Down* phase (factor "PHASE") (Wilcoxon signed rank test, α=0.05). A 2-way ANOVA was also performed after testing for normality of the involved distributions (Shapiro-Wilk). After initial comparisons at the single-channel level, reported using 2-D scalp maps, statistical analysis was performed on delta power averaged across all 8 recording channels.

[0074] *Results*

[0075] All subjects tolerated the stimulation and completed the experimental sessions without awakening during stimulation and without reporting any adverse events after waking up.

[0076] Slow waves modulation during sleep. Delta power during EAVANS runs was found to be lower compared to GANctrl stimulation or NREM baseline (No-Stim) for all the acquired time series (FIG. 7A). The result of the Friedman's ANOVA test demonstrated a significant effect of the presence and type of stimulation on frontal-central delta waves averaged across all the recording electrodes (χ_2=10.33, p=0.006). In particular, FIG. 7B showed decreased delta power during EAVANS runs compared to GANctrl (p=0.005) and No-Stim (p=0.1).

[0077] A 2-Way repeated measures ANOVA revealed a significant effect of *SITE x PHASE* interaction for average frontal delta Power (F(1,5)=6.02, p=0.045). **Table 1** reports the results of the relevant pairwise comparison between the two levels of factor *SITE*, EAVAN/GANctrl, and the two levels of factor *PHASE*, *Up/Down*. It was found that EAVANS delta power is reduced compared to GANctrl, while EAVANS Up delta power is reduced compared to EAVANS Down (p=0.03, FIG. 7C). No significant differences in delta power were found between GANctrl Up and GANctrl Down.

Table 1

Level-1	Level-2	W-value	p
EAVANS Down	GANctrl Down	13	0.688
	EAVANS Up	21	**0.031**
EAVANS Up	GANctrl Up	3	0.156
GANctrl Down	GANctrl Up	7	0.563

*Wilcoxon signed-rank test

[0078] *Discussion*

[0079] While delirium is the most common neuropsychiatric disorder observed in hospitalized patients, with an incidence of approximately 25% in older surgical patients, there

is a lack of effective treatment approaches that target the underlying neurophysiological mechanisms of this condition. Moreover, detection of delirium is typically based on measurements of patient arousal and cognitive state rather than objective metrics reflecting the underlying neurophysiology that, potentially, better predict future clinical phenotype.

[0080] We have developed a taVNS neuromodulatory approach, EAVANS, which combines noninvasive vagal stimulation with specific phase-based targeting of the neural feature of interest previously linked to delirium – i.e., the EEG delta wave (0.5 to 4 Hz). Furthermore, prior research has found that stimulation of this auricular territory targets the nucleus of the solitary tract (NTS) in the brainstem, while NTS projections are known to regulate the noradrenergic arousal systems [14]. Taken together, closed-loop modulation of delta waves, and the known upstream NTS connections indicate that EAVANS stimulation is a promising for disrupting the neural alterations characterizing delirium.

[0081] Our results obtained from real-time delta wave assessment and phase-locked stimulation in healthy volunteers during NREM sleep investigated EAVANS ability to modulate the diffuse slow waves (EEG delta rhythm). Stimulation accurately targeted specific *Up* and *Down* states in the delta rhythm that are common to sleep and delirium states. Analyses found that EAVANS demonstrated a reduction of delta power with moderate to large effect sizes ($\eta^2 = 0.65$), and that these reductions were greater compared to control stimulation at auricular sites not innervated by the auricular branch of the vagus nerve (i.e. the earlobe, innervated by the GAN).

[0082] The impact of the proposed device and method as a clinical intervention for treatment and prevention of delirium is promising as the results indicate that stimulation during the delta Up phase reduced delta power, which supports neural mechanisms shared across disorders of consciousness, narcolepsy, and neuroinflammatory disorders. EAVANS has the additional advantage of being relatively low cost, non-invasive, and highly portable, as

feasibility was demonstrated with a low density (8 channel) EEG array that can be safely administered in a variety of clinical settings. In summary, this technology has the potential to become widely adopted in both pre- and post-operative settings to address the current dearth of effective delirium treatments.

[0083] *Conclusion*

[0084] EEG-gated auricular vagal afferent nerve stimulation (EAVANS) is a closed-loop device able to target the neural mechanisms underlying the presence of increased delta waves during sleep, which extend to pathological disorders such as delirium. The present study demonstrated the ability of EAVANS to reduce delta power in healthy controls during NREM sleep, recognizing that reduced arousal marked by delta (0.5 to 4 Hz) waves in the EEG are a shared feature of sleep as well as impaired neurocognitive states such as delirium. The results indicate recruitment of neurophysiological pathways clinically relevant for altered states of consciousness such as delirium.

Example 2

[0085] *Materials and Methods*

[0086] A. Experimental Design

[0087] In this pilot study, clinical, behavioral, and physiological data were acquired from three surgical patients undergoing general anesthesia. A clinical assessment of delirium was performed using the 3D-CAM scale (3-minute Diagnostic Interview for Confusion Assessment Method), while reaction time and responsiveness to external stimuli were evaluated by performing an auditory Psychomotor Vigilance Task (aPVT) to assess the level of arousal. Before surgery, a 32-channel EEG cap was placed on the patient's head and acquired baseline data in which the patient was asked to rest quietly, with eyes open. Then, the auricular electrode was placed in the patient's left cymba conchae and a sensory threshold for electrical stimulation was identified using the method of limits. The current amplitude

(mA) corresponding to the participants' sensory threshold was employed for the post-surgery EEG-gated auricular vagal afferent nerve stimulation (EAVANS). After surgery, as soon as the patient returned to the Post Anesthesia Care Unit (PACU), EEG data were recorded during three consecutive runs: resting state, aPVT without EAVANS stimulation, and aPVT with EAVANS stimulation. The level of delirium was assessed before and after anesthesia as well as pre- and post-EAVANS stimulation. All study procedures were approved by the local Institutional Review Board, and written informed consent was provided and signed by all subjects.

[0088] B. EEG-gated neurostimulation

[0089] EAVANS is a closed-loop neuromodulatory device-based approach that targets a particular phase of the EEG-acquired Delta wave. The EEG gating was implemented by measuring electrical signals from the subjects' scalp using a wireless EEG system (Neuroelectrics Instrument Controller, NIC, Enobio 8). An 8-channel montage was selected containing 7 frontal electrodes (Fpz, Fp1, Fp2, AF3, AF4, F7, F8) and FCz to facilitate Laplacian referencing of the signal recorded by the Fpz electrode. An integrated software displayed in real-time the acquired signals and their main spectral properties enabling monitoring and online quality assessment. Raw EEG signals were received from LabStreamingLayer (LSL) to enable real-time or online EEG processing. An in-house developed MATLAB code was used for online preprocessing (band-pass filtering between 0.5 and 40 Hz, and down-sampling from 500 to 250 Hz) as well as to compute instantaneous phase and power. Specifically, state space models were used to estimate the instantaneous delta phase for each streamed segment of data (1s) and delivered the stimulation when the phase was rising in the interval between $-\pi/2$ and 0 radians, corresponding to an "Up" or "On" state in the brain. A MATLAB-controlled device (National Instruments USB DAQCard 6009, 14-bit i/o) was used to generate a 5 Volt analog output, to be sent to a miniature high-

frequency relay (G6Z-1P-DC5, Omron Electronics Components, Schaumburg, IL, USA), thereby controlling the onset and offset of stimulation. EAVANS stimuli consisted of monophasic rectangular pulse burst trains at 100Hz and with 300μs pulse width, provided by a constant-current electrostimulation unit (UROstim, schwa-medico GmbH, Ehringshausen, Germany). Stimuli to the auricle were delivered for 5 minutes using custom-built, ergonomic electrodes (Bionik Medical Devices, Bucaramanga, Colombia) placed within the cymba conchae of the left ear. A 100Hz stimulus frequency was chosen based on prior research suggesting optimal brainstem targeting.

[0090] C. Clinical Scale: 3D CAM

[0091] The 3D-CAM (for the Intensive Care Unit) is a validated scale to evaluate the presence and severity of delirium, characterizing patients' cognitive states following anesthesia and surgery. The 3D-CAM is a brief verbal assessment tool that can be completed in an average of 3 minutes. The scoring system for delirium severity based on the CAM (the CAM-S) has been proven to have predictive validity for important clinical outcomes. In particular, delirium is scored as present/absent based on the presence of 1) acute or fluctuating course, 2) inattention, and either 3) disorganized thinking or 4) altered level of consciousness. The CAM-S was created based on the severity rating of these 4 CAM diagnostic features. Acute change or fluctuating course was scored 0 points if absent or 1 if present. The remaining three CAM diagnostic features were scored as 0 points for no symptoms, 1 point for mild symptoms, and 2 points for severe symptoms. The CAM-S score represents a sum of points assigned for the four features and ranges between 0 and 7 (most severe). 3D-CAM assessment was performed before and after surgery, pre- and post-stimulation.

[0092] D. Behavioral Task: aPVT

[0093] The auditory Psychomotor Vigilance Task (aPVT) was employed to evaluate patients' vigilance, sustained attention, and reaction times. The aPVT required patients to respond by clicking a mouse to a sound played over a set of headphones at random intervals. This task was a complementary tool to the 3D-CAM scale, allowing for a comprehensive evaluation of the patient's level of arousal and cognitive and behavioral responses during the post-anesthesia awakening phase. The patient's performance was assessed in terms of correct answer rate (%) and reaction time, pre- and post-anesthesia, with and without EAVANS stimulation.

[0094] *Results*

[0095] A. Patient MGH-1

[0096] Location: Mass General Hospital (MGH)

[0097] Visit description: Patient MGH-1, a 60-year-old male undergoing laparoscopic low anterior colon resection and splenic flexure takedown, demonstrated improvement in cognitive function following the application of EAVANS during the post-anesthesia awakening phase. Before undergoing anesthesia and while fully conscious, the patient spontaneously expressed a history of multiple surgeries and having "a horrible time waking up from anesthesia". Consequently, the patient stated to be "open to anything that could help recover from anesthesia faster" and was excited to try EAVANS. After surgery, the patient arrived at the post-operative area in a confused state. The patient was more responsive after EAVANS stimulation started. The use of EAVANS did not impact the work of the clinical team, which was open to its use given the small size of the stimulator which did not get in the way of clinical care. No adverse events or discomfort were reported by the patient.

[0098] Clinical scale (3D-CAM): Prior to EAVANS stimulation, the patient exhibited signs of disorientation and confusion, as evidenced by a score of 4 on the 3D-CAM scale,

indicative of delirium. Following a 5-minute stimulation there was a reduction in the level of distraction, with a total score equal to 3 (see Table 2 and FIG. 8).

Table 2. Partial and total scores from 3D-CAM clinical scale measuring delirium. F1 to F4 refer to the four investigated features: acute change, inattention, disorganized thinking, and altered state of consciousness. Total score ranges between 0 and 7.

		3D-CAM scoring system				
		F1	F2	F3	F4	Total Score
MGH-1	Preop	0	0	0	0	**0**
	Postop Pre-EVANS	1	2	0	1	**4**
	Postop Post-EAVANS	1	1	0	1	**3**
SHC-1	Preop	0	0	0	0	**0**
	Postop Pre-EVANS	1	1	0	0	**2**
	Postop Post-EAVANS	1	0	0	0	**1**
SHC-2	Preop	0	1	0	0	**1**
	Postop Pre-EVANS	1	1	2	0	**4**
	Postop Post-EAVANS	0	0	1	0	**1**

[0099] Behavioral outcome (aPVT): Patient MGH-1 performance showed an increased percentage of correct answers and no significant difference in reaction times during aPVT with EAVANS stimulation compared to aPVT without EAVANS intervention (see Table 3 and FIG. 9).

[0100] B. Patient SHC-1

[0101] Location: Stanford Hospital

[0102] Visit description: Patient SHC-1, a 46-year-old male with tenosynovial giant cell tumor undergoing surgery for the excision of a left posterior knee mass, arrived at the post-operative area in a confused state. Having recently received opioid and dissociative medications (fentanyl and ketamine) as part of his anesthetic, he was disoriented to his circumstances. He underwent the EAVANS stimulation, EEG recording, and aPVT testing protocol. One hour after arrival in the post-operative area, after complete emergence from anesthesia and completion of the study protocol, he was alert and conversational, did not recall his post-operative study-related testing, and thanked the study team for a pleasant experience in which he was glad to participate. He reported no adverse events.

Table 3. Percentage of correct answers (CA), reaction time mean (RT mean) and standard deviation (RT std) related to the execution of the aPVT (auditory Psychomotor Vigilance Task) before and after anesthesia, pre- and post-stimulation.

		aPVT		
		CA (%)	RT mean (s)	RT std (s)
MGH-1	Preop	0.89	1358.4	458.72
	Postop Pre-EVANS	0.17	991.8	481.20
	Postop Post-EAVANS	0.36	1053.0	327.13
SHC-1	Preop	0.23	771.6	483.68
	Postop Pre-EVANS	0.43	858.6	454.82
	Postop Post-EAVANS	0.67	941.3	430.97
SHC-2	Preop	1.00	410.3	262.13
	Postop Pre-EVANS	0.88	596.8	246.32
	Postop Post-EAVANS	0.87	583.4	172.65

[0103] Clinical scale: Prior to EAVANS stimulation, the patient exhibited signs of disorientation and confusion, as well as a mild level of inattention with a total score of 2 on the 3D-CAM scale (see Table 2). Following a 5-minute stimulation there was a reduction in the level of distraction, with a total score equal to 1 (see FIG. 8).

[0104] Behavioral outcome (aPVT): Patient SHC-1 performance showed an increased percentage of correct answers and no significant difference in reaction times during aPVT with EAVANS stimulation compared to aPVT without EAVANS intervention (see Table 3 and FIG. 9).

[0105] C. Patient SHC-2

[0106] Location: Stanford Hospital

[0107] Visit description: Patient SHC-2, a 69-year-old male with clinically localized prostate cancer who underwent a robotic-assisted laparoscopic radical prostatectomy with bilateral pelvic lymph node dissection, arrived in the post-operative area after a minor medical complication delayed his exit from the operating room. Upon arrival to the post-operative area, he repeatedly stated that he wished "*to go back to sleep.*" He tolerated the study procedures without issue. By the end of the testing period, he remained sleepy but increasingly oriented in response to questions. He reported no adverse events.

[0108] Clinical scale: Prior to EAVANS stimulation, the patient exhibited signs of disorientation and confusion, as well as a mild level of inattention and a severe level of disorganized thinking (see Table 2). The 3D-CAM total score for Patient SHC-2 went from 4 (presence of delirium) before stimulation to a score of 1 (no delirium) after a 5-minute EAVANS session (see FIG. 8).

[0109] Behavioral outcome (aPVT): Patient SHC-1 performance did not show differences in the percentage of correct answers and reaction times during aPVT with EAVANS stimulation compared to aPVT without EAVANS intervention (see Table 3 and FIG. 9).

[0110] *Conclusion*

[0111] The utilization of EAVANS in the Post-Anesthesia Care Unit (PACU) for patients awakening from anesthesia proved to be a promising intervention. The preliminary findings from the pilot study indicate that EAVANS is a well-tolerated intervention that holds the potential to mitigate postoperative cognitive impairment and promote arousal and vigilance in this patient population. All three patients reported decreased levels of delirium after EAVANS according to the 3D-CAM and CAM-S scores. All three patients showed improvements in the inattention component of the 3D-CAM assessment, suggesting that EAVANS could enhance attention and related cognitive processes and ameliorate or counteract impairments of attention that could occur in the hospital setting or otherwise. In addition, the patients MGH-1 and SHC-1 who showed post-operative impairment of arousal measured by the aPVT percentage of missed stimuli, doubled the percentage of correct answers when stimulated by EAVANS, suggesting that EAVANS can enhance arousal or ameliorate or counteract impairments in arousal that could occur in the hospital setting or otherwise. These findings support the notion that EAVANS stimulation can mitigate delirium, cognitive impairment, and confusion states, and does so by modulating or improving arousal and attention.

[0112] As used in this specification and the claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0113] As used herein, "about", "approximately," "substantially," and "significantly" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which they are used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" and "approximately" will mean up to plus or minus 10% of the particular term and "substantially" and "significantly" will mean more than plus or minus 10% of the particular term.

[0114] As used herein, the terms "include" and "including" have the same meaning as the terms "comprise" and "comprising." The terms "comprise" and "comprising" should be interpreted as being "open" transitional terms that permit the inclusion of additional components further to those components recited in the claims. The terms "consist" and "consisting of" should be interpreted as being "closed" transitional terms that do not permit the inclusion of additional components other than the components recited in the claims. The term "consisting essentially of" should be interpreted to be partially closed and allowing the inclusion only of additional components that do not fundamentally alter the nature of the claimed subject matter.

[0115] The phrase "such as" should be interpreted as "for example, including." Moreover, the use of any and all exemplary language, including but not limited to "such as", is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

[0116] Furthermore, in those instances where a convention analogous to "at least one of A, B and C, etc." is used, in general such a construction is intended in the sense of one having ordinary skill in the art would understand the convention (*e.g.*, "a system having at least one of A, B and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together.). It will be

further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description or figures, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

[0117] All language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can subsequently be broken down into ranges and subranges. A range includes each individual member. Thus, for example, a group having 1-3 members refers to groups having 1, 2, or 3 members. Similarly, a group having 6 members refers to groups having 1, 2, 3, 4, or 6 members, and so forth.

[0118] The modal verb "may" refers to the preferred use or selection of one or more options or choices among the several described embodiments or features contained within the same. Where no options or choices are disclosed regarding a particular embodiment or feature contained in the same, the modal verb "may" refers to an affirmative act regarding how to make or use an aspect of a described embodiment or feature contained in the same, or a definitive decision to use a specific skill regarding a described embodiment or feature contained in the same. In this latter context, the modal verb "may" has the same meaning and connotation as the auxiliary verb "can."

[0119] The present disclosure has described one or more preferred embodiments, and it should be appreciated that many equivalents, alternatives, variations, and modifications, aside from those expressly stated, are possible and within the scope of the invention.

Claims

1. A neuromodulation system for modulating delta power comprising:

an electrode configured to be electrically coupled to an auricular branch of a vagus nerve of a subject;

a stimulation circuit connected to the electrode to deliver a stimulation signal to the electrode to stimulate the auricular branch of the vagus nerve;

an electroencephalography (EEG) sensor configured to acquire an EEG signal of the subject;

a controller configured to receive the EEG signal from the EEG sensor, wherein the controller extracts one or more EEG characteristics of interest and sends control signals to the stimulation circuit to deliver the stimulation signal based on the one or more EEG characteristics to modulate arousal or reduce delirium severity.

2. The system of claim 1, wherein the one or more characteristics includes a phase of a delta wave embedded in the EEG signal.

3. The system of claim 2, wherein the controller is configured to estimate an instantaneous phase or power of the delta wave.

4. The system of claim 2, wherein the controller is configured to control the stimulation circuit to reduce delta power in the subject experiencing or at risk of delirium.

5. The system of claim 2, wherein the controller is configured to cause the stimulation circuit to deliver the stimulation signal during a rising phase of the delta wave.

6. The system of claim 2, wherein the controller is configured to cause the stimulation circuit to deliver the stimulation signal in the range of $-\pi/2$, 0 radians.

7. The system of claim 1, wherein the electrode is configured to engage within a cymba conchae of the ear of the subject.

8. The system of claim 1, wherein the stimulation signal comprises a monophasic rectangular pulse burst train.

9. The system of claim 1, wherein the stimulation signal has a frequency of 100 Hz and with a pulse width of 300 μs.

10. The system of claim 1, wherein the EEG sensor includes a plurality of sensor electrodes configured to be placed on the subject's scalp for acquiring the EEG signal.

11. The system of claim 1, further comprising:

an amplifier configured to amplify the EEG signal; and

a display configured to provide a real-time display of the acquired EEG signal and its spectral properties.

12. The system of claim 1, wherein the controller is configured to control delirium severity in the subject during at least one of pre-operative and post-operative conditions.

13. The system of claim 1, wherein the controller is configured to send control signals to the stimulation circuit to deliver the stimulation signal to cause a reduction of neuroinflammation coordinated via the activation of cholinergic anti-inflammatory pathways and efferent feedback connections to the vagal innervation of the spleen.

14. A method for modulating delta power comprising:

positioning on a subject an electrode configured to be electrically coupled to an auricular branch of a vagus nerve of the subject;

delivering, by a stimulation circuit connected to the electrode, a stimulation signal to the electrode, thereby stimulating the auricular branch of the vagus nerve;

acquiring, via an electroencephalography (EEG) sensor, an EEG signal of the subject;

receiving, via a controller, the EEG signal from the EEG sensor;

extracting, via the controller, one or more EEG characteristics of interest;

sending, via the controller, control signals to the stimulation circuit; and

delivering, via the stimulation circuit, a stimulation signal based on the one or more EEG characteristics, wherein the stimulation signal is delivered to modulate arousal or reduce delirium sensitivity.

15. The method of claim 14, wherein the one or more characteristic includes a phase of a delta wave embedded in the EEG signal.

16. The method of claim 15, wherein the controller is configured to estimate an instantaneous phase or power of the delta wave.

17. The method of claim 15, wherein the controller is configured to control the stimulation circuit to reduce delta power in the subject experiencing or at risk of delirium.

18. The method of claim 15, wherein the controller is configured to cause the stimulation circuit to deliver the stimulation signal during a rising phase of the delta wave.

19. The method of claim 15, wherein the controller is configured to cause the stimulation circuit to deliver the stimulation signal in the range of $-\pi/2$, 0 radians.

20. The method of claim 14, wherein the electrode is configured to engage within a cymba conchae of the ear of the subject.

21. The method of claim 14, wherein the stimulation signal comprises a monophasic rectangular pulse burst train.

22. The method of claim 14, wherein the stimulation signal has a frequency of 100 Hz and with a pulse width of 300 μs.

23. The method of claim 14, wherein the EEG sensor includes a plurality of sensor electrodes configured to be placed on the subject's scalp for acquiring the EEG signal.

24. The method of claim 14, further comprising:

amplifying, using an amplifier, the acquired EEG signal; and

displaying in real time, using a display, the acquired EEG signal and its spectral properties.

25. The method of claim 14, wherein the controller is configured to control delirium severity in the subject during at least one of pre-operative and post-operative conditions.

26. The method of claim 14, wherein the controller is configured to send control signals to the stimulation circuit to deliver the stimulation signal to cause a reduction of neuroinflammation coordinated via the activation of cholinergic anti-inflammatory pathways and efferent feedback conditions to the vagal innervation of the spleen.

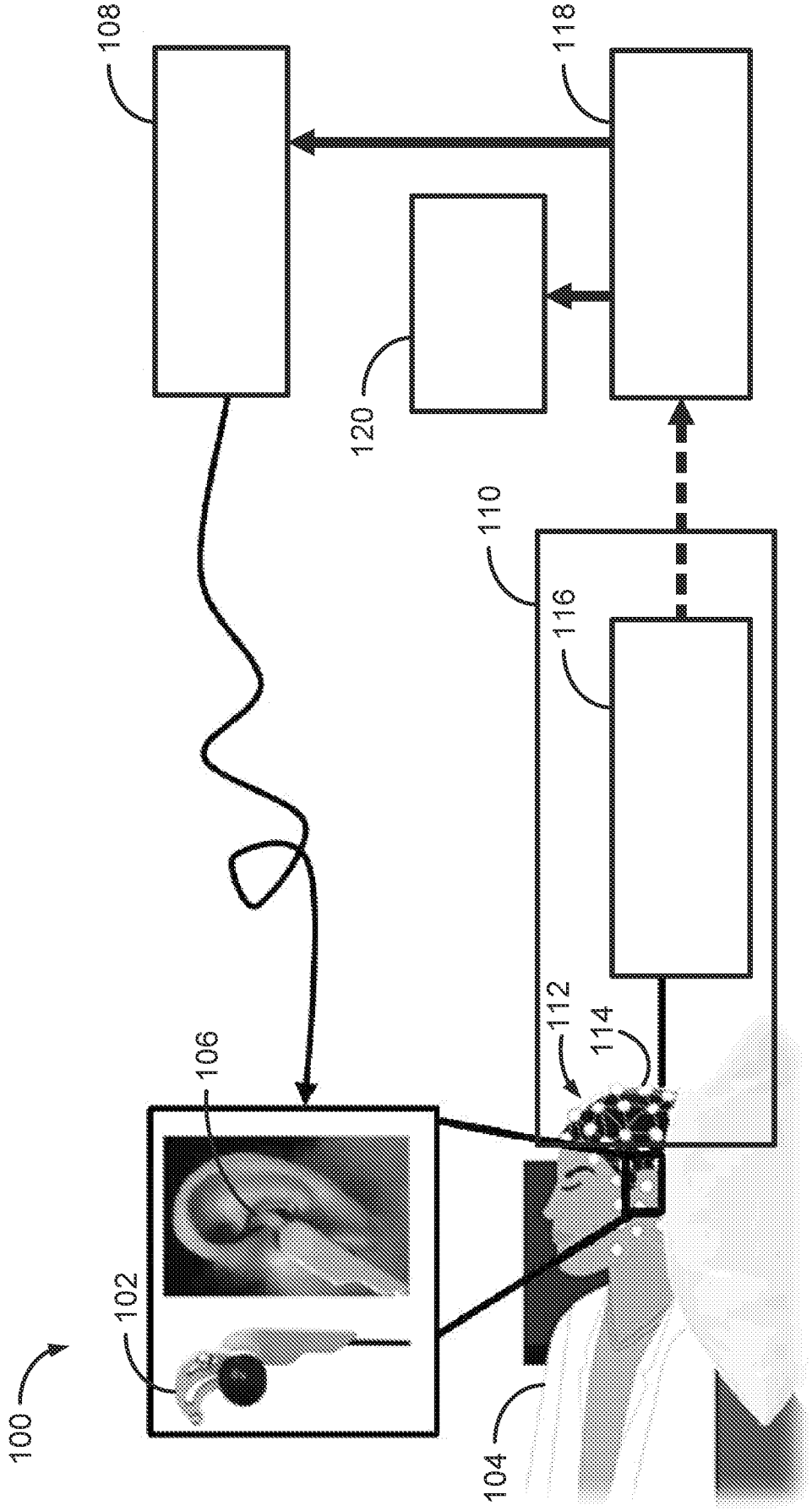


FIG. 1

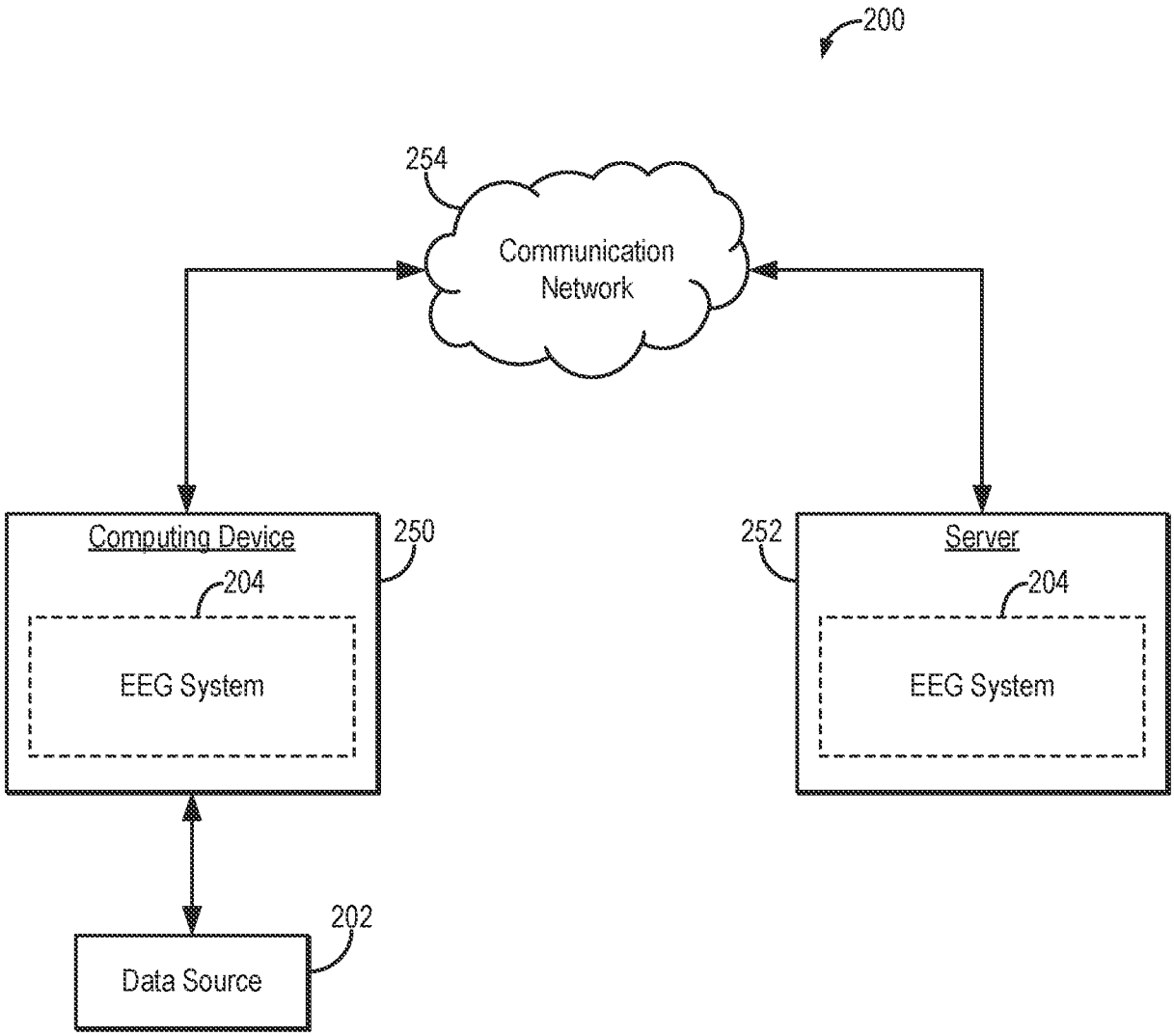

200
254
Communication Network
Computing Device
250
204
EEG System
252
Server
204
EEG System
202
Data Source

FIG. 2

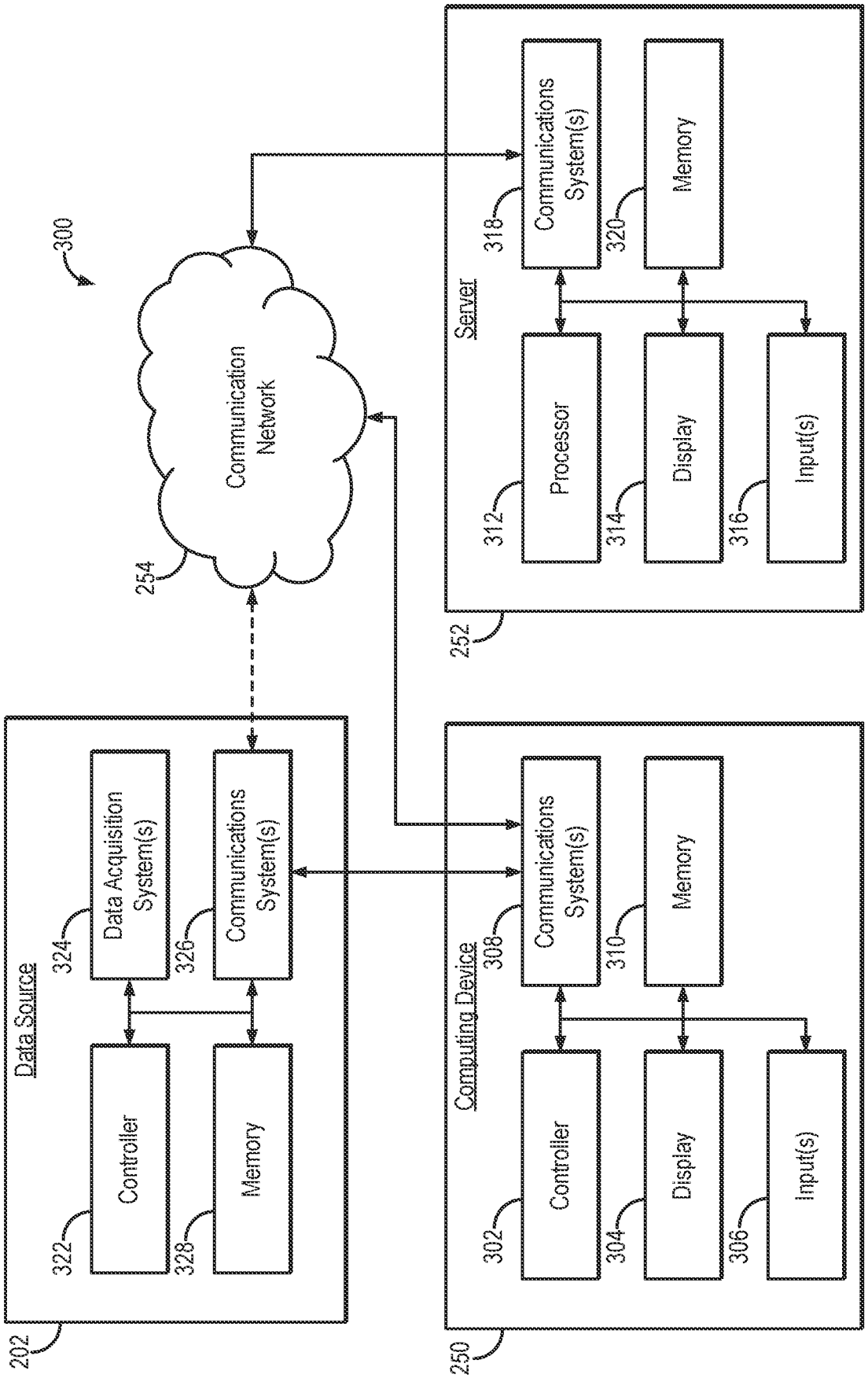

300
Communication Network
254
Server
252
Communications System(s)
318
Memory
320
Processor
312
Display
314
Input(s)
316
Data Source
202
Data Acquisition System(s)
324
Communications System(s)
326
Controller
322
Memory
328
Computing Device
250
Communications System(s)
308
Memory
310
Controller
302
Display
304
Input(s)
306

FIG. 3

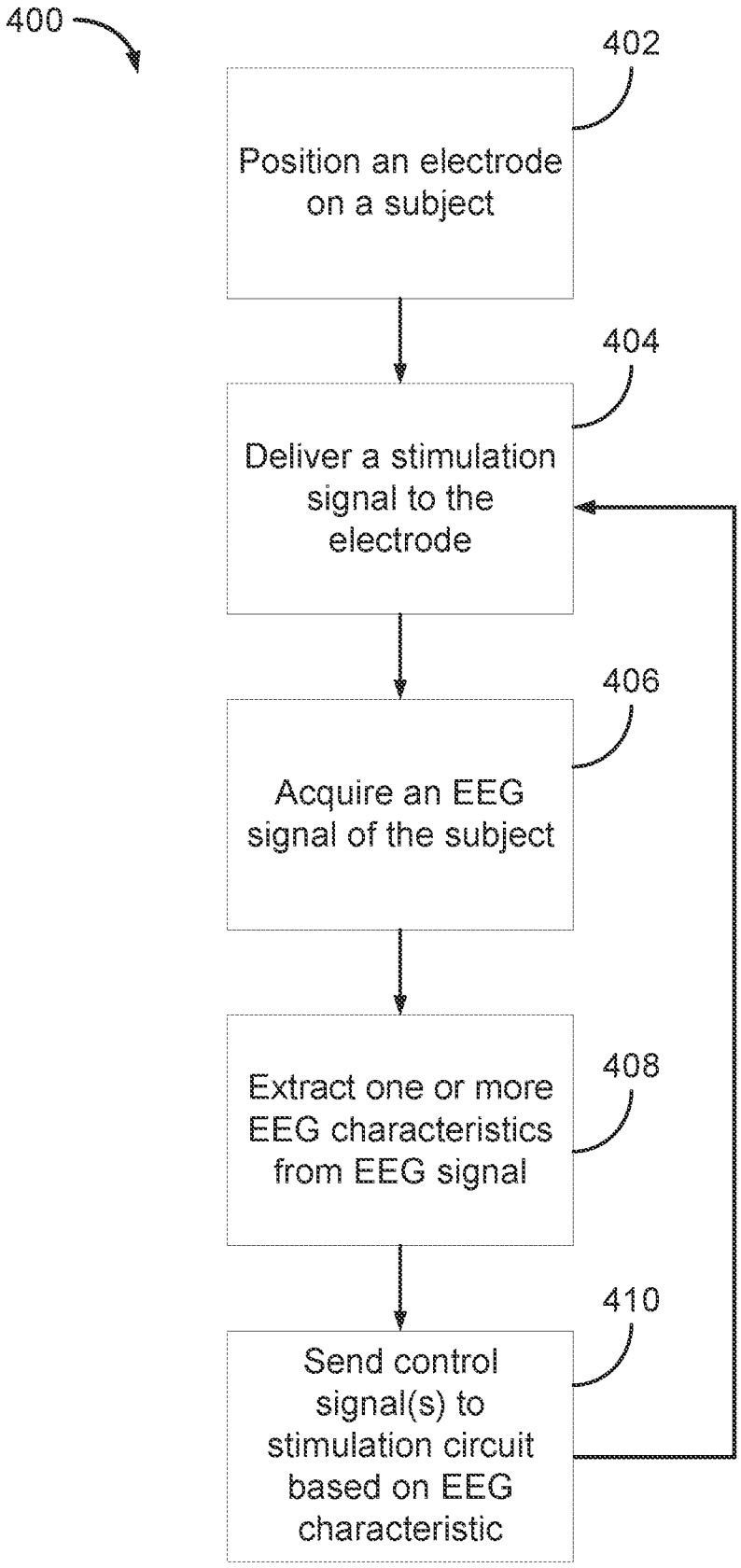

400
402
Position an electrode on a subject
404
Deliver a stimulation signal to the electrode
406
Acquire an EEG signal of the subject
408
Extract one or more EEG characteristics from EEG signal
410
Send control signal(s) to stimulation circuit based on EEG characteristic

FIG. 4

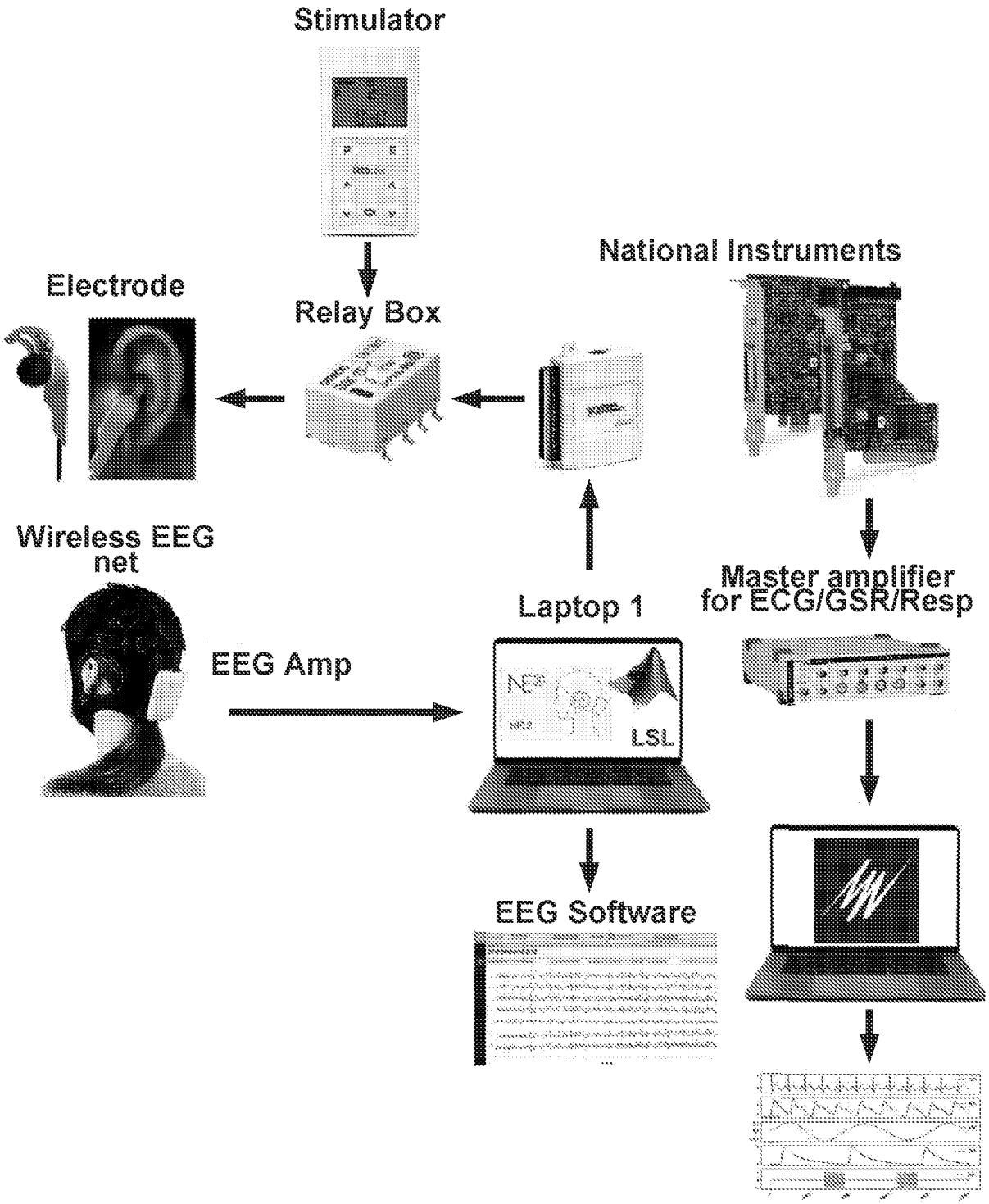

Stimulator
National Instruments
Electrode
Relay Box
Wireless EEG net
EEG Amp
Laptop 1
Master amplifier for ECG/GSR/Resp
LSL
EEG Software

FIG. 5

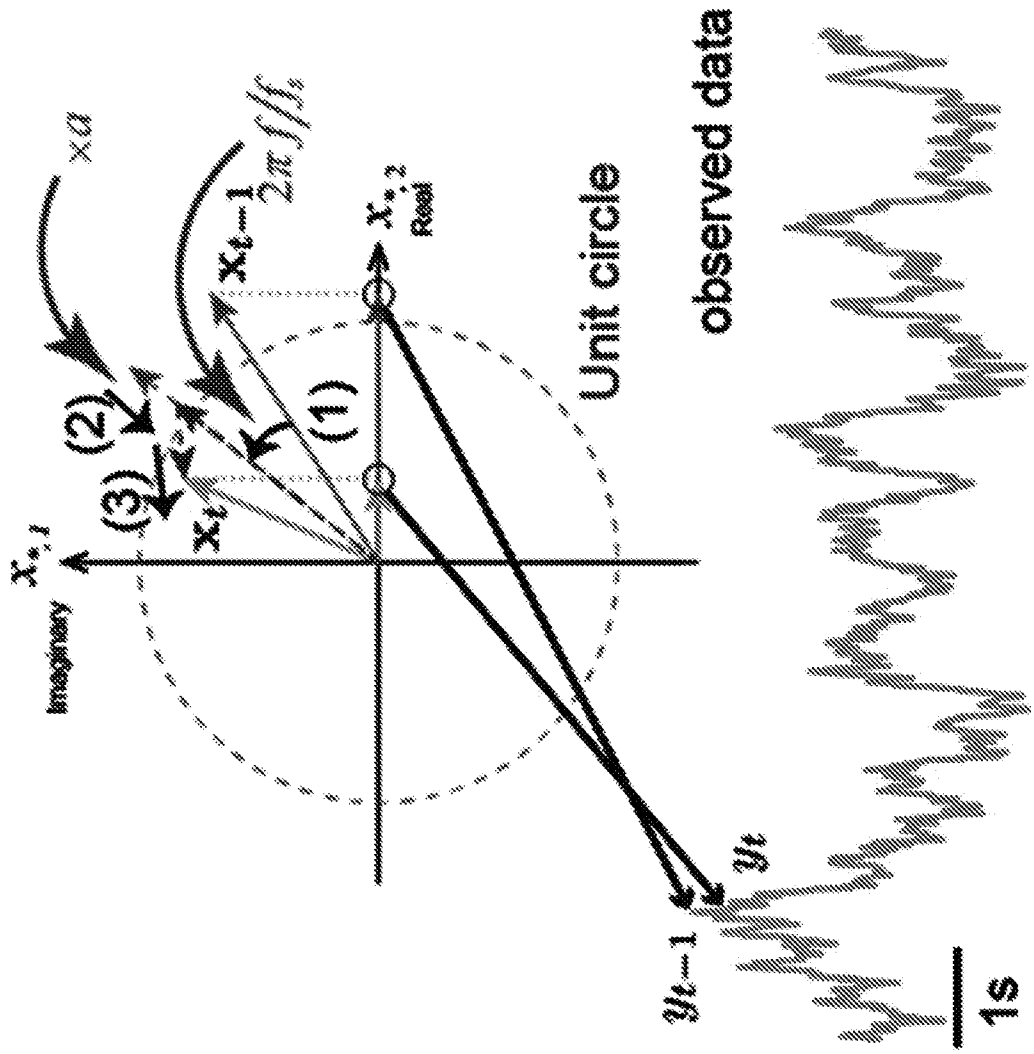


FIG. 6

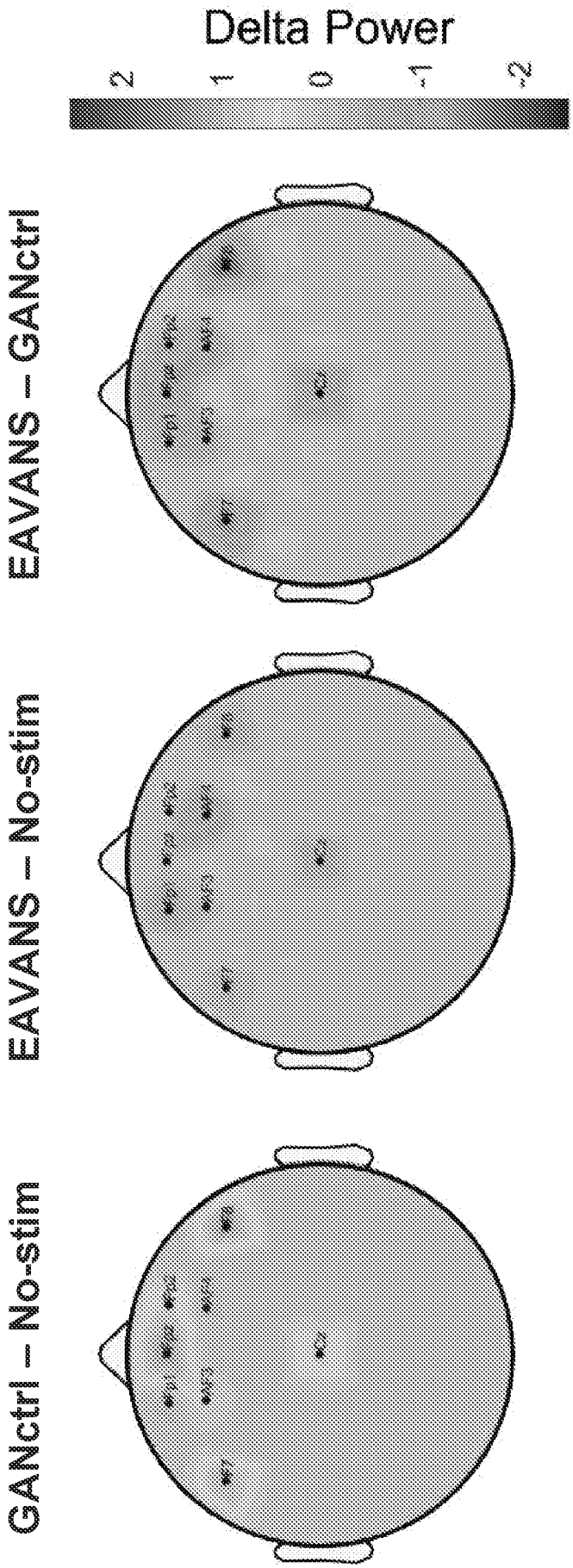

Delta Power
2
1
0
-1
-2
EAVANS – GANctrl
EAVANS – No-stim
GANctrl – No-stim

FIG. 7A

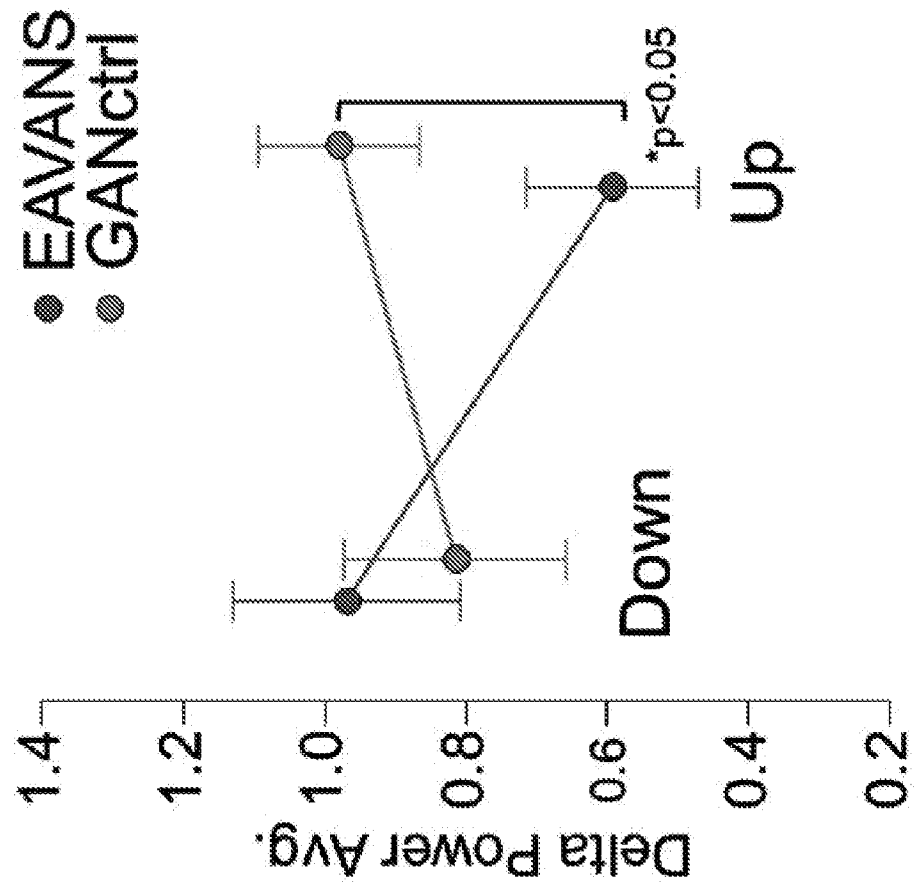

EAVANS
GANctrl
*p<0.05
Up
Down
Delta Power Avg.
1.4
1.2
1.0
0.8
0.6
0.4
0.2

FIG. 7C

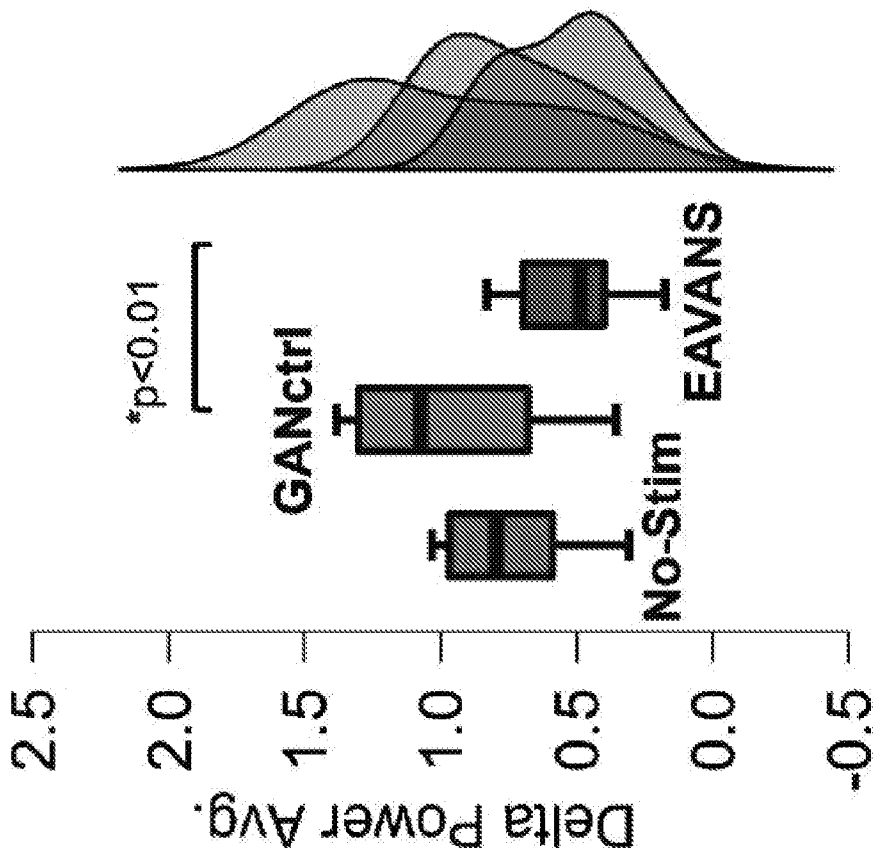

*p<0.01
GANctrl
EAVANS
No-Stim
Delta Power Avg.
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

FIG. 7B

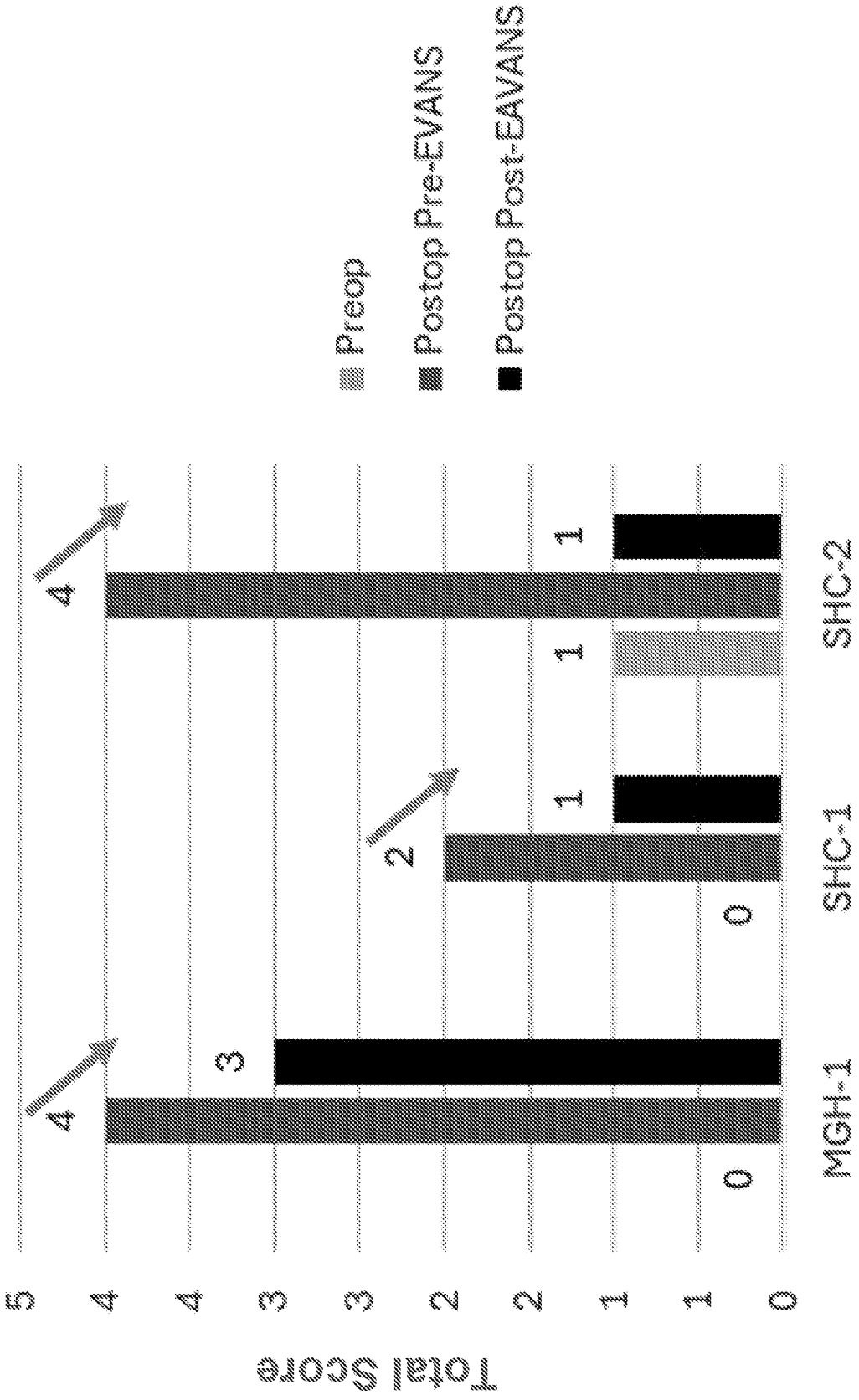

Preop
Postop Pre-EVANS
Postop Post-EAVANS
Total Score
5
4
4
3
3
2
2
1
1
0
MGH-1
SHC-1
SHC-2
4
3
4
2
1
1
1
0
0
1

FIG. 8

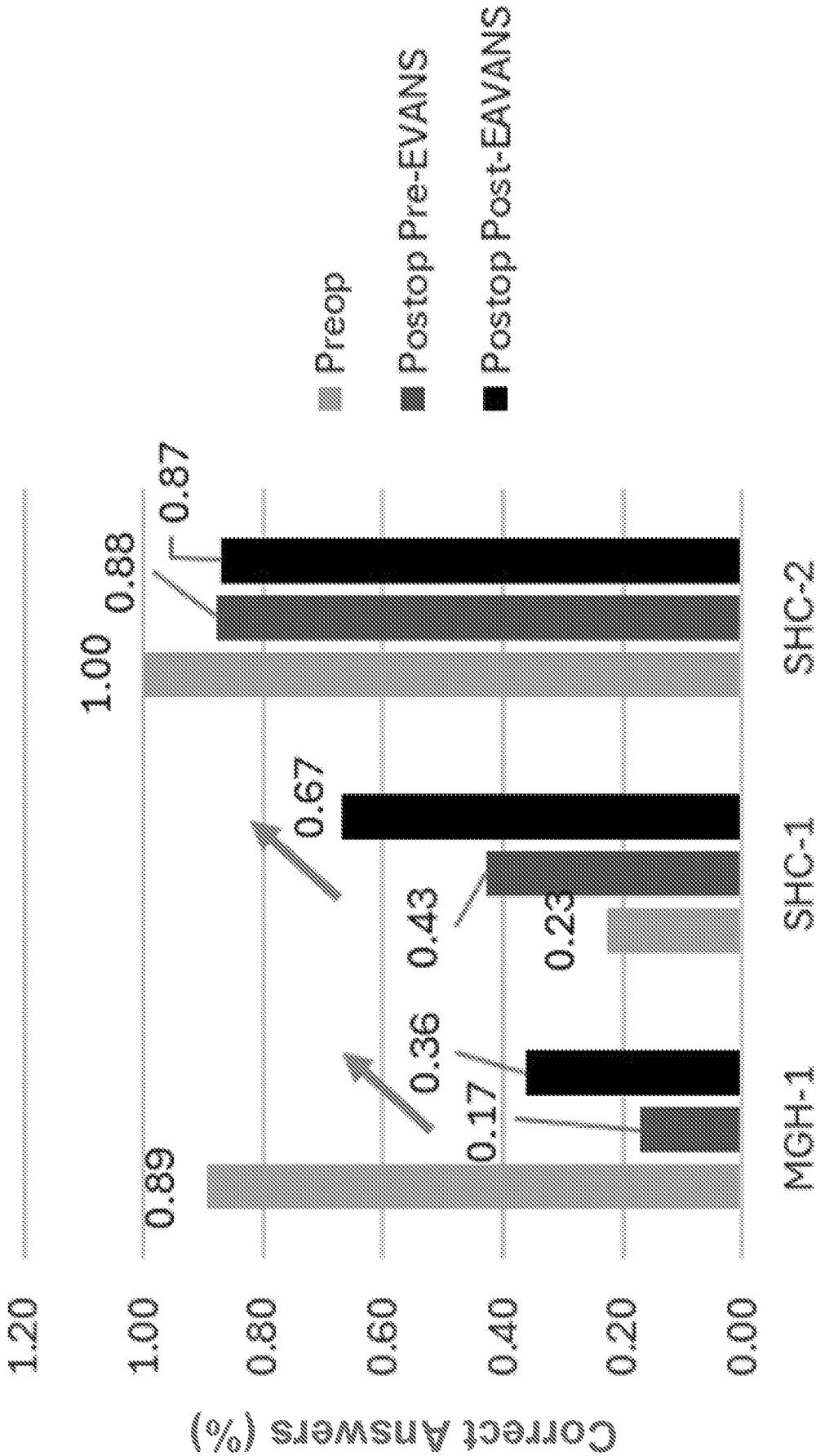

Preop
Postop Pre-EVANS
Postop Post-EAVANS
Correct Answers (%)
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0.89
1.00
0.88
0.87
0.36
0.17
0.67
0.43
0.23
MGH-1
SHC-1
SHC-2

FIG. 9