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stone Lane, Richardson, TX 75080 (US). **ROSELLINI, Will** [US/US]; 12147 Leuders Lane, Dallas, TX 75230 (US).

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(74) Agent: **CAIN, David, C.**; Microtransponder, Inc., P.O. Box 863387, Plano, TX 75086 (US).

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(71) Applicants (for all designated States except US): **MI-CRO TRANSPONDER INC.** [US/US]; 12147 Leuders Lane, Dallas, TX 75230 (US). **BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM** [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KILGARD, Michael** [US/US]; 205 Crooked Creek, Richardson, TX 75080 (US). **CAULLER, Larry** [US/US]; 205 Crooked Creek, Richardson, TX 75080 (US). **ENGINEER, Nazer** [IN/US]; 6201 Chapel Hill Blvd., #2013, Plano, TX 75093 (US). **MCINTYRE, Christa** [US/US]; 911 Fire-

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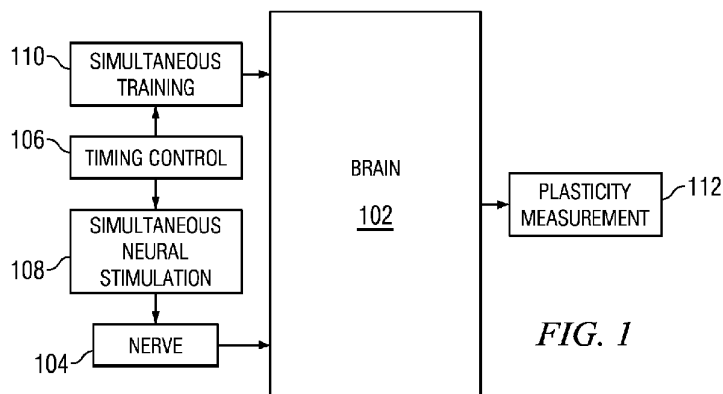


FIG. 1

(57) Abstract: The present application claims priority benefits under 35 U.S. C. § 119(e) from U.S. Provisional Application No. 61/077,648, filed on July 2, 2008 and entitled "Treatment of Tinnitus with Vagus Nerve Stimulation"; U.S. Provisional Application No. 61/078,954, filed on July 8, 2008 and entitled "Neuroplasticity Enhancement"; U.S. Provisional Application No. 61/086,116, filed on August 4, 2008 and entitled "Tinnitus Treatment Methods and Apparatus"; and U.S. Provisional Application No. 61/149,387, filed on February 3, 2009 and entitled "Healing the Human Brain: The Next Medical Revolution." The present application incorporates the foregoing disclosures herein by reference. Background: The present disclosure relates generally to therapy, rehabilitation and training including induced plasticity. More particularly, the disclosure relates to methods and systems of enhancing therapy, rehabilitation and training using nerve stimulation paired with training experiences.



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SYSTEMS, METHODS AND DEVICES FOR PAIRED PLASTICITY**PRIORITY CLAIM**

[0001] The present application claims priority benefits under 35 U.S.C. § 119(e) from U.S. Provisional Application No. 61/077,648, filed on July 2, 2008 and entitled “Treatment of Tinnitus with Vagus Nerve Stimulation”; U.S. Provisional Application No. 61/078,954, filed on July 8, 2008 and entitled “Neuroplasticity Enhancement”; U.S. Provisional Application No. 61/086,116, filed on August 4, 2008 and entitled “Tinnitus Treatment Methods and Apparatus”; and U.S. Provisional Application No. 61/149,387, filed on February 3, 2009 and entitled “Healing the Human Brain: The Next Medical Revolution.” The present application incorporates the foregoing disclosures herein by reference.

Background

[0002] The present disclosure relates generally to therapy, rehabilitation and training including induced plasticity. More particularly, the disclosure relates to methods and systems of enhancing therapy, rehabilitation and training using nerve stimulation paired with training experiences.

SUMMARY

[0003] For purposes of summarizing the invention, certain aspects, advantages, and novel features of the invention have been described herein. It is to be understood that not necessarily all such advantages may be achieved in accordance with any particular embodiment of the invention. Thus, the invention may be embodied or carried out in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other advantages as may be taught or suggested herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] The disclosed inventions will be described with reference to the accompanying drawings, which show important sample embodiments of the invention and which are incorporated in the specification hereof by reference, wherein:

[0005] Figure 1 is a block diagram depicting a paired training system, in accordance with an embodiment;

[0006] Figure 2 is a block diagram depicting a paired training system affecting a sub-cortical region, in accordance with an embodiment;

[0007] Figure 3 is a block diagram depicting a paired training system affecting the nucleus basalis, in accordance with an embodiment;

[0008] Figure 4 is a block diagram depicting a paired training system affecting the locus coeruleus, in accordance with an embodiment;

[0009] Figure 5 is a block diagram depicting a paired training system affecting the amygdala, in accordance with an embodiment;

[0010] Figure 6 is a block diagram depicting a paired training system affecting the nucleus of the solitary tract (NTS), in accordance with an embodiment;

[0011] Figure 7 is a block diagram depicting a paired training system affecting the cholinergic system, in accordance with an embodiment;

[0012] Figure 8 is a block diagram depicting a paired training system affecting the noradrenergic system, in accordance with an embodiment;

[0013] Figure 9 is a simplified diagram depicting a stimulator, in accordance with an embodiment;

[0014] Figure 10 is a simplified diagram depicting a wireless stimulator, in accordance with an embodiment;

[0015] Figure 11 is a simplified diagram depicting a dual stimulator configuration, in accordance with an embodiment;

[0016] Figure 12 is a simplified diagram depicting a multi-stimulator configuration, in accordance with an embodiment;

[0017] Figure 13 is a graph depicting a constant current stimulation pulse, in accordance with an embodiment;

[0018] Figure 14 is a graph depicting an exponential stimulation pulse, in accordance with an embodiment;

[0019] Figure 15 is a graph depicting a train of constant current stimulation pulses, in accordance with an embodiment;

[0020] Figure 16 is a block diagram depicting a synchronizing control system, in accordance with an embodiment;

[0021] Figure 17 is a graph depicting synchronized pairing, in accordance with an embodiment;

[0022] Figure 18 is a block diagram depicting a response control system, in accordance with an embodiment;

[0023] Figure 19 is a graph depicting response pairing, in accordance with an embodiment;

[0024] Figure 20 is a block diagram depicting a manual control system, in accordance with an embodiment;

[0025] Figure 21 is a graph depicting manual pairing, in accordance with an embodiment;

[0026] Figure 22 is a block diagram depicting a closed loop control system, in accordance with an embodiment;

[0027] Figure 23 is a graph depicting closed loop pairing, in accordance with an embodiment;

[0028] Figure 24 is a block diagram depicting an initiated control system, in accordance with an embodiment;

[0029] Figure 25 is a graph depicting initiated pairing, in accordance with an embodiment;

[0030] Figure 26 is a block diagram depicting a delayed response timing control system, in accordance with an embodiment; and

[0031] Figure 27 is a graph depicting delayed response pairing, in accordance with an embodiment.

DETAILED DESCRIPTION OF THE DRAWINGS

[0032] The numerous innovative teachings of the present application will be described with particular reference to presently preferred embodiments (by way of example, and not of limitation). The present application describes several inventions, and none of the statements below should be taken as limiting the claims generally. Where block diagrams have been used to illustrate the invention, it should be recognized that the physical location where described functions are performed are not necessarily represented by the blocks. Part of a function may be performed in one location while another part of the same function is performed at a distinct location. Multiple functions may be performed at the same location.

[0033] With reference to Figure 1, a paired training system is shown. A timing control system 106 is communicably connected to a neural stimulator system 108 and a training system 110. Receiving timing instruction from the timing control system 106, the neural stimulator system 108 provides stimulation to a nerve 104. Similarly receiving timing instruction from the timing control system 106, or providing timing instruction to the timing control system, the training system 110 generates desired mental images, ideas, formations or states in the brain 102. The stimulation of the nerve 104 affects the brain 102 by inducing plasticity. The temporally paired combination of training and stimulation generates manifestations of plasticity in the brain 102 that may be measured by a plasticity measure system 112.

[0034] The timing controls system 106 generally provides the simultaneous nature of the pairing. The stimulation and the training are simultaneous in that they occur at the same time, that is, there is at least some overlap in the timing. In some embodiments, the stimulation may lead the start of the training while in other embodiments, the stimulation may follow the start of the training. In many cases, the stimulation is shorter in duration than the training, such that the stimulation occurs near the beginning of the training. Plasticity resulting from stimulation has been shown to last minutes or hours, so a single stimulation pulse may suffice for the whole duration of extended training.

[0035] In the treatment of tinnitus, for example, the training may consist of brief audible sounds including selected therapeutic frequencies, paired with stimulations. Because the duration of the sounds may be short, the timing may be controlled very precisely so that the sound coincides temporally with the stimulation. This kind of precision may typically require some form of computer control. In other forms of rehabilitation or education, the timing of the training and/or the stimulation may be controlled manually. Further therapies and training may include training triggered timing or physical condition feedback to provide a closed-loop system.

[0036] The neural stimulation system 108 may provide stimulation of the nerve 104 using electrical stimulation, chemical stimulation, magnetic stimulation, optical stimulation, mechanical stimulation or any other form of suitable nerve stimulation. In accordance with an embodiment, an electrical stimulation is provided to the left vagus nerve. In an electrical stimulation system, suitable stimulation pulses may include a variety of waveforms, including constant current pulses, constant voltage pulses, exponential pulses or any other appropriate waveform. An electrical stimulation system may use a single stimulation pulse or a train of stimulation pulses to stimulate the nerve 104. Stimulation parameters are selected to affect the brain 102 appropriately, with reference to the affected brain regions or systems, plasticity measures, desynchronization or any other appropriate stimulation parameter measure. A half

second train of biphasic stimulation pulses, with a pulse width of 100 microseconds, at .8 milliamps and at 30 Hz has been used effectively in the treatment of tinnitus.

[0037] Paired stimulation could be accomplished using deep brain stimulation, cortical stimulation, transcranial magnetic stimulation and any other suitable neural stimulation.

[0038] One indication of appropriate stimulation may be desynchronization of the cortical EEG. A .8 milliamp pulse has been shown to cause cortical desynchronization at frequencies between 30 and 150 Hz. .4 milliamp pulses desynchronize the cortex at higher frequencies of 100 to 150 Hz. Desynchronization has been shown to last for at least four seconds in response to stimulation of the vagus nerve.

[0039] The simultaneous training system 110 generates the sensory input, motor sequences, cognitive input, mental images, ideas, formations or states that are to be retained by the brain 102. A training system 110 may provide sensory information, such as visual, auditory, olfactory, tactile or any other suitable sensory information. Training system 110 may include physical therapies, cognitive therapies, emotional therapies, chemical therapies, or any other suitable therapies. Training system 110 may present educational information. Training system 110 may include the subject, physically, mentally, emotionally or in any other suitable fashion. Training system 110 may include teachers, doctors, therapists, counselors, instructors, coaches or any other suitable training provider. Training system 110 may evoke specific patterns of neural activity by direct brain stimulation, for example by electrical, magnetic, optical, or any other suitable pattern evocation systems. Training system 110 may inactivate specific brain regions via chemical agents, cooling, magnetic stimulation, or other suitable methods.

[0040] The paired training system of Figure 1 affects the brain 102 to generate plasticity that can be measured by a plasticity measure system 112. In the treatment of tinnitus, a cortical map may be used to measure the map distortion and correction that accompanies the successful treatment of tinnitus. Less invasively, the plasticity can be measured by behaviorally reactions to stimuli, such as a startle test for tinnitus. Further, plasticity can be measured by inquiring about the subjective experience of a subject. If a tinnitus patient no longer experiences a persistent noise, plasticity has been measured.

[0041] With reference to Figure 2, a paired training system affecting a subcortical region 114 of the brain 102, in accordance with an embodiment is shown. The stimulation of nerve 104 affects a subcortical region 114. The subcortical region 114, in turn, affects the brain to induce plasticity. Stimulation of nerves 104 such as the trigeminal nerve and other cranial nerves are known to affect the subcortical region 114.

[0042] With reference to Figure 3, a paired training system affecting the nucleus basalis 116, in accordance with an embodiment, is shown. The stimulation of nerve 104 affects the nucleus basalis 116. The nucleus basalis, in turn, affects the brain 102 to induce plasticity.

[0043] With reference to Figure 4, a paired training system affecting the locus coeruleus 118, in accordance with an embodiment, is shown. The stimulation of nerve 104 affects the locus coeruleus 118. The locus coeruleus 118, in turn, affects the brain 102 to induce plasticity.

[0044] With reference to Figure 5, a paired training system affecting the amygdala 120, in accordance with an embodiment, is shown. The stimulation of nerve 104 affects the amygdala 120. The amygdala 120, in turn, affects the brain 102 to induce plasticity.

[0045] With reference to Figure 6, a paired training system affecting the NTS 122, in accordance with an embodiment, is shown. The stimulation of nerve 104 affects the NTS 122. The NTS 122, in turn, affects the brain 102 to induce plasticity.

[0046] With reference to Figure 7, a paired training system affecting the cholinergic system 124, in accordance with an embodiment, is shown. The stimulation of nerve 104 affects the cholinergic system 124. The cholinergic system 124 releases acetylcholine (ACh) into the brain 102 inducing plasticity.

[0047] With reference to Figure 8, a paired training system affecting the noradrenergic system 126, in accordance with an embodiment, is shown. The stimulation of nerve 104 affects the noradrenergic system 126. The noradrenergic system 126 releases noradrenaline (NE) into the brain 102 inducing plasticity.

[0048] With reference to Figure 9, a neural stimulator system, in accordance with an embodiment, is shown. A neural stimulator control 109 is communicably connected to a neurostimulator 128. Neurostimulator 128 provides a stimulation pulse to a nerve 104 via a pair of electrodes 130a and 130b. Electrodes 103a and 130b could be cuff electrodes, conductive plates or any other suitable neural stimulation electrode. The neurostimulator may be powered by a piezoelectric powering system as well as near field inductive power transfer, far-field inductive power transfer, battery, rechargeable battery or any other suitable neurostimulator power system. When neural stimulator control 109 receives timing instructions from a timing control system (not shown), the neural stimulator control 109 initiates a stimulation pulse from the neurostimulator 128 via electrodes 130a and 130b.

[0049] With reference to Figure 10, a wireless neural stimulator system, in accordance with an embodiment is shown. Neurostimulator 128 communicates with the neural stimulation system 109 using an inductive transponder coil 132. The neural stimulator system 109 includes an external coil 134. Information may be communicated between the neural

stimulator system 109 and the neurostimulator 128. Power may be transferred to the neurostimulator 128 by the neural stimulator system.

[0050] With reference to Figure 11, a dual neurostimulator system, in accordance with an embodiment, is shown. Two neurostimulators 128 may stimulate neural 104. The neurostimulators may be controlled to reinforce each other, as redundancy, or to prevent efferent signals from projecting away from the brain.

[0051] With reference to Figure 12, a multi-neurostimulator system, in accordance with an embodiment, is shown. A plurality of neurostimulators 128 may stimulate nerve 104. The neurostimulators may be controlled to reinforce each other, as redundancy, or to prevent efferent signals from projecting away from the brain.

[0052] With reference to Figure 13, a graph shows a constant current stimulation pulse, in accordance with an embodiment.

[0053] With reference to Figure 14, a graph shows an exponential stimulation pulse, in accordance with an embodiment.

[0054] With reference to Figure 15, a graph shows a train of constant current stimulation pulses, in accordance with an embodiment.

[0055] With reference to Figure 16, a synchronized timing control system, in accordance with an embodiment, is shown. The synchronized timing control system includes a synchronizing timing control 186. The synchronizing timing control 186 is communicably connected to the neural stimulation system 108 and the training system 110. The synchronizing timing control 136 provides timing instructions to the neural stimulation system 108 and the training system 110 so that the stimulation and training occur simultaneously. In the treatment of tinnitus, the stimulation of the nerve may slightly precedes each training sound, to give the stimulation time to affect the brain when the training sound is presented. Further embodiments may include other suitable timing variations.

[0056] With reference to Figure 17, a graph shows a possible timing relationship between event and stimulation for a synchronized timing control system.

[0057] With reference to Figure 18, a response timing control system, in accordance with an embodiment, is shown. The response timing control system includes a response timing control 138. The response timing control 138 is communicably connected to the neural stimulation system 108 and a simultaneous event monitor 140. The response timing control 138 receives timing instructions from the event monitor 140 and provides timing instructions to the neural stimulation system 108, so that the stimulation and training occur simultaneously. Because the stimulation is generated in response to an event, the stimulation will generally lag

the event by some finite time Δt . In cases where there is an event precursor that can be monitored, the timing can be made more exact.

[0058] With reference to Figure 19, a graph shows a possible timing relationship between a monitored event and a nerve stimulation.

[0059] With reference to Figure 20, a manual timing control system, in accordance with an embodiment, is shown. The manual timing control system includes a response timing control 138. The response timing control 138 is communicably connected to the neural stimulation system 108 and a manual input 142. The response timing control 138 receives timing instructions from the manual input 142 and provides timing instructions to the neural stimulation system 108, so that the stimulation and training occur simultaneously.

[0060] With reference to Figure 21, a graph shows a possible timing relationship between an event, a manual input and a neural stimulation.

[0061] With reference to Figure 22, a closed loop timing control system, in accordance with an embodiment, is shown. The closed loop timing control system includes a closed loop timing control 144. The closed loop timing control 138 is communicably connected to the neural stimulation system 108 and a sensor 146. The closed loop timing control 144 receives timing instructions from the sensor 146 and provides timing instructions to the neural stimulation system 108, so that the stimulation and training occur simultaneously.

[0062] With reference to Figure 23, a graph shows a possible timing relationship between an sensed training event and a neural stimulation is shown.

[0063] Sensor 146 may monitor external or internal events, including heart-rate, blood pressure, temperature, chemical levels or any other parameter that may indicate a training event.

[0064] With reference to Figure 24, a initiated timing control system, in accordance with an embodiment, is shown. The initiated timing control system includes an initiated timing control 148. The initiated timing control 148 is communicably connected to a neural stimulation system 106 and an event generator 150. The initiated timing control 148 receives timing information from the neural stimulation system 106, indicating that a nerve has been stimulated. The initiated timing control 148 provides timing instructions to the event generator 150, such as a therapeutic sound generator connected by Bluetooth, such that the event generator 150 generates an event during the stimulation pulse.

[0065] With reference to Figure 25, a graph shows a possible timing relationship between a neural stimulation and an event generation.

[0066] With reference to Figure 26, a delayed response timing control system, in accordance with an embodiment, is shown. The delayed response timing control system

includes an delayed response timing control 152. The delayed response timing control 152 is communicably connected to a neural stimulation system 106 and a preliminary event sensor 154. The preliminary event sensor 154 detects a preliminary event that anticipates a pairing event. The delayed response timing control 148 receives timing information from the preliminary event sensor 154, indicating that a preliminary event has been detected. The delay response timing control 148 provides timing instructions to the neural stimulation system 106 to initiate nerve stimulation. In the depicted embodiment, the timing control 152 initiates the stimulation before the beginning of the pairing event, giving a negative delta t. A delay response timing system may initiate stimulation at the same time as the beginning of the pairing event, or after the beginning of the pairing event.

[0067] With reference to Figure 27, a graph shows a possible timing relationship between a neural stimulation, a preliminary event and a pairing event.

[0068] The plasticity induced by neural stimulation can be paired with a variety of therapies, rehabilitation, training and other forms of personal improvement. Each therapy acts as a training source. The specific timing requirements associated with each therapy are derived from the specifics of the therapy, such that the stimulation occurs during the training, and most effectively near the beginning of the training. Some possible therapies may include behavioral therapies such as sensory discrimination for sensory deficits, motor training for motor deficits, with or without robotic assistance and cognitive training/rehabilitation for cognitive deficits. Exercise and motor therapy could be paired to treat motor deficits arising from traumatic brain injury, stroke or Alzheimer's disease and movement disorders. Constraint induced therapy could be paired to help prevent the use of alternative strategies in order to force use of impaired methods. Speech therapy could be paired for speech and language deficits. Cognitive therapies could be paired for cognitive problems.

[0069] Sensory therapies, such as tones, could be paired to treat sensory ailments such as tinnitus. In treating tinnitus, the paired tones may be at frequencies distinct from the frequencies perceived by the tinnitus patient.

[0070] Exposure or extinction therapy could be paired to treat phobias or post-traumatic stress disorder.

[0071] Computer-based therapies such as FastForward for dyslexia, Brain Fitness Program Classic or Insight, could be paired to enhance their effects. Psychotherapy could be paired, as well as other therapeutic activities in the treatment of obsessive-compulsive disorder, depression or addiction.

[0072] Biofeedback therapy could be paired. For example, temperature readings or galvanic skin responses could be paired to treat anxiety or diabetes. An electromyograph could

be paired to improve motor control after brain spinal or nerve damage. A pneumograph could be paired to improve breathing control in a paralyzed patient. A real-time fMRI could be paired to improve pain control or treat OCD. An electrodermograph, EEG, EMG or electrocardiograph could be paired to treat disorders such as anxiety. An electroencephalograph could be paired to treat epilepsy. An hemoencephalography could be paired to treat migraines. A photoplethysmograph could be paired to treat anxiety. A capnometer could be paired to treat anxiety. Virtual reality therapy could be paired to treat disorders such as addiction, depression, anxiety or posttraumatic stress disorder. Virtual reality therapy could also be paired to enhance cognitive rehabilitation or performance. Drug therapies could be paired to treat a variety of conditions. Amphetamine-like compounds could be paired to enhance neuromodulators and plasticity. SSRI's could be paired to enhance neuromodulators and plasticity. MOA inhibitors could be paired to enhance neuromodulators and plasticity. Anti-coagulants could be paired to act as clot busters during acute stroke. Various drugs could be paired to stop spasm after nerve or brain damage such as Botulinum toxin, Lidocaine, etc. Small doses of drugs of abuse could be paired to extinguish cravings in addicts.

[0073] Hormone therapy could be paired. For example, progesterone, estrogen, stress, growth, or thyroid hormone, etc. could be paired to treat traumatic brain injury or Alzheimer's disease. Glucose therapy could be paired to treat anxiety. Electrical or magnetic stimulation of the central or peripheral nervous system could be paired. For example, transcranial magnetic stimulation could be used to enhance or reduce activity in a specific brain area and thereby focus the directed cortical plasticity. Transcutaneous electrical nerve stimulation could be paired to treat chronic pain, tinnitus and other disorders. Subcutaneous electrical nerve stimulation could be paired to treat chronic pain. Stem cell therapy could be paired to treat disorders such as Parkinson's disease. Gene therapy could be paired to treat conditions such as Down's syndrome, Huntington's disease or fragile X syndrome. Hyperbaric oxygen therapy could be paired to treat carbon monoxide poisoning

[0074] Multiple therapies could be paired simultaneously or sequentially.

[0075] None of the description in the present application should be read as implying that any particular element, step, or function is an essential element which must be included in the claim scope: THE SCOPE OF PATENTED SUBJECT MATTER IS DEFINED ONLY BY THE ALLOWED CLAIMS. Moreover, none of these claims are intended to invoke paragraph six of 35 USC section 112 unless the exact words "means for" are followed by a participle.

[0076] The claims as filed are intended to be as comprehensive as possible, and NO subject matter is intentionally relinquished, dedicated, or abandoned.

WHAT IS CLAIMED IS:

1. A therapeutic system comprises:
 - a neural stimulator providing stimulation to a nerve during a stimulation period;
 - a training source providing training during a training period; and
 - a timing control communicably connected to said neural stimulator and said training source, wherein said timing control instructs said neural stimulator to provide stimulation to a nerve so that the stimulation period is during said training period.
2. The system of claim 1, such that the stimulation period begins before the beginning of said training period.
3. The system of claim 1, such that the stimulation period begins after the beginning of said training period.
4. The system of claim 1, wherein said nerve is a vagus nerve.
5. The system of claim 1, wherein stimulation of said nerve affects the nucleus basalis.
6. The system of claim 1, wherein stimulation of said nerve affects the amygdala.
7. The system of claim 1, wherein said training comprises an audible sound.
8. The system of claim 1, wherein said training comprises visual information.
9. The system of claim 1, wherein said training comprises physical motion.
10. The system of claim 1, wherein said training comprises chemical therapy.

11. A method of training comprising:
 - providing training during a training period;
 - stimulating a nerve during a stimulation period, wherein said stimulation period occurs during said training period; and
 - producing measurable plasticity.
12. The method of claim 11, wherein said training is therapeutic.
13. The method of claim 11, wherein said training is educational.
14. The method of claim 11, wherein said nerve is stimulated electrically.
15. The method of claim 11, wherein said nerve is stimulated optically.

16. A stimulation pairing system comprises:
 - a neurostimulator providing stimulation to a nerve; and
 - a timing control communicably connected to said neurostimulator, wherein the timing control initiates stimulation of said nerve during a training period.
17. The system of claim 16, wherein said timing control is communicably connected to said neurostimulator by wires.
18. The system of claim 16, wherein said timing control is communicably connected to said neurostimulator by inductive coils.
19. The system of claim 16 wherein said stimulation is a train of .8 milliamp electrical pulses.
20. The system of claim 19 wherein said electrical pulses are at 30 Hz.

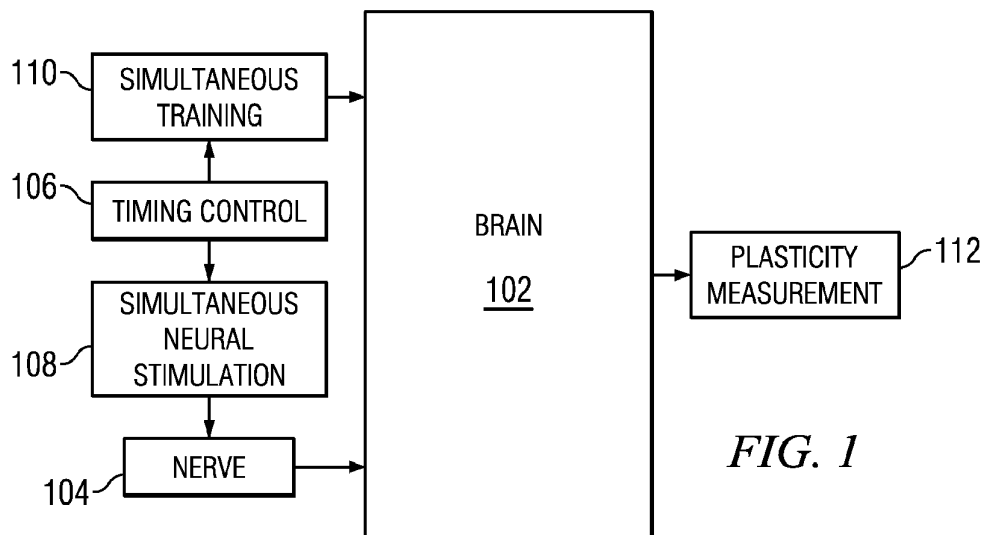


FIG. 1

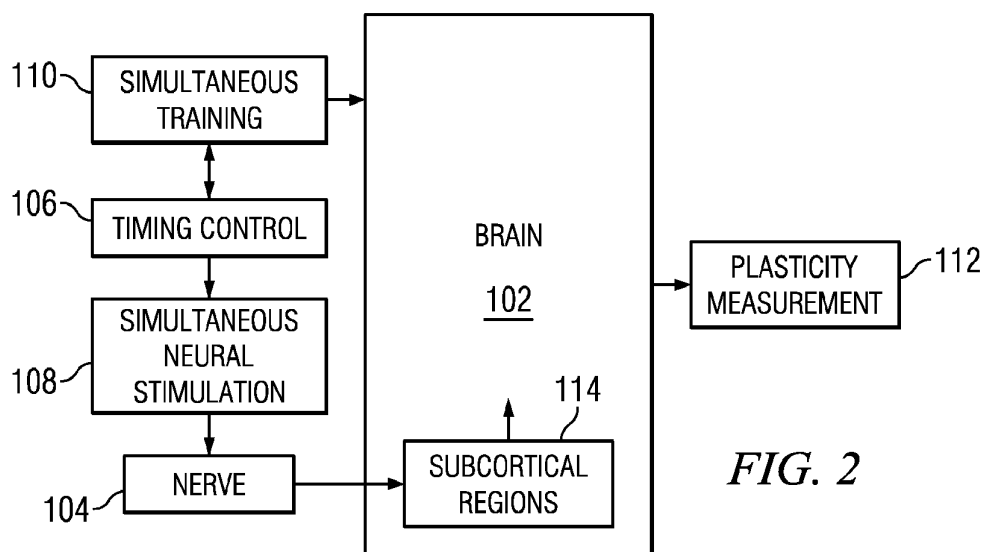


FIG. 2

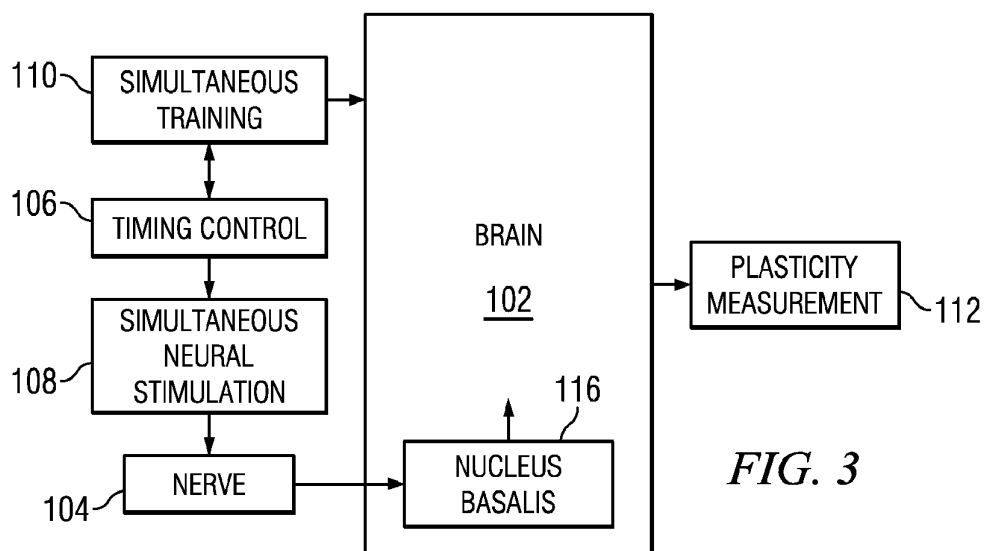


FIG. 3

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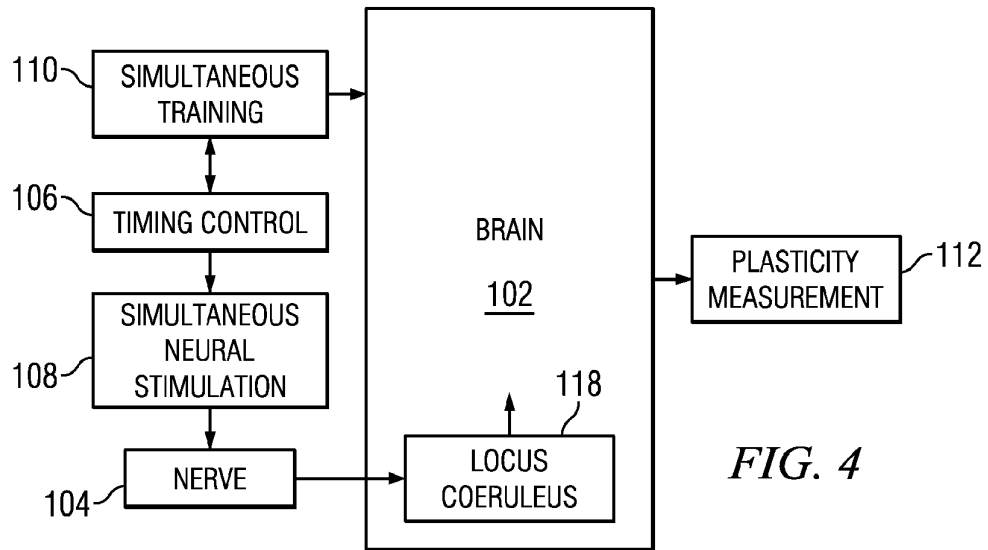


FIG. 4

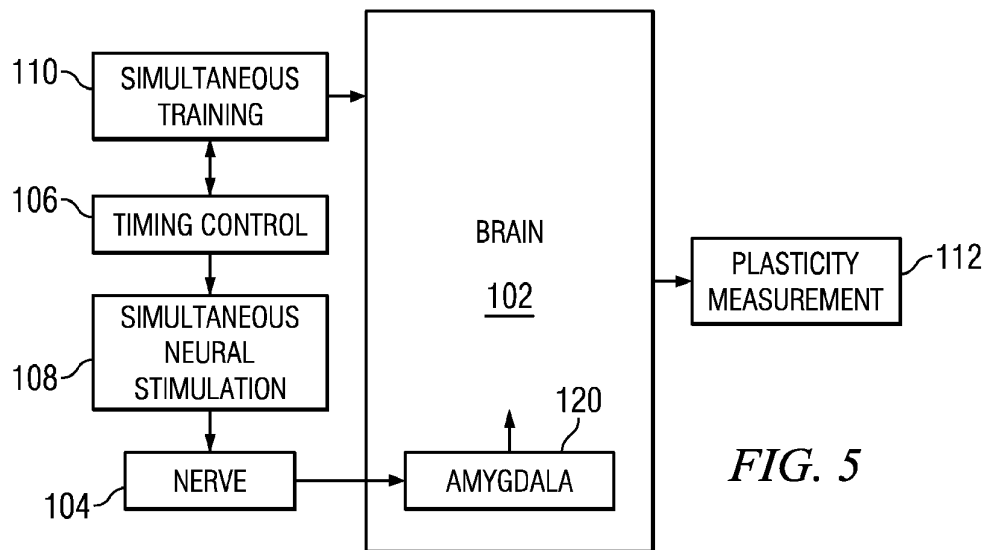


FIG. 5

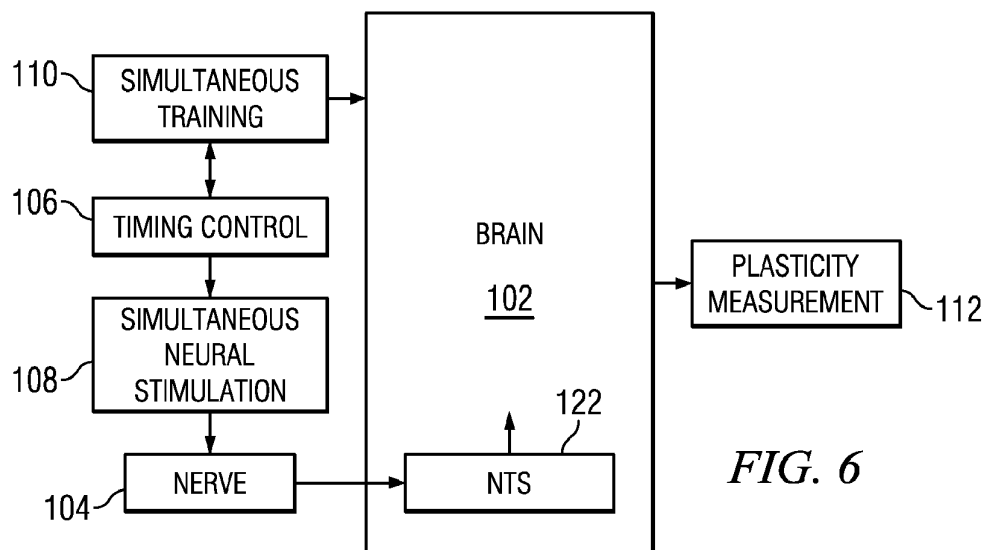


FIG. 6

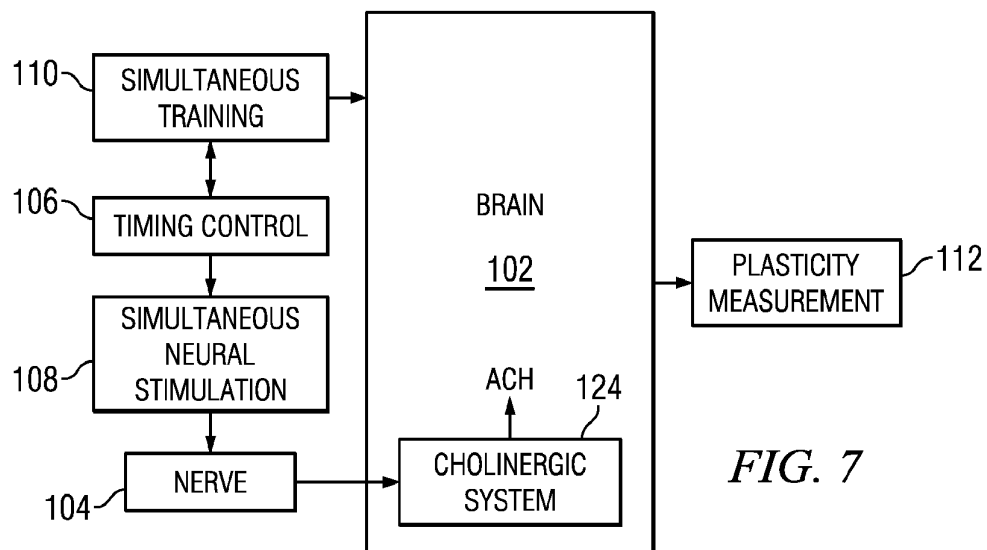


FIG. 7

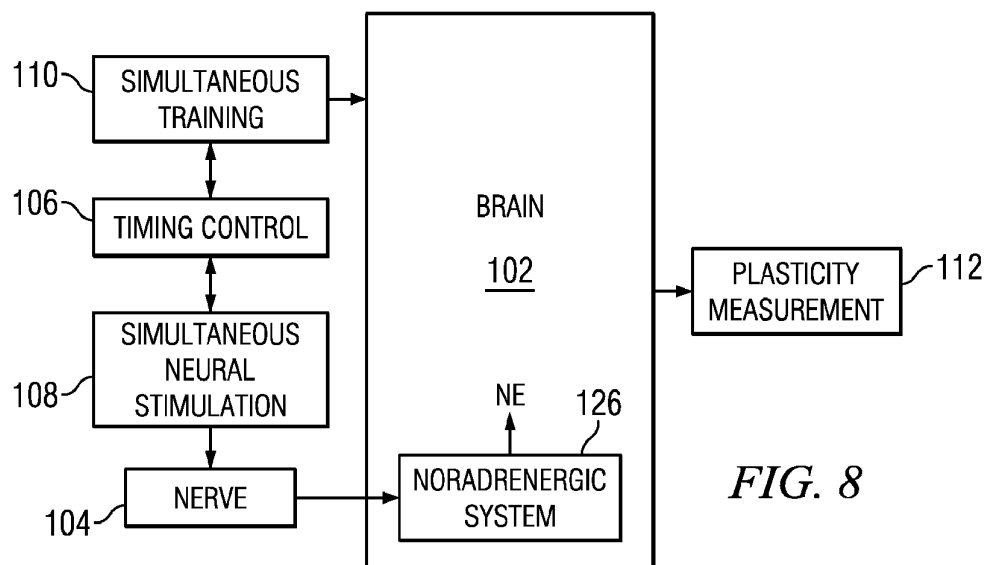


FIG. 8

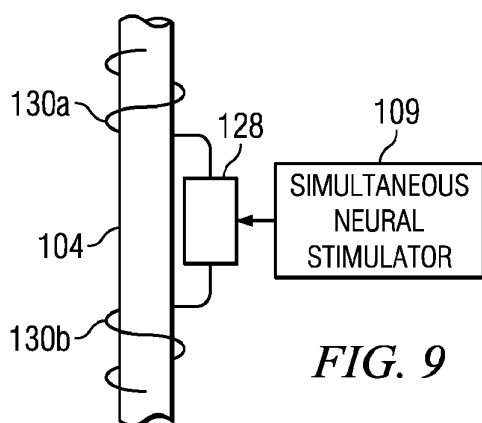


FIG. 9

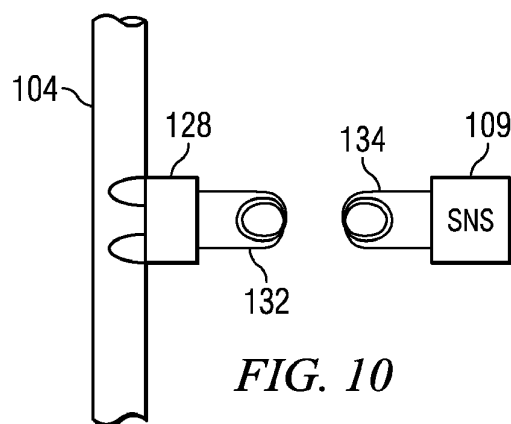
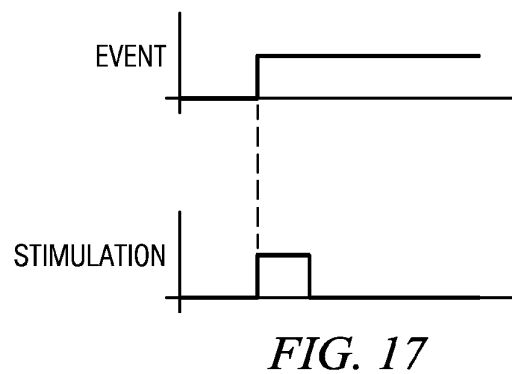
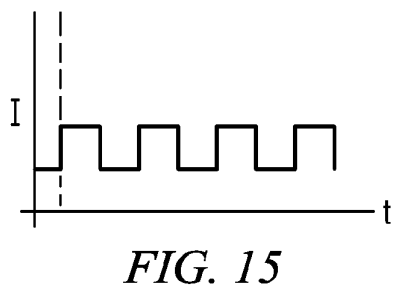
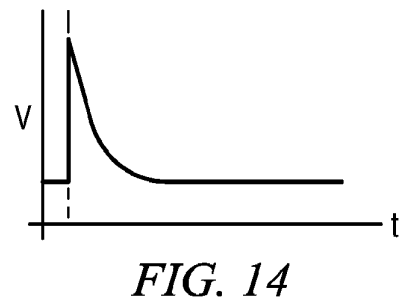
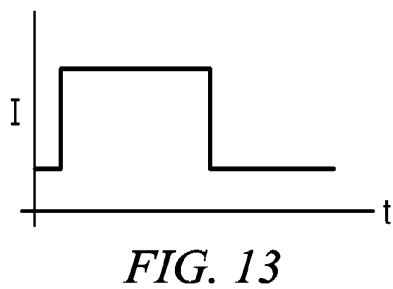
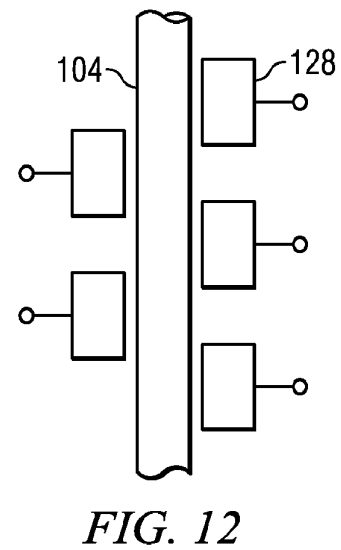
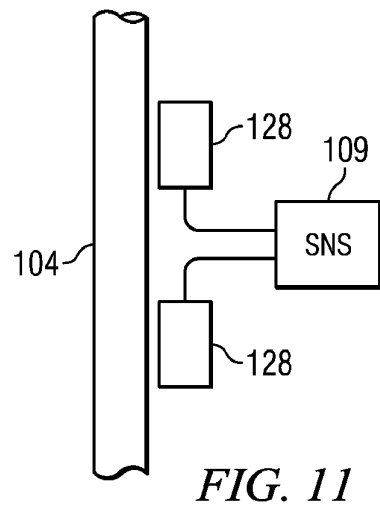
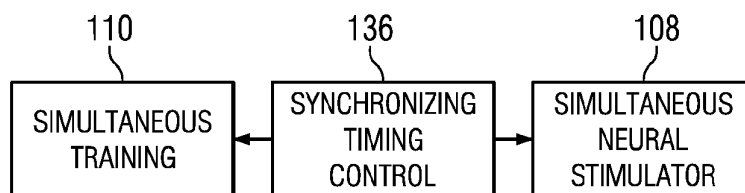
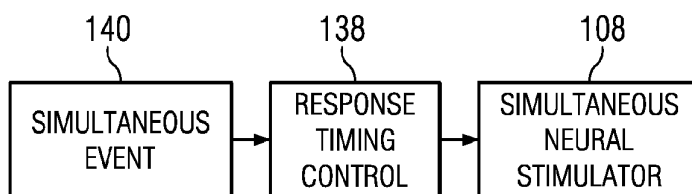
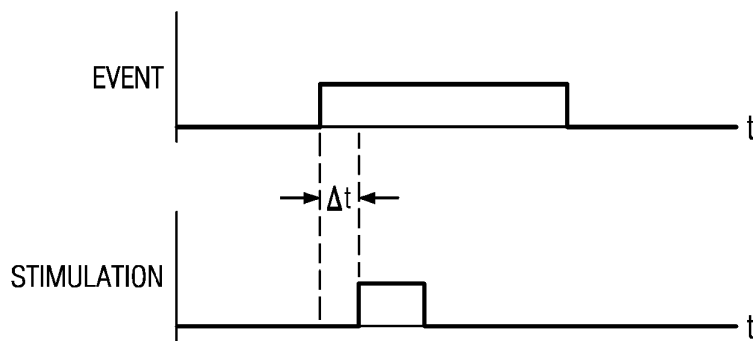
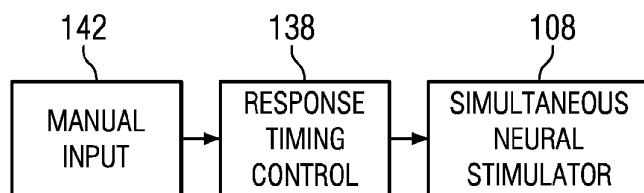
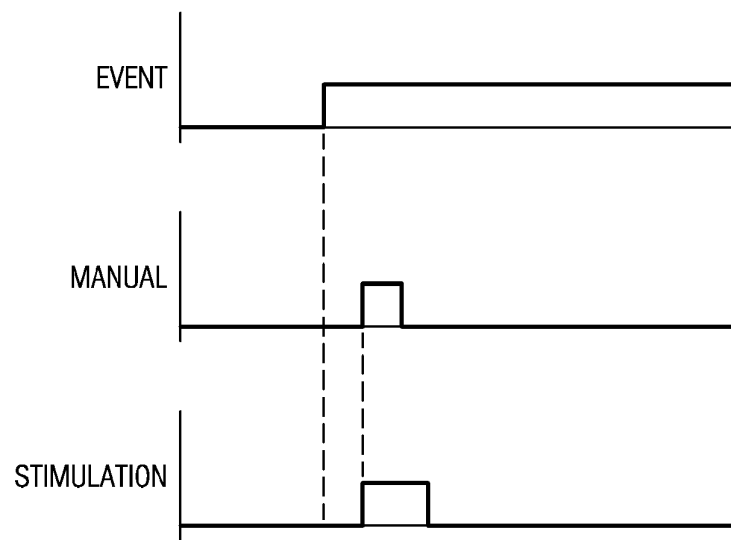
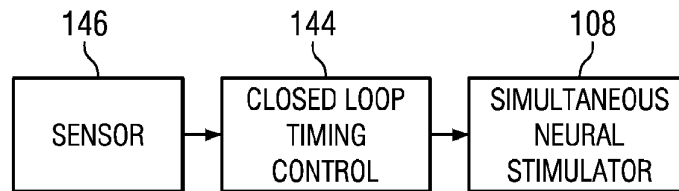
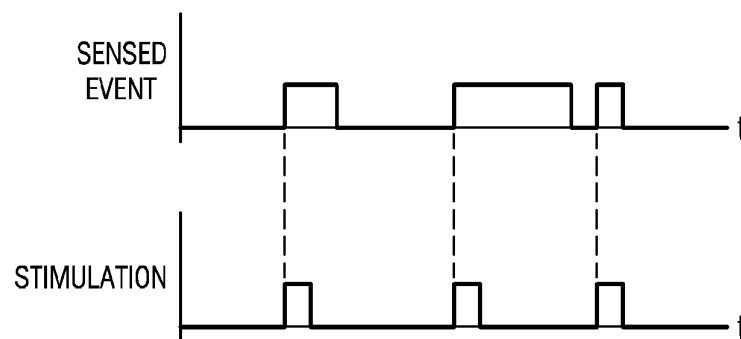


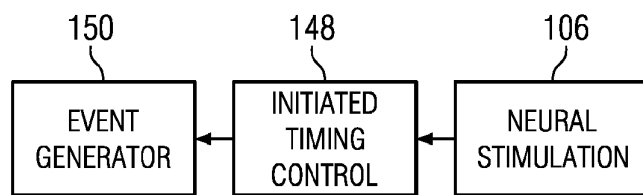
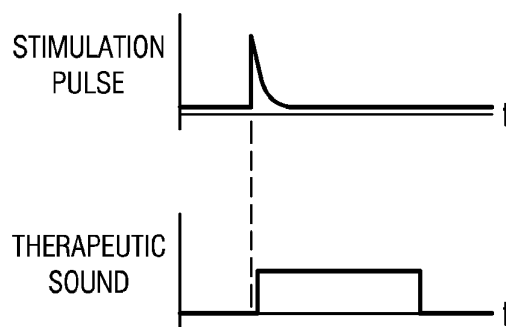
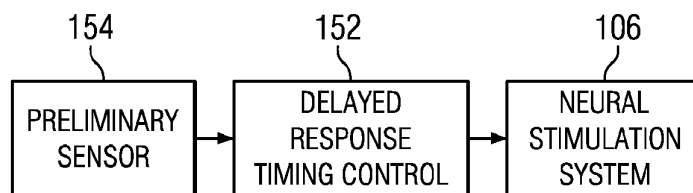
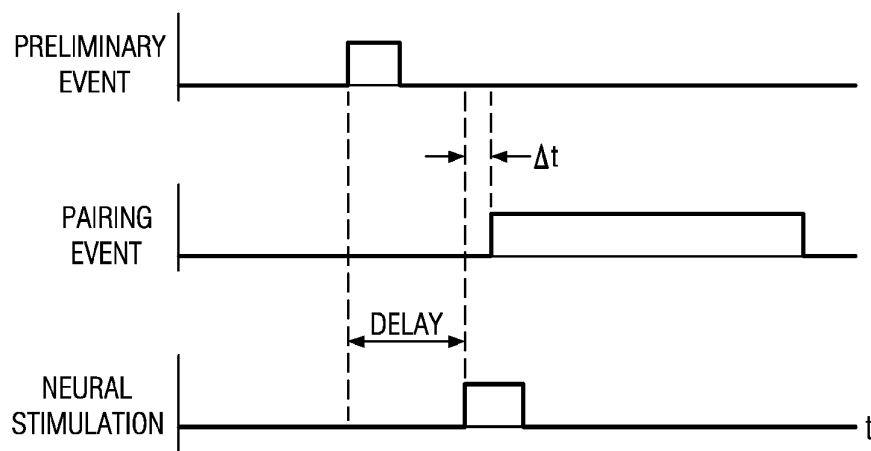
FIG. 10



*FIG. 16**FIG. 18**FIG. 19**FIG. 20*

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*FIG. 21**FIG. 22**FIG. 23*

*FIG. 24**FIG. 25**FIG. 26**FIG. 27*