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(54) **Title:** MOTION-ACTIVATED, CLOSED-LOOP NON-INVASIVE VAGUS NERVE STIMULATION FOR NEUROREHABILITATION

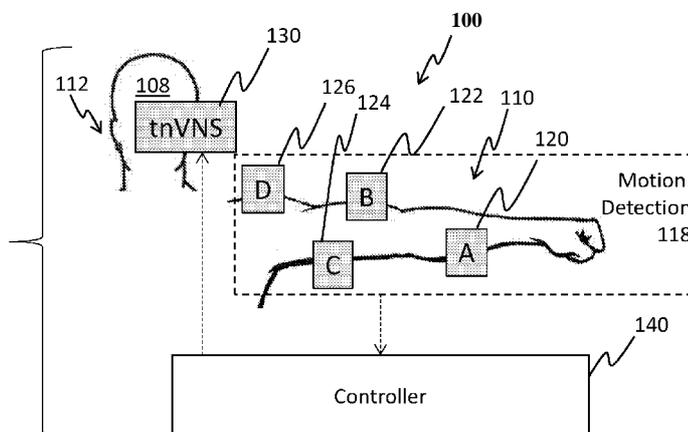


FIG. 1

(57) **Abstract:** A system for neurorehabilitation is disclosed that includes a motion detector configured to generate a motion detection feedback signal, a transcutaneous auricular vagus nerve stimulation module, and a controller configured to receive the motion detection feedback signal and send a stimulation signal to the transcutaneous auricular vagus nerve stimulation module based on the motion detection feedback signal meeting a minimum threshold criteria. A method for neurorehabilitation is disclosed that includes the steps of detecting patient motor activity, determining if the detected patient motor activity meets a minimum threshold criteria, and stimulating a vagus nerve through transcutaneous auricular vagus nerve stimulation if the minimum threshold criteria is met.



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MOTION-ACTIVATED, CLOSED-LOOP NON-INVASIVE VAGUS NERVE
STIMULATION FOR NEUROREHABILITATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application No. 62/867,989, filed June 28, 2019 and incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED
RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under grant number 5P20GM109040-04 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Nearly 800,000 people in the United States have a stroke annually, with motor impairments being the most common long-term functional disability. 85% of stroke cases result in reductions in upper limb function, and this has a severe negative impact on daily living. Motor recovery is achieved most commonly through professionally assisted motor rehabilitation training, and experimentally through various robotic, virtual reality, and brain stimulation techniques. Many of these rehabilitation techniques attempt to restore pathologically insufficient neural activity post-stroke to regain function, as the stroke induces damage to brain tissue and subsequent reorganization of cortical motor representations in surrounding undamaged tissue.

[0004] Invasive cervical vagus nerve stimulation (invasive cVNS) is a surgically invasive neuromodulation technique developed in the 1980's to treat intractable epilepsy and chronic refractory major depression. Invasive cVNS involves wrapping a cuff electrode around the left cervical bundle of the vagus nerve and has seen a reemergence in the past decade following several promising animal model findings demonstrating the ability to induce neuroplasticity in a target-dependent manner. In animal models, the temporal pairing of cVNS bursts paired with motor rehabilitation can restore pathologically insufficient neural activity post-stroke or correct maladaptive activity in tinnitus. This intricate pairing of VNS and restorative behavioral intervention is known as "targeted plasticity" and is a promising approach to treatment of neuropsychiatric interventions, with potentially transformative potential in post stroke rehabilitation.

[0005] Underlying basic fundamentals of neuroplasticity is the release of neuromodulators that influence this dynamic neural process. Plasticity may be endogenously influenced (via repeated behavioral training) or exogenously influenced (via noninvasive brain stimulation). One of these exogenous influencers of plasticity is vagus nerve stimulation (VNS), which delivers electricity to the vagus nerve, sending an afferent signal to the brainstem, activating the brain's primary source of norepinephrine (locus coeruleus) which results in broad downstream neuroplastic cellular effects. Lesions to locus coeruleus inhibit this noradrenergic-driven neuroplasticity. VNS is an influencer of neural plasticity and has been paired with various forms of training in animal models to restore deficient or aberrant neural activity. Most notably, rats with implanted VNS electrodes were concurrently stimulated while receiving rehabilitative

training post-ischemic stroke induction. In one study, 100% of the rats receiving the paired intervention fully recovered forelimb function compared to 22% of rats in the control condition. Cortical reorganization in the VNS group restored pathologically inactive circuits. These findings have led to large scale clinical trials (Microtransponder, 2012) exploring the use of VNS-paired rehabilitation to restore upper limb function and are early positive indications of using paired-therapy for rehabilitation.

[0006] Recently, a noninvasive alternative known as transcutaneous auricular vagus nerve stimulation (taVNS) has emerged as a promising alternative to conventionally implanted cVNS. taVNS, however, targets the auricular branch of the vagus nerve, which innervates the human ear and activates the afferent and efferent vagal networks, allowing for a noninvasive, simple, and rapid translation of cervically implanted VNS findings. Although paired taVNS rehab is promising, there is no reliable system or method for translating this rehab modality into the clinic.

[0007] Thus, there is a need in the art for an improved noninvasive form of stroke rehabilitation that shortens treatment time, does not permanently rely on the use of medical devices, and does not rely on expensive equipment or prolonged treatment, therefore providing superior patient outcomes and accelerated recovery times, all at a lower cost to patients and healthcare providers.

SUMMARY OF THE INVENTION

[0008] In one embodiment, a system for neurorehabilitation includes a motion detector configured to generate a motion detection feedback signal, a transcutaneous auricular vagus nerve stimulation module, and a controller configured to receive the

motion detection feedback signal and send a stimulation signal to the transcutaneous auricular vagus nerve stimulation module based on the motion detection feedback signal meeting a minimum threshold criteria. In one embodiment, the transcutaneous auricular vagus nerve stimulation module comprises a surface electrode. In one embodiment, the controller is configured to synchronize delivery of the stimulation signal with a detected motion with a delay of 2 seconds or less. In one embodiment, the controller is configured to synchronize delivery of the stimulation signal with a detected motion with a delay of 1 second or less. In one embodiment, the controller is configured to synchronize delivery of the stimulation signal with a detected motion with a delay of 100ms or less. In other embodiments, the controller is configured to synchronize delivery of the stimulation signal with the detected motions with a delay of 900ms, 800ms, 700ms, 600ms, 500ms, 400ms, 300ms, or 200ms. In other embodiments, the controller is configured to synchronize delivery of the stimulation signal with the detected motions with a delay of 90ms, 80ms, 70ms, 60ms, 50ms, 40ms, 30ms, 20ms or 10ms. In one embodiment, the stimulation signal comprises an electrical intensity greater than 0mA and up to 10mA, a frequency of greater than 0Hz and up to 100Hz, and a pulse width greater than 0 μ s and up to 1000 μ s. In one embodiment, the stimulation signal comprises an electrical intensity greater than 0.5mA and up to 5mA, a frequency of greater than 10Hz and up to 50Hz, and a pulse width greater than 100ps and up to 500ps. In one embodiment, the stimulation signal comprises an electrical intensity greater than 1mA and up to 3mA, a frequency of greater than 25Hz and up to 50Hz, and a pulse width greater than 250ps and up to 500ps.

[0009] In one embodiment, the stimulation is a theta burst stimulation, wherein stimulation is applied in a triplicate pattern in that stimulation is grouped into sets of three burst applied in rapid succession, with: an intensity greater than 0mA and up to 10mA, more specifically greater than 0.5mA and up to 5mA, and most specifically greater than 1mA and up to 5mA; wherein each burst within a triplet possesses a frequency greater than 0Hz and up to 100Hz, more specifically greater than 25Hz and up to 75Hz, and most specifically greater than 40Hz and up to 60Hz, and wherein the group of triplets possess a frequency of greater than 0Hz and up to 100Hz, more specifically greater than 1Hz and up to 25Hz, and most specifically greater than 1Hz and up to 10Hz; and a pulse width greater than 0ps and up to 1000ps, more specifically greater than 100ps and up to 500ps, and most specifically greater than 250ps and up to 500ps.

[001 0] In other embodiments the electrical intensity can be: 0.1 mA, 0.2mA, 0.3mA, 0.4mA, 0.5mA, 0.6mA, 0.7mA, 0.8mA, 0.9mA, 1.0mA, 1.1 mA, 1.2mA, 1.3mA, 1.4mA, 1.5mA, 1.6mA, 1.7mA, 1.8mA, 1.9mA, 2.0mA, 2.1 mA, 2.2mA, 2.3mA, 2.4mA, 2.5mA, 2.6mA, 2.7mA, 2.8mA, 2.9mA, 3.0mA, 3.1 mA, 3.2mA, 3.3mA, 3.4mA, 3.5mA, 3.6mA, 3.7mA, 3.8mA, 3.9mA, 4.0mA, 4.1 mA, 4.2mA, 4.3mA, 4.4mA, 4.5mA, 4.6mA, 4.7mA, 4.8mA, 4.9mA, 5.0mA, 5.1 mA, 5.2mA, 5.3mA, 5.4mA, 5.5mA, 5.6mA, 5.7mA, 5.8mA, 5.9mA, 6.1 mA, 6.2mA, 6.3mA, 6.4mA, 6.5mA, 6.6mA, 6.7mA, 6.8mA, 6.9mA, 7.0mA, 8.1 mA, 8.2mA, 8.3mA, 8.4mA, 8.5mA, 8.6mA, 8.7mA, 8.8mA, 8.9mA, 9.0mA, 9.1 mA, 9.2mA, 9.3mA, 9.4mA, 9.5mA, 9.6mA, 9.7mA, 9.8mA, 9.9mA, or 10mA.

[001 1] In other embodiments the frequency can be: 1Hz, 2Hz, 3Hz, 4Hz, 5Hz, 6Hz, 7Hz, 8Hz, 9Hz, 10Hz, 11Hz, 12Hz, 13Hz, 14Hz, 15Hz, 16Hz, 17Hz, 18Hz, 19Hz, 20Hz,

21Hz, 22Hz, 23Hz, 24Hz, 25Hz, 26Hz, 27Hz, 28Hz, 29Hz, 30Hz, 31Hz, 32Hz, 33Hz, 34Hz, 35Hz, 36Hz, 37Hz, 38Hz, 39Hz, 40Hz, 41Hz, 42Hz, 43Hz, 44Hz, 45Hz, 46Hz, 47Hz, 48Hz, 49Hz, 50Hz, 51Hz, 52Hz, 53Hz, 54Hz, 55Hz, 56Hz, 57Hz, 58Hz, 59Hz, 61Hz, 62Hz, 63Hz, 64Hz, 65Hz, 66Hz, 67Hz, 68Hz, 69Hz, 70Hz, 71Hz, 72Hz, 73Hz, 74Hz, 75Hz, 76Hz, 77Hz, 78Hz, 79Hz, 80Hz, 81Hz, 82Hz, 83Hz, 84Hz, 85Hz, 86Hz, 87Hz, 88Hz, 89Hz, 90Hz, 91Hz, 92Hz, 93Hz, 94Hz, 95Hz, 96Hz, 97Hz, 98Hz, 99Hz, or 100Hz

[0012] In other embodiments the pulse width can be: 10 μ s, 20 μ s, 30 μ s, 40 μ s, 50 μ s, 60 μ s, 70 μ s, 80 μ s, 90 μ s, 100 μ s, 110 μ s, 120 μ s, 130 μ s, 140 μ s, 150 μ s, 160 μ s, 170 μ s, 180 μ s, 190 μ s, 200 μ s, 210 μ s, 220 μ s, 230 μ s, 240 μ s, 250 μ s, 260 μ s, 270 μ s, 280 μ s, 290 μ s, 300 μ s, 310 μ s, 320 μ s, 330 μ s, 340 μ s, 350 μ s, 360 μ s, 370 μ s, 380 μ s, 390 μ s, 400 μ s, 410 μ s, 420 μ s, 430 μ s, 440 μ s, 450 μ s, 460 μ s, 470 μ s, 480 μ s, 490 μ s, 500 μ s, 510 μ s, 520 μ s, 530 μ s, 540 μ s, 550 μ s, 560 μ s, 570 μ s, 580 μ s, 590 μ s, 610 μ s, 620 μ s, 630 μ s, 640 μ s, 650 μ s, 660 μ s, 670 μ s, 680 μ s, 690 μ s, 700 μ s, 710 μ s, 720 μ s, 730 μ s, 740 μ s, 750 μ s, 760 μ s, 770 μ s, 780 μ s, 790 μ s, 800 μ s, 810 μ s, 820 μ s, 830 μ s, 840 μ s, 850 μ s, 860 μ s, 870 μ s, 880 μ s, 890 μ s, 900 μ s, 910 μ s, 920 μ s, 930 μ s, 940 μ s, 950 μ s, 960 μ s, 970 μ s, 980 μ s, 990 μ s, or 1000 μ s.

[0013] In one embodiment, the transcutaneous auricular vagus nerve stimulation module comprises a surface electrode configured to interface with an anterior wall of an outer ear canal. In one embodiment, the transcutaneous auricular vagus nerve stimulation module is configured to stimulate an auricular branch of the vagus nerve. In one embodiment, the motion detector comprises one or more of an EMG electrode, an EEG electrode, a camera, a robotic apparatus, an exoskeleton apparatus and an

accelerometer. In one embodiment, the muscle activity feedback signals are based on at least one muscle from the group consisting of flexor carpi radialis, flexor capri ulnaris, biceps, triceps, anterior deltoid, middle deltoid, gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot inverters and evertors, biceps femoris, semitendinosus and/or semimembranosus. In one embodiment, the motion detection feedback signal is based on a plurality of muscle activity feedback signals. In one embodiment, the muscle activity feedback signals are based on two or more muscles from the group consisting of flexor carpi radialis, flexor capri ulnaris, biceps, triceps, anterior deltoid and middle deltoid. In one embodiment, the muscle activity signals are based on at least a first signal from an upper limb indicative of movement from one or more of a trapezius, deltoid, biceps brachii, triceps, flexor/extensor carpi radialis, flexor/extensor digitorum, and flexor/extensor pollicis brevis; and at least a second signal from a lower limb indicative of movement from one or more of a gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot inverters and evertors, biceps femoris, semitendinosus and semimembranosus. In one embodiment, the minimum threshold criteria comprises an EMG motor evoked potential of at least 50uV. In one embodiment, the minimum threshold criteria comprises a motion sufficient to be detectable by an accelerometer. In one embodiment, the minimum threshold criteria comprises a motion sufficient to be detectable via a depth camera, video camera or other visual motion sensor device. In one embodiment, the minimum threshold criteria comprises a force sufficient to trigger a pressure sensing floor mat. In one embodiment, the minimum threshold criteria is determined by an

observer and manually triggered. In one embodiment, the minimum threshold criteria is a minimum threshold for contraction.

[0014] In one embodiment, a method for neurorehabilitation includes the steps of detecting patient motor activity, determining if the detected patient motor activity meets a minimum threshold criteria, and stimulating a vagus nerve through transcutaneous auricular vagus nerve stimulation if the minimum threshold criteria is met. In one embodiment, detecting patient motor activity comprises detecting muscle electrical activity. In one embodiment, detecting patient motor activity comprises detecting a plurality of muscle activity feedback signals. In one embodiment, detecting patient motor activity includes patient imaging. In one embodiment, detecting patient motor activity includes utilizing an accelerometer affixed to the patient. In one embodiment, the minimum threshold criteria comprises a force sufficient to trigger a pressure sensing floor mat. In one embodiment, the minimum threshold criteria is determined by an observer and manually triggered. In one embodiment, the muscle activity feedback signals are based on at least one muscle from the group consisting of flexor carpi radialis, flexor carpi ulnaris, biceps, triceps, anterior deltoid, middle deltoid, gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot inverters and evertors, biceps femoris, semitendinosus and/or semimembranosus. In one embodiment, the plurality of muscle activity feedback signals are based on two or more muscles from the group consisting of flexor carpi radialis, flexor carpi ulnaris, biceps, triceps, anterior deltoid and middle deltoid. In one embodiment, the plurality of muscle activity feedback signals are based on: at least a first signal from an upper limb indicative of movement from one or more of a trapezius, deltoid, biceps brachii, triceps,

flexor/extensor carpi radialis, flexor/extensor digitorum, and flexor/extensor pollicis brevis; and at least a second signal from a lower limb indicative of movement from one or more of a gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot inverters and evertors, biceps femoris, semitendinosus and semimembranosus. In one embodiment, detecting patient motor activity comprises mechanical feedback from a robotic or exoskeleton apparatus. In one embodiment, stimulating a vagus nerve comprises stimulating an auricular branch of the vagus nerve. In one embodiment, the minimum threshold criteria comprises one or more of a minimum signal amplitude, a minimum signal frequency, a minimum signal duration, a comparison to a model signal, a comparison to a preset value, and a comparison to a previously measured signal. In one embodiment, delivery of the stimulation is synchronized with a detected motion with a delay of 100ms or less. In one embodiment, the stimulation comprises an electrical intensity greater than 0mA and up to 10mA, a frequency of greater than 0Hz and up to 100Hz, and a pulse width greater than 0 μ s and up to 500 μ s. In one embodiment, the stimulation comprises an electrical intensity greater than 0.5mA and up to 5mA, a frequency of greater than 10Hz and up to 25Hz, and a pulse width greater than 100 μ s and up to 250 μ s. In one embodiment, the stimulation is delivered to an anterior wall of an outer ear canal. In one embodiment, the minimum threshold criteria comprises an EMG motor evoked potential of at least 50 μ V. In another embodiment, the minimum threshold criteria comprises a motion sufficient to be detectable by an accelerometer. In yet another embodiment, the minimum threshold criteria comprises a motion sufficient to be detectable via a depth camera, video camera or other visual motion sensor device. In one embodiment, the

minimum threshold criteria comprises a force sufficient to trigger a pressure sensing floor mat. In one embodiment, the minimum threshold criteria is determined by an observer and manually triggered. In one embodiment, the minimum threshold criteria is a minimum threshold for contraction. Notably, any of the embodiment described herein can possess any of the stimulation delays, intensities, frequencies or pulse widths described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The foregoing purposes and features, as well as other purposes and features, will become apparent with reference to the description and accompanying figures below, which are included to provide an understanding of the invention and constitute a part of the specification, in which like numerals represent like elements, and in which:

[0016] Figure 1 is a diagram of a neurorehabilitation system according to one embodiment.

[0017] Figure 2 is a method of neurorehabilitation according to one embodiment.

[0018] Figure 3 is an experimental setup showing therapist-guided motor rehabilitation senses motion via EMG electrodes placed on the affected limb of the stroke patient according to one embodiment.

[0019] Figure 4 is an experimental setup showing that robotics utilized as an alternative to standard task-specific motor training administered by a therapist according to one embodiment.

[0020] Figure 5A is a graph of percent of movements with corrects MAAVNS trigger according to one experimental example, and Figure 5B is a graph of average time of movement according to one experimental example.

DETAILED DESCRIPTION OF THE INVENTION

[0021] It is to be understood that the figures and descriptions of the present invention have been simplified to illustrate elements that are relevant for a more clear comprehension of the present invention, while eliminating, for the purpose of clarity, many other elements found in systems and methods of neurorehabilitation. Those of ordinary skill in the art may recognize that other elements and/or steps are desirable and/or required in implementing the present invention. However, because such elements and steps are well known in the art, and because they do not facilitate a better understanding of the present invention, a discussion of such elements and steps is not provided herein. The disclosure herein is directed to all such variations and modifications to such elements and methods known to those skilled in the art.

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

[0023] As used herein, each of the following terms has the meaning associated with it in this section.

[0024] The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0025] “About” as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 20\%$, $\pm 10\%$, $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are appropriate.

[0026] Ranges: throughout this disclosure, various aspects of the invention can 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. Where appropriate, 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, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

[0027] Referring now in detail to the drawings, in which like reference numerals indicate like parts or elements throughout the several views, in various embodiments, presented herein is system and method for neurorehabilitation.

[0028] Embodiments of the motor activated auricular vagus nerve stimulation (MAAVNS) described herein utilize a closed-loop system that allows for the simple

administration of noninvasive vagus nerve stimulation (VNS) that is precisely paired with motor activity. Because this is closed loop system, the application of this system makes for easy use by rehabilitation therapists in the clinic and can be implemented at at-home, remote or telehealth rehab settings. In one embodiment, vagus nerve stimulation is utilized to enhance motor rehabilitation by increasing neuroplasticity and accelerating the restoration of neural activity and function when paired in a temporally synchronized manner. Embodiments of the system and method described herein implement noninvasive vagus nerve stimulation as an enhancer of neuroplasticity to accelerate motor restoration in post-stroke rehabilitation. In one embodiment, using motion tracking (for example via EMG electrodes, EEG electrodes, infrared cameras, depth cameras, video cameras, pressure mats, accelerometers, real time observers, pneumatics, robotics, or exoskeleton), a computerized system can receive inputs of this movement and deliver simultaneous noninvasive vagus nerve stimulation (electrical stimulation of the auricular branch of the vagus nerve). This movement-induced stimulation allows for intricate pairing of stimulation with movement to enhance the effects of rehabilitation training post-stroke. This neurorehabilitation system can accelerate the time needed for rehabilitation therapy and enhance the magnitude of effects of standard motor therapy of the upper or lower limbs post-stroke. The system can be used for example as a therapeutic tool, a research tool, and/or a tool to enhance rehabilitation of upper and lower limb function post-stroke.

[0029] Using motion tracking (e.g. via EMG electrodes, EEG electrodes, infrared cameras, video cameras, pressure mats, accelerometers, real time observers, pneumatics, robotics, or exoskeleton), a computerized system can receive inputs of this

movement and deliver simultaneous noninvasive vagus nerve stimulation (electrical stimulation of the auricular branch of the vagus nerve). This movement-induced stimulation allows for intricate pairing of stimulation with movement to enhance the effects of rehabilitation training post-stroke. This neurorehabilitation system can accelerate the time needed for rehabilitation therapy and enhance the magnitude of effects of standard motor therapy of the upper or lower limbs post-stroke. The system can be used for example as a therapeutic tool, a research tool, and/or a tool to enhance rehabilitation of upper and lower limb function post-stroke.

[0030] With reference now to Fig. 1, according to one embodiment, a system 100 for neurorehabilitation on a patient 108 includes a motion detector 118 configured to generate a motion detection feedback signal related to motion of the limb 110 being trained. A transcutaneous auricular vagus nerve stimulation module 130 is attached (e.g. via a surface electrode) to the head or neck area 112 of the patient 108 (e.g. the ear). A controller 140 is configured to receive the motion detection feedback signal and send a stimulation signal to the transcutaneous auricular vagus nerve stimulation module 130 based on the motion detection feedback signal meeting a minimum threshold criteria. The transcutaneous auricular vagus nerve stimulation module 130 can include a surface electrode, which in certain embodiments is configured to interface with an anterior wall of an outer ear canal, the tragus or an earlobe. The controller 140 can be connected to motion detection elements wirelessly or by hard wired connections. The controller 140 can be configured to synchronize delivery of the stimulation signal with a detected motion. In one embodiment, the controller 140 delivers the synchronized delivery with a delay of 100ms or less. In one embodiment, the controller

is configured to synchronize delivery of the stimulation signal with a detected motion with a delay of 2 seconds or less. In one embodiment, the controller is configured to synchronize delivery of the stimulation signal with a detected motion with a delay of 1 second or less. In other embodiments, the controller is configured to synchronize delivery of the stimulation signal with the detected motions with a delay of 900ms, 800ms, 700ms, 600ms, 500ms, 400ms, 300ms, or 200ms. In other embodiments, the controller is configured to synchronize delivery of the stimulation signal with the detected motions with a delay of 90ms, 80ms, 70ms, 60ms, 50ms, 40ms, 30ms, 20ms or 10ms. The minimum threshold criteria can be a minimum threshold for contraction. In one embodiment, the minimum threshold criteria comprises an EMG motor evoked potential of at least 50uV. Thresholding EEG may for example require a raw signal to be acquired using EEG electrodes on scalp, signal preprocessed, with feature extraction and classification of a motor movement. In one embodiment, the minimum threshold criteria comprises a motion sufficient to be detectable by an accelerometer. In one embodiment, the minimum threshold criteria comprises a motion sufficient to be detectable via a depth camera, video camera or other visual motion sensor device. In one embodiment, the minimum threshold criteria comprises a force sufficient to trigger a pressure sensing floor mat. In one embodiment, the minimum threshold criteria is determined by an observer and manually triggered.

[0031] Motion detection 118 may for example focus on detection motion of various muscle groups, including for example detecting contraction of the forearm (A) 120, biceps (B) 122, Triceps (C) 124 and Anterior/Middle Deltoid (D) 126. Motion detection 118 can be implemented through various modalities such as:

[0032] Electromyography (EMG) - Adhesive sensors can be attached to the limb undergoing rehabilitation. Motor evoked potentials will be then measured when motor activity is initiated and can deliver stimulation.

[0033] Electroencephalogram (EEG) - Motor activity measured from directly from electrical potentials generated by the brain can be recorded and real-time processed using EEG leads placed over the motor areas of the brain (EEG positions C3, C4) of the patient.

[0034] In addition to EMG and EEG, motion detection 118 can be accomplished by a variety of means disclosed herein including, but not limited to accelerometers, infrared or LED tracking cameras, depth or video cameras, pressure mats, or real time observers.

[0035] Accelerometers - Wearable sensors can be worn on the wrist or affected limb that is undergoing rehabilitation.

[0036] Infrared or LED tracking cameras - Infrared sensors or LED lights can be attached to the limb that is undergoing rehabilitation and camera can track these sensors and lights to determine whether movement occurred.

[0037] Depth cameras - Depth cameras (like Xbox Kinect) can track movement without sensors. These can be used to detect movement and initiate stimulation.

[0038] Pressure Mats - A pressure mat (like a Q-Pad by LiteGait® or other mat commonly employed in rehabilitation environments) can be used to track movement via

a pressure sensitive surface. These can be used to detect movement and initiate stimulation.

[0039] Real time observers - An individual, other than the patient being stimulated, can observe the patient being stimulated and visually detect movement of the patient and initiate stimulation via a manual trigger.

[0040] Thus, in one embodiment, detecting patient motor activity includes utilizing an accelerometer affixed to the patient. In one embodiment, the minimum threshold criteria comprises a force sufficient to trigger a pressure sensing floor mat. In one embodiment, the minimum threshold criteria is determined by an observer and manually triggered. In one embodiment, the muscle activity feedback signals are based on at least one muscle from the group consisting of flexor carpi radialis, flexor carpi ulnaris, biceps, triceps, anterior deltoid, middle deltoid, gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot invertors and evertors, biceps femoris, semitendinosus and/or semimembranosus.

[0041] The stimulation signal sent by the controller 140 to the transcutaneous auricular vagus nerve stimulation module 130 can in certain embodiments have wherein the stimulation signal has an electrical intensity greater than 0mA and up to 10mA, a frequency of greater than 0Hz and up to 100Hz, and a pulse width greater than 0 μ s and up to 500 μ s. In one embodiment, the stimulation signal has an electrical intensity greater than 0.5mA and up to 5mA, a frequency of greater than 10Hz and up to 25Hz, and a pulse width greater than 100 μ s and up to 250 μ s. In one embodiment, the stimulation signal comprises an electrical intensity greater than 0mA and up to 10mA, a

frequency of greater than 0Hz and up to 100Hz, and a pulse width greater than 0 μ s and up to 1000 μ s. In one embodiment, the stimulation signal comprises an electrical intensity greater than 0.5mA and up to 5mA, a frequency of greater than 10Hz and up to 50Hz, and a pulse width greater than 100 μ s and up to 500 μ s. In one embodiment, the stimulation signal comprises an electrical intensity greater than 1mA and up to 3mA, a frequency of greater than 25Hz and up to 50Hz, and a pulse width greater than 250 μ s and up to 500 μ s.

[0042] In one embodiment, the stimulation is a theta burst stimulation, wherein stimulation is applied in a triplicate pattern in that stimulation is grouped into sets of three burst applied in rapid succession, with an intensity greater than 0mA and up to 10mA, more specifically greater than 0.5mA and up to 5mA, and most specifically greater than 1mA and up to 5mA; wherein each burst within a triplet possesses a frequency greater than 0Hz and up to 100Hz, more specifically greater than 25Hz and up to 75Hz, and most specifically greater than 40Hz and up to 60Hz, and wherein the group of triplets possess a frequency of greater than 0Hz and up to 100Hz, more specifically greater than 1Hz and up to 25Hz, and most specifically greater than 1Hz and up to 10Hz; and a pulse width greater than 0 μ s and up to 1000 μ s, more specifically greater than 100 μ s and up to 500 μ s, and most specifically greater than 250 μ s and up to 500 μ s.

[0043] In other embodiments the electrical intensity can be 0.1 mA, 0.2mA, 0.3mA, 0.4mA, 0.5mA, 0.6mA, 0.7mA, 0.8mA, 0.9mA, 1.0mA, 1.1 mA, 1.2mA, 1.3mA, 1.4mA, 1.5mA, 1.6mA, 1.7mA, 1.8mA, 1.9mA, 2.0mA, 2.1 mA, 2.2mA, 2.3mA, 2.4mA, 2.5mA, 2.6mA, 2.7mA, 2.8mA, 2.9mA, 3.0mA, 3.1 mA, 3.2mA, 3.3mA, 3.4mA, 3.5mA, 3.6mA,

3.7mA, 3.8mA, 3.9mA, 4.0mA, 4.1 mA, 4.2mA, 4.3mA, 4.4mA, 4.5mA, 4.6mA, 4.7mA, 4.8mA, 4.9mA, 5.0mA, 5.1 mA, 5.2mA, 5.3mA, 5.4mA, 5.5mA, 5.6mA, 5.7mA, 5.8mA, 5.9mA, 6.1 mA, 6.2mA, 6.3mA, 6.4mA, 6.5mA, 6.6mA, 6.7mA, 6.8mA, 6.9mA, 7.0mA, 8.1 mA, 8.2mA, 8.3mA, 8.4mA, 8.5mA, 8.6mA, 8.7mA, 8.8mA, 8.9mA, 9.0mA, 9.1 mA, 9.2mA, 9.3mA, 9.4mA, 9.5mA, 9.6mA, 9.7mA, 9.8mA, 9.9mA, or 10mA.

[0044] In other embodiments the frequency can be 1Hz, 2Hz, 3Hz, 4Hz, 5Hz, 6Hz, 7Hz, 8Hz, 9Hz, 10Hz, 11Hz, 12Hz, 13Hz, 14Hz, 15Hz, 16Hz, 17Hz, 18Hz, 19Hz, 20Hz, 21Hz, 22Hz, 23Hz, 24Hz, 25Hz, 26Hz, 27Hz, 28Hz, 29Hz, 30Hz, 31Hz, 32Hz, 33Hz, 34Hz, 35Hz, 36Hz, 37Hz, 38Hz, 39Hz, 40Hz, 41Hz, 42Hz, 43Hz, 44Hz, 45Hz, 46Hz, 47Hz, 48Hz, 49Hz, 50Hz, 51Hz, 52Hz, 53Hz, 54Hz, 55Hz, 56Hz, 57Hz, 58Hz, 59Hz, 61Hz, 62Hz, 63Hz, 64Hz, 65Hz, 66Hz, 67Hz, 68Hz, 69Hz, 70Hz, 71Hz, 72Hz, 73Hz, 74Hz, 75Hz, 76Hz, 77Hz, 78Hz, 79Hz, 80Hz, 81Hz, 82Hz, 83Hz, 84Hz, 85Hz, 86Hz, 87Hz, 88Hz, 89Hz, 90Hz, 91Hz, 92Hz, 93Hz, 94Hz, 95Hz, 96Hz, 97Hz, 98Hz, 99Hz, or 100Hz

[0045] In other embodiments the pulse width can be 10 μ s, 20 μ s, 30 μ s, 40 μ s, 50 μ s, 60 μ s, 70 μ s, 80 μ s, 90 μ s, 100 μ s, 110 μ s, 120 μ s, 130 μ s, 140 μ s, 150 μ s, 160 μ s, 170 μ s, 180 μ s, 190 μ s, 200 μ s, 210 μ s, 220 μ s, 230 μ s, 240 μ s, 250 μ s, 260 μ s, 270 μ s, 280 μ s, 290 μ s, 300 μ s, 310 μ s, 320 μ s, 330 μ s, 340 μ s, 350 μ s, 360 μ s, 370 μ s, 380 μ s, 390 μ s, 400 μ s, 410 μ s, 420 μ s, 430 μ s, 440 μ s, 450 μ s, 460 μ s, 470 μ s, 480 μ s, 490 μ s, 500 μ s, 510 μ s, 520 μ s, 530 μ s, 540 μ s, 550 μ s, 560 μ s, 570 μ s, 580 μ s, 590 μ s, 610 μ s, 620 μ s, 630 μ s, 640 μ s, 650 μ s, 660 μ s, 670 μ s, 680 μ s, 690 μ s, 700 μ s, 710 μ s, 720 μ s, 730 μ s, 740 μ s, 750 μ s, 760 μ s, 770 μ s, 780 μ s, 790 μ s, 800 μ s, 810 μ s, 820 μ s, 830 μ s, 840 μ s,

850 μ s, 860 μ s, 870 μ s, 880 μ s, 890 μ s, 900 μ s, 910 μ s, 920 μ s, 930 μ s, 940 μ s, 950 μ s, 960 μ s, 970 μ s, 980 μ s, 990 μ s, or 1000 μ s.

[0046] In certain embodiments, the stimulation signal has a frequency of 15-35Hz and a pulse width of 150-600 μ s, or a frequency of 20-30Hz and a pulse width of 200-300 μ s, or a frequency of 20-30Hz and a pulse width of 450-550 μ s, or a frequency of substantially 25Hz and a pulse width of substantially 250 μ s, or a frequency of substantially 25Hz and a pulse width of substantially 500 μ s. In certain embodiments, the stimulation signal can be theta burst stimulation as further described herein above. Signal waveforms can be for example direct current, alternating current and random noise waveforms.

[0047] The signal can also change based on feedback. Physiology monitoring (ie Heart Rate) can indicate whether signal input is working, so physiology may be used to modify the signal intensity to optimize therapy. A reliable biomarker of effective stimulation using taVNS is activation of the parasympathetic nervous system. Various signal intensities may be administered to the user, and physiology monitoring via wearable cardiac sensors can determine whether a reduction in heart rate occurs in response to stimulation. Signal intensity can be varied based on the feedback of this autonomic activation in a closed-loop automated parameter optimization paradigm.

[0048] The motion detector 118 can utilize one or more of an EMG electrode, an EEG electrode, a camera, a robotic apparatus, an exoskeleton apparatus, an accelerometer or a real time observer. In one embodiment, the muscle activity feedback signals are based on at least one muscle from the group consisting of flexor

carpi radialis, flexor capri ulnaris, bice μ s, trice μ s, anterior deltoid, middle deltoid, gluteus maximus, quadrice μ s femoris, anterior compartment of the leg, quadrice μ s femoris, foot inverters and evertors, bice μ s femoris, semitendinosus and/or semimembranosus. In one embodiment, for example, an EMG electrode array can be placed on target muscle groups, including forearm (A) 120, bice μ s (B) 122, Trice μ s (C) 124 and Anterior/Middle Deltoid (D) 126. Group muscle movements can be detected at these target locations. The EMG array is used to detect a threshold movement criteria for determining whether a stimulation signal will be delivered. Thus, the motion detection feedback signal can be based on a plurality of muscle activity feedback signals. The muscle activity feedback signals can be based on two or more muscles from the group consisting of flexor carpi radialis, flexor capri ulnaris, bice μ s, trice μ s, anterior deltoid and middle deltoid. The Muscle activity signals can be based on at least a first signal from an upper limb indicative of movement from one or more of a trapezius, deltoid, bice μ s brachii, trice μ s, flexor/extensor carpi radialis, flexor/extensor digitorum, and flexor/extensor pollicis brevis, and at least a second signal from a lower limb indicative of movement from one or more of a gluteus maximus, quadrice μ s femoris, anterior compartment of the leg, quadrice μ s femoris, foot inverters and evertors, bice μ s femoris, semitendinosus and semimembranosus.

[0049] With reference now to Fig. 2, according to one embodiment, a method 200 for neurorehabilitation includes instructing patient motor activity 202 (e.g. reach, grasp, single joint movement), detecting patient motor activity 204, determining if the detected patient motor activity meets a minimum threshold criteria 206, and stimulating a vagus nerve through transcutaneous auricular vagus nerve stimulation if the minimum

threshold criteria is met 210, or otherwise not stimulating if the minimum threshold is not met.

[0050] Since the system and method are non-invasive, embodiments of the system and method described herein can also be used for feedback shape and improve any behavioral output, regardless of whether they're recovering from a stroke or otherwise healthy. For example, users could use embodiments of the system and method for skill learning (e.g. developing good golf swing), cognitive tests or motor recovery, or paired with EEG or imaging to correct activation of any part of the brain.

EXPERIMENTAL EXAMPLES

[0051] The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only and the invention should in no way be construed as being limited to these Examples, but rather should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

[0052] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the present invention and practice the claimed methods. The following working examples therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

[0053] According to one experimental setup, with reference to Fig. 3, according to one embodiment, therapist-guided motor rehabilitation senses motion via EMG electrodes placed on the affected limb of the stroke patient. These EMG electrodes will sense when movement occurs during rehabilitation training, and will deliver noninvasive VNS via ear or neck stimulation electrodes. This system will be setup by the therapist and run independently while the patient receives motor rehabilitation.

[0054] With reference to the experimental setup of Fig. 4, according to one embodiment, robotics and exoskeletons can be utilized as an alternative to standard task-specific motor training administered by a therapist. In this case, a robotic arm can be used in rehabilitation and can send outputs regarding movements making EMG electrodes unnecessary. The robotics can send motion signals to a stimulator which then delivers the noninvasive VNS.

[0055] According to one study, system testing was performed in five Patients with unilateral hemiparesis. Five participants (2 female, mean age= 62.6) were enrolled with unilateral hemiparesis caused by a stroke (3 ischemic, 2 hemorrhagic). Participants attended a single, 1-hour session where the research team connected the motor activated auricular vagus nerve stimulation (MAAVNS) system to their affected arm.

[0056] The MAAVNS system was connected in two different configurations for each participant. MAAVNS hardware was setup identically with the exception of the placement of the electromyography (EMG) sensors - which were placed on either the middle or anterior deltoid.

[0057] After connecting the participant to the respective MAAVNS configuration, a therapist instructed them to conduct 3 different movements (reach, pour, and manipulation). Each movement was repeated 8 times. One participant did not complete the manipulation movements due to time constraints. The number of successful MAAVNS triggers in response to upper limb movement was recorded. We also recorded the average time of each movement.

[0058] With reference now to the graph in Fig. 5A, the MAAVNS system in the anterior deltoid muscle configuration performed significantly better on reach tasks than middle deltoid (AD: 95% vs MD: 55.1%). Both configurations performed well for alternative movements such as the pour and manipulations.

[0059] With reference now to the graph in Fig. 5B, average timing of movements were consistent between MAAVNS configurations, suggesting the MAAVNS sensors do not impede movements. Furthermore, these data suggest that the amount of stimulation delivered with MAAVNS must be between 2.88s - 5.5s. This will ensure stimulation is delivered throughout the entire movement.

[0060] The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A system for neurorehabilitation comprising:
a motion detector configured to generate a motion detection feedback signal;
a transcutaneous auricular vagus nerve stimulation module; and
a controller configured to receive the motion detection feedback signal and send a stimulation signal to the transcutaneous auricular vagus nerve stimulation module based on the motion detection feedback signal meeting a minimum threshold criteria.
2. The system of claim 1, wherein the transcutaneous auricular vagus nerve stimulation module comprises a surface electrode.
3. The system of claim 2, wherein the controller is configured to synchronize delivery of the stimulation signal with a detected motion with a delay of 100ms or less.
4. The system of claim 3, wherein the stimulation signal comprises an electrical intensity greater than 0mA and up to 10mA, a frequency of greater than 0Hz and up to 100Hz, and a pulse width greater than 0 μ s and up to 500 μ s.
5. The system of claim 3, wherein the stimulation signal comprises an electrical intensity greater than 0.5mA and up to 5mA, a frequency of greater than 10Hz and up to 25Hz, and a pulse width greater than 100 μ s and up to 250 μ s.
6. The system of claim 1, wherein the transcutaneous auricular vagus nerve stimulation module comprises a surface electrode configured to interface with an anterior wall of an outer ear canal.
7. The system of claim 1, wherein the transcutaneous auricular vagus nerve stimulation module is configured to stimulate an auricular branch of the vagus nerve.

8. The system of claim 1, wherein the motion detector comprises one or more of an EMG electrode, an EEG electrode, a camera, a robotic apparatus, an exoskeleton apparatus and an accelerometer.
9. The system of claim 1, wherein the motion detection feedback signal is based on a plurality of muscle activity feedback signals.
10. The system of claim 9, wherein the muscle activity feedback signals are based on two or more muscles from the group consisting of flexor carpi radialis, flexor carpi ulnaris, biceps, triceps, anterior deltoid and middle deltoid.
11. The system of claim 9, wherein the muscle activity signals are based on:
 - at least a first signal from an upper limb indicative of movement from one or more of a trapezius, deltoid, biceps brachii, triceps, flexor/extensor carpi radialis, flexor/extensor digitorum, and flexor/extensor pollicis brevis; and
 - at least a second signal from a lower limb indicative of movement from one or more of a gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot inverters and evertors, biceps femoris, semitendinosus and semimembranosus.
12. The system of claim 1, wherein the minimum threshold criteria comprises an EMG motor evoked potential of at least 50uV.
13. The system of claim 1, wherein the minimum threshold criteria is a minimum threshold for contraction.
14. A method for neurorehabilitation comprising:
 - detecting patient motor activity;
 - determining if the detected patient motor activity meets a minimum threshold criteria; and

stimulating a vagus nerve through transcutaneous auricular vagus nerve stimulation if the minimum threshold criteria is met.

15. The method of claim 14, wherein detecting patient motor activity comprises detecting muscle electrical activity.

16. The method of claim 14, wherein detecting patient motor activity comprises detecting a plurality of muscle activity feedback signals.

17. The method of claim 14, wherein detecting patient motor activity comprises patient imaging.

18. The method of claim 14, wherein the plurality of muscle activity feedback signals are based on two or more muscles from the group consisting of flexor carpi radialis, flexor capri ulnaris, biceps, triceps, anterior deltoid and middle deltoid

19. The method of claim 14, wherein the plurality of muscle activity feedback signals are based on:

at least a first signal from an upper limb indicative of movement from one or more of a trapezius, deltoid, biceps brachii, triceps, flexor/extensor carpi radialis, flexor/extensor digitorum, and flexor/extensor pollicis brevis; and

at least a second signal from a lower limb indicative of movement from one or more of a gluteus maximus, quadriceps femoris, anterior compartment of the leg, quadriceps femoris, foot inverters and evertors, biceps femoris, semitendinosus and semimembranosus.

20. The method of claim 14, wherein detecting patient motor activity comprises mechanical feedback from a robotic or exoskeleton apparatus.

21. The method of claim 14, wherein stimulating a vagus nerve comprises stimulating an auricular branch of the vagus nerve.

22. The method of claim 14, wherein the minimum threshold criteria comprises one or more of a minimum signal amplitude, a minimum signal frequency, a minimum signal duration, a comparison to a model signal, a comparison to a preset value, and a comparison to a previously measured signal.

23. The method of claim 14, wherein delivery of the stimulation is synchronized with a detected motion with a delay of 100ms or less.

24. The method of claim 14, wherein the stimulation comprises an electrical intensity greater than 0mA and up to 10mA, a frequency of greater than 0Hz and up to 100Hz, and a pulse width greater than 0 μ s and up to 500 μ s.

25. The system of claim 14, wherein the stimulation comprises an electrical intensity greater than 0.5mA and up to 5mA, a frequency of greater than 10Hz and up to 25Hz, and a pulse width greater than 100 μ s and up to 250 μ s.

26. The method of claim 14, wherein the stimulation is delivered to an anterior wall of an outer ear canal.

27. The method of claim 14, wherein the minimum threshold criteria comprises an EMG motor evoked potential of at least 50 μ V.

28. The method of claim 14, wherein the minimum threshold criteria is a minimum threshold for contraction.

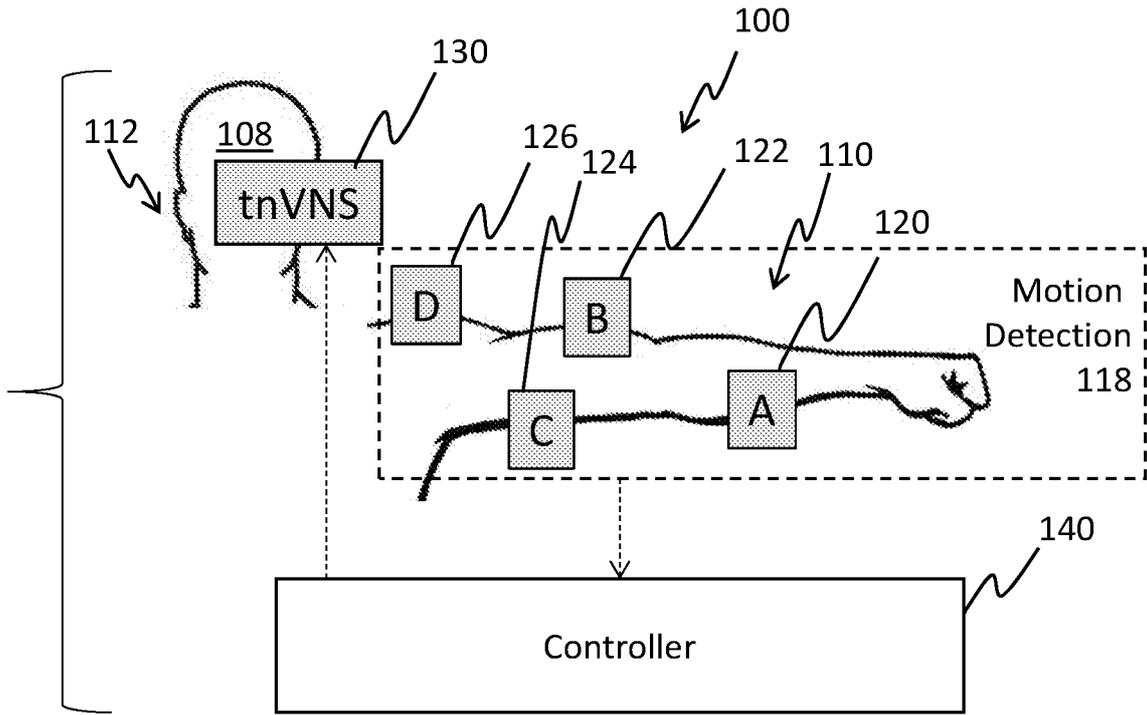


FIG. 1

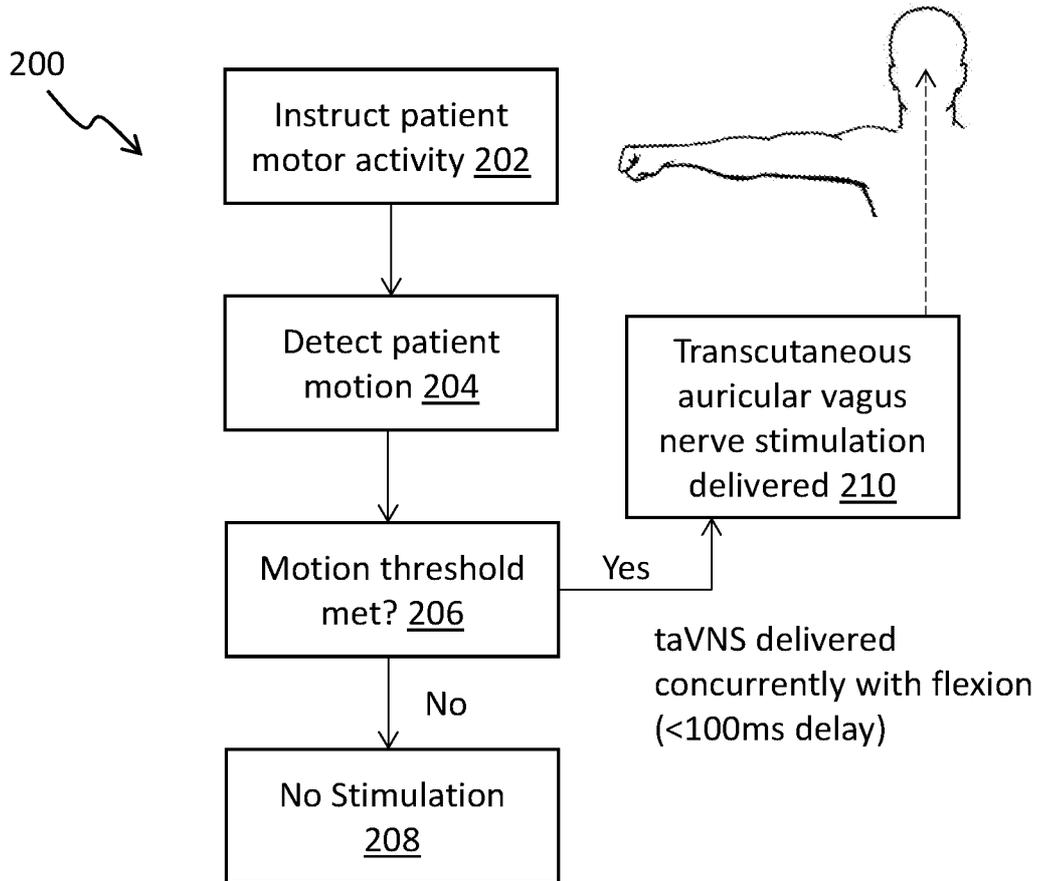


FIG. 2

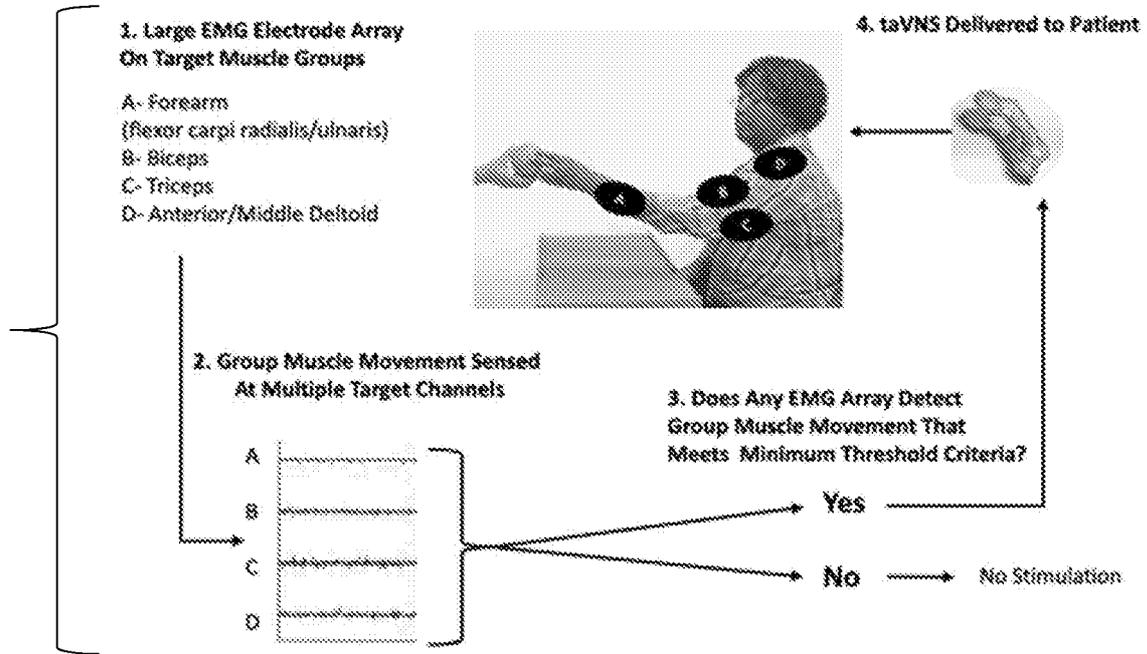


FIG. 3



FIG. 4

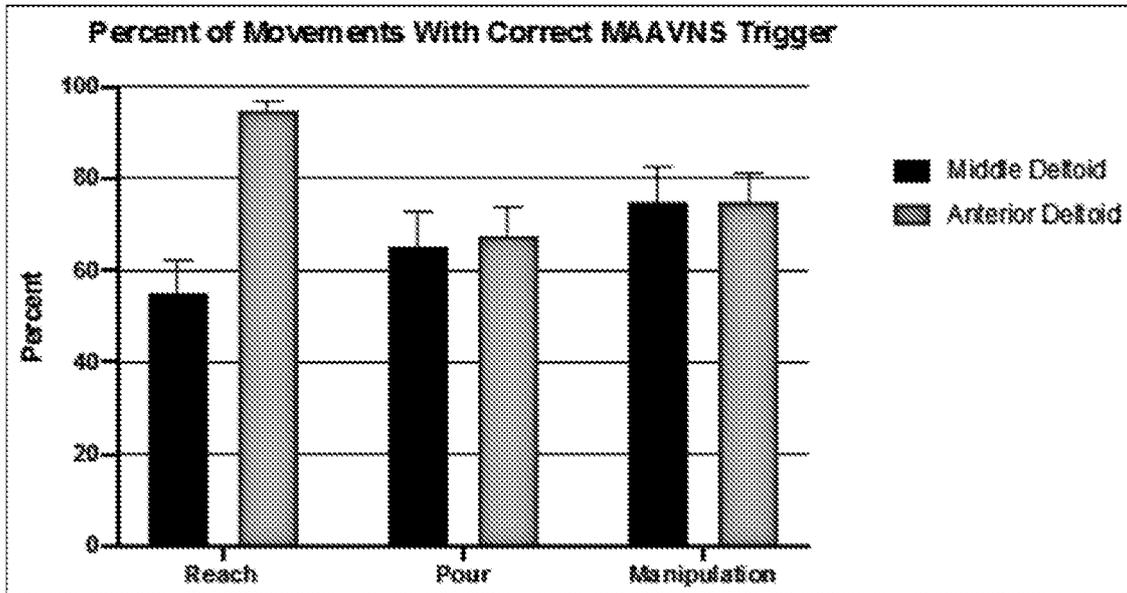


FIG. 5A

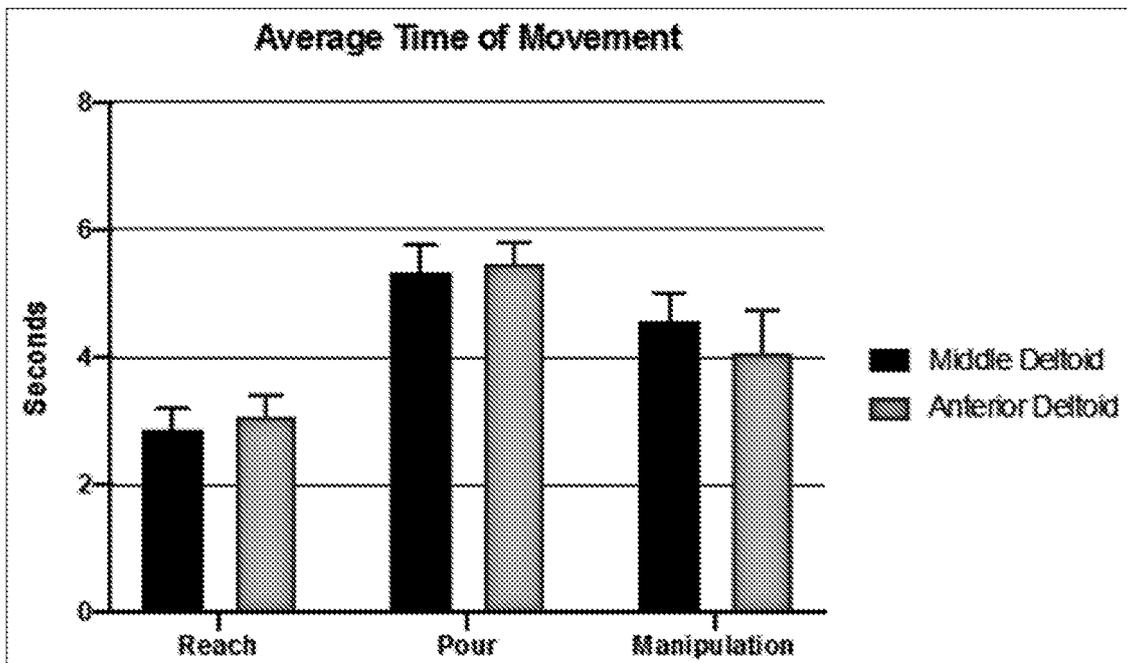


FIG. 5B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/40121

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61N 1/36 (2020.01)

CPC - A61N 1/36135

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/109633 A1 (COGNIGUARD MEDICAL HOLDINGS LIMITED); 21 June 2018 (21.06.2018); entire document, especially Fig. 1; Abstract; pg. 6, ln 26-pg. 7, ln 35; pg. 8, ln 5-15.	1-2, 6-8, 14, 21-22, 26
X -- Y	US 2015/0073493 A1 (MICROTRANSPONDER, INC); 12 March 2015 (12.03.2015); entire document, especially Fig. 14; para. [0040], [0096]-[0098], [0102], [0134].	1-5 ----- 17, 23
X -- Y -- A	US 2010/0339238 A1 (AHMED et al.); 24 November 2016 (24.11.2016); entire document, especially Fig. 18B; para. [0082], [0123], [0140].	1, 12-15, 24-25, 27-28 ----- 9-10, 16-18, 23 ----- 11, 19-20
Y	US 2012/0083700 A1 (OSORIO); 5 April 2012 (05.04.2012); entire document, especially Abstract, para. [0001], Table 1.	9, 16
Y -- A	US 2008/0234781 A1 (EINAV et al.); 25 September 2008 (25.09.2008); entire document, especially Abstract, para. [0050].	9-10, 16-18 ----- 11, 19
A	WO 2014/136852 A1 (KURUME UNIVERSITY); 12 September 2014 (12.09.2014); entire document, Fig. 2.	20

Further documents are listed in the continuation of Box C, See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date of priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance.	"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
"D" document cited by the applicant in the international application	"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
"E" earlier application or patent but published on or after the international filing date.	"&" document member of the same patent family
"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(s) 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	

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2020	3 0 SEP 2020

Name and mailing address of the ISA/US; Mail Stop, PCT, Attn.: ISA/US, Commissioner for Patents; P.O. Box 1450, Alexandria, Virginia 22313-1450) Facsimile No. 571-273-8300)	Authorized officer: Lee Young) Telephone No. PCT Helpdesk: 571-272-4300)
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