

**DEVICES AND SYSTEMS FOR NEURAL, VISUAL, AUDITORY, OR HAPTIC
STIMULATION AND METHODS OF USING THE SAME****CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/618,268 filed on January 5, 2024, which is incorporated by reference in its entirety.

BACKGROUND

[0002] Neural oscillation occurs in humans or animals and includes rhythmic or repetitive neural activity in the central nervous system. Neural oscillations can be characterized by their frequency, amplitude, and phase. Neural oscillations of the gamma waveform frequency specifically control the connectivity between different brain regions, which is crucial for perception, movement, memory, and emotion. Studies have linked abnormal gamma oscillations to conditions of the central nervous system, including Alzheimer's disease, Parkinson's disease, and schizophrenia. The present disclosure provides systems, devices, and methods of restoring normal gamma oscillations in brain regions of a subject by applying a non-invasive therapeutic stimulus with a gamma waveform frequency, thereby benefiting a cognitive state or function of a brain of a subject.

SUMMARY

[0003] The present disclosure provides systems, methods, and devices for neurostimulation.

[0004] In one aspect, provided herein is a portable neurostimulation system for use by a subject in need thereof, said portable system comprising: a) a first stimulus emitting component comprising a visual source configured to emit a visual stimulus having a frequency of about 20 Hz to about 60 Hz; and b) a second stimulus emitting component comprising an audio source configured to emit an auditory stimulus having a frequency of about 20 Hz to about 60 Hz, wherein said visual source and said audio source are operatively connected and comprised in a single headset device, and wherein said visual source is rotatable about said audio source. In some embodiments, use of said system induces gamma oscillations in a brain region of said subject, thereby slowing progression of a mild cognitive impairment or dementia in said subject. In some embodiments, said visual source comprises a light emitting diode that projects said visual stimulus towards a screen, wherein the visual stimulus comprises light pulses. In some embodiments, said visual source comprises a light emitting diode driver. In some embodiments, said audio source comprises a set of headphones. In some embodiments, said audio source comprises supra-aural headphones. In some embodiments, said supra-aural headphones further comprise a removable headband configured to secure said portable system to said head of said subject. In some embodiments, said light pulses have a frequency of about 40 Hz to about 60 Hz. In some embodiments, said light pulses have a frequency of about 35 Hz to about 45 Hz. In some

embodiments, said light pulses have a frequency of about 40 Hz. In some embodiments, said auditory stimulus has a frequency of about 40 Hz to about 60 Hz. In some embodiments, said auditory stimulus has a frequency of about 35 Hz to about 45 Hz. In some embodiments, said auditory stimulus has a frequency of about 40 Hz. In some embodiments, said visual source comprises glasses. In some embodiments, said glasses comprise a lens that is not opaque. In some embodiments, said lens comprises a translucent lens. In some embodiments, said lens comprises a transmittance of about 0% to about 100%. In some embodiments, said portable system further comprises a third stimulus emitting component comprising a haptic source, wherein said haptic source produces a haptic stimulus. In some embodiments, said haptic stimulus has a frequency of about 40 Hz to about 60 Hz. In some embodiments, said haptic stimulus has a frequency of about 35 Hz to about 45 Hz. In some embodiments, said haptic stimulus has a frequency of about 40 Hz. In some embodiments, said haptic stimulus comprises a vibration. In some embodiments, said portable system further comprises an input device comprising a hand-held controller. In some embodiments, said hand-held controller receives and transmits a signal dictating a dosing parameter corresponding to a frequency of said visual stimulus, a duration of said visual stimulus, a brightness of said visual stimulus, a color of said visual stimulus, a duration of said audio or haptic stimulus, an intensity of said audio or haptic stimulus, a frequency of said audio or haptic stimulus, or any combination thereof. In some embodiments, said hand-held controller further comprises an independent power supply comprising batteries. In some embodiments, said hand-held controller further comprises a rechargeable battery. In some embodiments, said hand-held controller is operably connected to receive and transmit said signal to said portable system using Wi-Fi or Bluetooth signals. In some embodiments, said portable system further comprises adjustable inputs. In some embodiments, said adjustable input for said portable system comprises an input for powering on and powering off said portable system. In some embodiments, said adjustable input for said portable system comprises an input for pausing said visual, haptic, or audio stimulus. In some embodiments, said portable system further comprises adjustable inputs for said audio source. In some embodiments, said adjustable inputs for said audio source comprise an adjustable volume input. In some embodiments, said portable system further comprises adjustable inputs for said haptic source. In some embodiments, said adjustable inputs for said haptic source comprise an adjustable intensity input. In some embodiments, said portable system further comprises adjustable inputs for said visual source. In some embodiments, said adjustable inputs for said visual source comprise an adjustable brightness input. In some embodiments, said hand-held controller comprises said adjustable inputs. In some embodiments, said visual source comprises said adjustable inputs. In some embodiments, said visual source comprising said adjustable inputs comprises a pair of

glasses. In some embodiments, said single headset device provides improved comfort, portability, patient adherence, ease of use, or cognitive function of said subject's brain as compared to a portable system for benefiting a cognitive state or function of a brain of a subject comprising a visual source and an audio source that are not operatively configured to comprise a single headset device. In some embodiments, said portable system further comprises a rechargeable battery. In some embodiments, said portable system further comprises a base. In some embodiments, said base is configured to house said portable system and a hand-held controller. In some embodiments, said base is configured to provide a charge for said rechargeable battery of said portable system and a hand-held controller. In some embodiments, use of said system slows progression of a neurological disease. In some embodiments, said neurological disease is Alzheimer's disease. In some embodiments, said neurological disease is Parkinson's disease. In some embodiments, said neurological disease is dementia. In some embodiments, said portable system is configured to transmit data to a clinician. In some embodiments, said data comprises records of said subject's use of the portable system, dosing parameters used by said subject, said subject's cognitive state or function, or a combination thereof. In some embodiments, said system further comprises: c) a processor; d) a memory device; and e) a feedback sensor, wherein said processor receives an indication of a physiological assessment, cognitive assessment, neural assessment, or physical assessment of said subject through said feedback sensor and instructs said first stimulus-emitting component, said second stimulus-emitting component, or said third stimulus-emitting component based on said indication to adjust at least one parameter associated with said auditory, visual, or haptic stimulus. In some embodiments, said adjustment of at least one parameter associated with said auditory, visual, or haptic stimulus comprises an adjustment that induces gamma oscillations in a brain region of said subject. In some embodiments, said physical assessment of said subject involves ascertaining at least one of said subject's: compliance with proper use and positioning of said system, eye status, alert or sleep status, or environment and surroundings. In some embodiments, said neural assessment of said subject is received using brain wave sensors, an electroencephalography (EEG) device, an electrooculography (EOG) devices, or a magnetoencephalography (MEG) device. In some embodiments, said cognitive assessment of said subject is obtained through questions posed to said subject, activities and tasks performed by said subject in response to a prompt, or behaviors exhibited by said subject. In some embodiments, said processor further instructs said stimulus-emitting component to lengthen or shorten a duration of stimulation in response to said indication of said physiological, cognitive, neural, and/or physical assessment. In some embodiments, said physical assessment of said subject is performed to determine hearing of said subject. In some embodiments, said system is used to treat, prevent, or mitigate cognitive

dysfunction in said subject. In some embodiments, use of said portable system comprises inducing one or more improvements in said brain region of said subject. In some embodiments, said one or more improvements comprises maintaining or improving cognitive function in said brain region of said subject. In some embodiments, said maintaining or improving cognitive function comprises maintaining or improving recognition, discrimination, spatial memory, working memory, attention, or a combination thereof. In some embodiments, said one or more improvements comprises maintaining or reducing tau phosphorylation in said brain region of said subject. In some embodiments, said one or more improvements comprises maintaining or reducing an amount of amyloid- β (A β) peptide in said brain region of said subject. In some embodiments, said one or more improvements comprises maintaining or reducing an amount of C-terminal fragments (CTFs) of amyloid precursor protein (APP) in said brain region of said subject. In some embodiments, said one or more improvements comprises maintaining or reducing cleavage of APP into CTFs and NTFs by β -secretase (BACE1) in said brain region of said subject. In some embodiments, said one or more improvements comprises maintaining or reducing cleavage of APP into CTFs and NTFs by γ -secretase in said brain region of said subject. In some embodiments, said one or more improvements comprises maintaining or reducing a number of endosomes in said brain region of said subject. In some embodiments, said one or more improvements comprises promoting clearance of A β peptide in said brain region of said subject. In some embodiments, said one or more improvements comprises increasing uptake of A β peptide by microglia in said brain region of said subject. In some embodiments, said dementia comprises Alzheimer's disease, vascular dementia, Lewy body dementia, Pick's disease, fronto-temporal dementia (FTD), AIDS dementia, age-related cognitive impairments, and age-related memory impairments. In some embodiments, said one or more improvements are increased by about 1% to about 100% in said subject as compared to a subject that does not use said portable system. In some embodiments, said brain region comprises an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof.

[0005] In one aspect, provided herein is a method comprising stimulating a subject with a visual, auditory, or haptic stimulus as disclosed herein generated by a portable system as disclosed herein, thereby inducing gamma oscillations in a brain region of said subject. In some embodiments, said gamma oscillations comprise synchronized gamma oscillations. In some embodiments, said visual, auditory, or haptic stimulus is administered at a frequency of about 20 Hz to about 60 Hz, about 30 Hz to about 60 Hz, about 30 Hz to about 50 Hz, or about 40 Hz. In

some embodiments, said visual, auditory, or haptic stimulus is administered to said subject for about 10 minutes, about 30 minutes, about 45 minutes, about 1 hour, or more than about 1 hour per day. In some embodiments, said visual, auditory, or haptic stimulus is administered to said subject at least once, twice, three times, or more than three times per day. In some embodiments, said subject comprises a mammal. In some embodiments, said mammal comprises a non-human primate. In some embodiments, said mammal comprises a human. In some embodiments, said method further comprises a) identifying an activity being performed by a subject; and b) administering said visual, auditory, or haptic stimulus to said subject during said activity to induce a gamma oscillation in a brain region of said subject.

[0006] In one aspect, provided herein is a method of benefiting a cognitive state or function of a brain of a subject, comprising providing a subject a portable system as disclosed herein, and stimulating said subject with a visual, auditory, or haptic stimulus as disclosed herein, wherein use of said system induces gamma oscillations in at least one brain region of said subject and causes an improvement in one or more cognitive functions of said subject's brain, thereby slowing progression of mild cognitive impairment or Alzheimer's disease in said subject. In some embodiments, said gamma oscillations comprise synchronized gamma oscillations. In some embodiments, said visual, auditory, or haptic stimulus is administered at a frequency of about 20 Hz to about 60 Hz, about 30 Hz to about 60 Hz, about 30 Hz to about 50 Hz, or about 40 Hz. In some embodiments, said visual, auditory, or haptic stimulus is administered to said subject for about 10 minutes, about 30 minutes, about 45 minutes, about 1 hour, or more than about 1 hour per day. In some embodiments, said visual, auditory, or haptic stimulus is administered to said subject at least once, twice, three times, or more than three times per day. In some embodiments, said subject comprises a mammal. In some embodiments, said mammal comprises a non-human primate. In some embodiments, said mammal comprises a human. In some embodiments, said method further comprises a) identifying an activity being performed by a subject; and b) administering said visual, auditory, or haptic stimulus to said subject during said activity to induce a gamma oscillation in a brain region of said subject.

INCORPORATION BY REFERENCE

[0007] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also “Figure” and “FIG.” herein), of which:

[0009] **FIGURE 1** illustrates a block diagram depicting a system for performing neuromodulation using a visual stimulus, in accordance with an embodiment.

[0010] **FIGURES 2A-2F** illustrate visual stimulus signals for neuromodulation, in accordance with some embodiments.

[0011] **FIGURES 3A-3C** illustrate fields of vision in which visual stimulus can be transmitted for brain entrainment, in accordance with some embodiments.

[0012] **FIGURES 4A-4C** illustrate devices configured to display visual stimulus for neuromodulation, in accordance with some embodiments.

[0013] **FIGURES 5A-5D** illustrate devices configured to display visual stimulus for neuromodulation, in accordance with some embodiments.

[0014] **FIGURES 6A AND 6B** illustrate devices configured to receive feedback to facilitate neuromodulation, in accordance with some embodiments.

[0015] **FIGURES 7A and 7B** schematically illustrate depict block diagrams of computing devices that can be operatively coupled to various embodiments disclosed herein.

[0016] **FIGURE 8** schematically illustrates a method for neuromodulation using a visual stimulus, in accordance with some embodiments.

[0017] **FIGURE 9** schematically illustrates a block diagram depicting a system for neuromodulating a subject using an auditory stimulus, in accordance with some embodiments.

[0018] **FIGURE 10A-10I** illustrate auditory stimuli for neuromodulation, in accordance with some embodiments.

[0019] **FIGURE 11A** illustrates an auditory stimulus generated using binaural beats, in accordance with some embodiments.

[0020] **FIGURE 11B** illustrates an auditory stimulus having isochronic tones, in accordance with some embodiments.

[0021] **FIGURE 11C** illustrates an auditory stimulus having a modulation technique including audio filters, in accordance with some embodiments.

[0022] **FIGURES 12A-12C** illustrate configurations of systems for neuromodulation using auditory stimulus, in accordance with some embodiments.

[0023] **FIGURE 13** illustrates a configuration for a system for room-based auditory stimulation for neuromodulation, in accordance with some embodiments.

[0024] **FIGURE 14** illustrates devices configured to receive feedback to facilitate neuromodulation using auditory stimulus, in accordance with some embodiments.

[0025] **FIGURE 15** schematically illustrates a method for performing brain entrainment using auditory stimulus, in accordance with some embodiments.

[0026] **FIGURE 16A** schematically illustrates a system for neuromodulation through peripheral nerve stimulation, in accordance with some embodiments.

[0027] **FIGURE 16B** schematically illustrates a system for neuromodulation using multiple modes of neuromodulating stimulus, in accordance with some embodiments.

[0028] **FIGURE 17A** schematically illustrates a system for neuromodulation using visual stimulus and auditory stimulus, in accordance with some embodiments.

[0029] **FIGURE 17B** schematically illustrates gamma oscillation inducing waveforms used for neuromodulation using visual stimulus and auditory stimulus, in accordance with some embodiments.

[0030] **FIGURE 18** schematically illustrates a method for neuromodulation using visual stimulus and auditory stimulus, in accordance with some embodiments.

[0031] **FIGURE 19** is an efficacy summary chart for the modified intent to treat (mITT) population, including p-values, difference, confidence intervals (CI), and a standardized estimate of efficacy based on the values.

[0032] **FIGURE 20** shows the separate means analysis, on the left, and the linear model analysis, on the right, of the Alzheimer's Disease composite score (ADCOMS) as optimized for mid and moderate Alzheimer's Disease (MADCOMS) for the sham and active treatment groups.

[0033] **FIGURE 21** shows the separate means analysis, on the left, and a linear model analysis, on the right, of the Alzheimer's Disease Assessment Scale–Cognitive Subscale 14 (ADAS-Cog14) values for the sham and active treatment groups.

[0034] **FIGURE 22** shows the separate means analysis, on the left, and a linear model analysis, on the right, of the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) values for the sham and active treatment groups.

[0035] **FIGURE 23** shows the separate means analysis, on the left, and a linear model analysis, on the right, of the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) scores for the sham and active treatment groups.

[0036] **FIGURE 24** shows the linear model analysis of the Mini-Mental State Examination (MMSE) score, as measured after six months of neuromodulation treatment (i.e., at the last time point).

[0037] **FIGURE 25** shows the linear model analysis of magnetic resonance imaging (MRI) results of whole brain volume value, on the left, and hippocampal volume, on the right, after six months of neuromodulation treatment.

[0038] **FIGURE 26** is a table depicting a summary of efficacy findings resulting from the human clinical trial, including p-values, treatment differences, CI values and the percentage of slowing of brain atrophy.

[0039] **FIGURE 27** shows graphs that demonstrate the observed improvement (panels **a** and **b**) in sleep quality as measured by a reduction in sleep fragmentation, expressed as a higher frequency longer rest durations, over a 24 week period of exemplary neuromodulation treatment for a first 12-week period of treatment (indicated by the line closest to the white arrow), and second 12-week period of treatment (indicated by the line furthest from the white arrow), in mild to moderate AD subjects. Panels **c** and **d** demonstrate the observed impact of the sham treatment on sleep quality as measured by a reduction in sleep fragmentation.

[0040] **FIGURES 28A-B** demonstrate power changes responsive to (40 Hz LED stimulus for 1 hour in an example embodiment showing 40 Hz steady state oscillation and enhanced alpha power during and following neuromodulation stimulus in a young healthy subject. FIGs. 28A-B both illustrate the time-frequency domain decomposition of EEG activity recorded over the occipital pole (Oz, channel-64) before, during and after 40 Hz gamma stimulation. The start and stop of gamma stimulation are marked with STIM ON and STIM OFF boundaries in FIGs. 28A-B. The **FIG. 28A** illustrates enhanced 40 Hz power during stimulation indicating steady-state visually evoked potential (SSVEP). The **FIG. 28B** shows alpha-power dynamics during eyes-open (EYO) and eyes-closed (EYC) conditions, and the enhanced alpha power both during eyes-open gamma stimulation, as well as following the one-hour 40 Hz gamma stimulation.

[0041] **FIGURES 29A-B** depict the composite global cognitive summary score as a function of average sleep fragmentation (**FIG. 29A**), and composite expression of genes enriched in aged microglia (**FIG. 29B**). The dotted lines show 95% confidence intervals of estimate.

[0042] **FIGURE 30** provides an oscilloscope capture of the visual (upper signal) and audio (lower signal) signals of an example gamma oscillation inducing waveform with fs equal to about 40 Hz, vd equal to about 50%, VD equal to about 50%; ft equal to about 7,000 Hz, and AD equal to about 0.57%.

[0043] **FIGURE 31** shows a schematic of some aspects and parameters characterizing stimulus audio and visual components of gamma oscillation inducing waveform as delivered respectively by Audio Stimulus Module (110; **FIG. 33**) and Visual Stimulus Module (120; **FIG. 33**) of Stimulus Delivery System (170; **FIG. 33**).

[0044] **FIGURE 32** demonstrates an overview of enrollment, treatment, and control for an example embodiment of neuromodulation treatment for improving sleep quality in mild to moderate AD subjects. Treatment was delivered to two thirds of the subjects (12) using 40 Hz frequency audio, and one third of subjects (6, “control”) at an alternate frequency.

[0045] **FIGURE 33** schematically illustrates a stimulus delivery system and analysis and monitoring system, said analysis and monitoring system comprising modules specific to sleep-related monitoring and/or analysis, in accordance with some embodiments.

[0046] **FIGURE 34** provides actigraphy data from 24 hours of activity levels (gray bar) over two days for a single example patient. This corresponds to 1501 in **FIG. 37**. The data was centered around 12 AM (indicated by double-sided arrow) along with a median filtered curve was generated. This corresponds to 1507 in **FIG. 37** (labeled with dotted arrows in **FIG. 34**). The horizontal axis of **FIG. 34** shows time of day, and the vertical axis is relative activity recorded on a wrist-worn actigraphic measuring device (arbitrary log scale). Calculated sleep periods (corresponding to 1508 in **FIG. 37**) along with individual sample rest periods (corresponding to 1509 in **FIG. 37**) are shown: with the top panel (a) showing an example pattern for frequent movements and short rest periods during sleep periods, and the bottom panel (b) showing an example pattern of less frequent movements and longer rest periods during sleep periods.

[0047] **FIGURE 35** provides example patterns of actigraphy (arbitrary units, see **FIG. 34**) over several days showing actigraphy (see gray lines; corresponding to 1501 in **FIG. 37**), and a smooth curve is superposed. A cutoff line (black) separates active versus rest periods (corresponding to 1505 in **FIG. 37**). Black squares represent initial estimation for the mid-night point (corresponding to 1507 in **FIG. 37**). The final assessment of the mid-night points is determined through optimization algorithm (corresponding to 1508 in **FIG. 37**).

[0048] **FIGURE 36** provides example cumulative distribution of rest periods from a single patient (corresponding to 1511 in **FIG. 37**). Data from a first example 12 weeks of neuromodulation treatment (dark gray, weeks 0-12) and a second example 12 weeks of neuromodulation treatment (light gray, weeks 12-24) is shown. In some embodiments, the distribution is characterized by an exponential distribution (corresponding to 1512 in **FIG. 37**). In some embodiments, an increase in the exponential decay constant represents an improvement in sleep quality (corresponding to 1513 in **FIG. 37**). In the present example, $\tau_{2} = 45 \text{ min}$, $\tau_{1} = 40 \text{ min}$, and $\tau_{\text{diff}} = 5 \text{ min} > 0$.

[0049] **FIGURE 37** schematically illustrates analysis steps responsive to actigraphy data, provided in some embodiments at least in part by Actigraphy Monitoring Module 130 (**FIG. 33**), in accordance with some embodiments. In some embodiments, analysis is directed at determining the cumulative distribution of rest periods for one or more subjects over a period of one or more

nighttime sleep periods (1511). In some embodiments, analysis is further directed at fitting an exponential distribution to the determined cumulative distribution (1512). In some embodiments, analysis is further directed at computing summary statistics or characteristic parameters for the fitted exponential distribution. In an exemplary embodiment, the exponential decay constant for the fitted exponential distribution is determined (1512; **FIG. 36**). In **FIG. 37**, terms in *italics* and in brackets refer to MATLAB (R2020a) APIs employed in the corresponding steps in an example embodiment, *e.g.*, “*medfilt1*” refers to 1-D median filtering. In some embodiments, alternate APIs, methods, or processes, with equivalent function can be employed (*e.g.*, Wolfram Language’s “ButterworthFilterModel” can be substituted for “butter”).

[0050] FIGURE 38 provides sample actigraphy recordings from a single patient, said sample actigraphy recording demonstrating the effect of neuromodulation treatment on sleep through recordings taken five consecutive nights prior to neuromodulation treatment, and five consecutive nights following neuromodulation treatment. The dark gray, horizontal bars below the X axis indicate continuous activity periods, with the continuous activity periods appearing significantly higher in the actigraphy recordings taken prior to neuromodulation treatment than the actigraphy recordings taken following neuromodulation treatment.

[0051] FIGURES 39A-B provides a cumulative distribution of rest and active durations in nighttime based on data pooled from all participants. The black squares indicate active periods, and the gray squares indicate rest periods. **FIG. 39A** shows the cumulative distribution using a log-linear scale, and **FIG. 39B** shows the cumulative distribution using a log-log scale.

[0052] FIGURES 40A-B shows graphs comparing the relative change in active durations, with the Y-axis indicating change relative to Weeks 1-12 during Weeks 13-24. The figures demonstrates a reduction in duration of active periods for the neuromodulation treatment group and, consequently, a reduction in sleep fragmentation leading to increased sleep quality. In contrast, the opposite effect was seen with the sham group, which is represented by the line closest to the gray arrow. **FIG. 40A** shows the relative change based on the duration of active periods, and **FIG. 40B** shows the normalized nighttime active durations, calculated by dividing the duration of each active period by the duration of the matching entire nighttime period.

[0053] FIGURE 41 shows the effect of neuromodulation treatment on maintenance of daytime activities, assessed by Activities of Daily Living (ADCS-ADL) scope. The graph shows that changes in daytime activities significantly improved in the neuromodulation treatment group and declined in the sham group. The X-axis compares the period from Week 1-12 and the period from Week 13-24. The Y-axis demonstrates the change in ADCS-ADL score during Weeks 13-24 relative to Weeks 1-12.

[0054] **FIGURE 42** schematically illustrates a proposed relationship between Alzheimer's disease and sleep dysfunction, in accordance with some embodiments. This figure is adapted from Wang, C. and D. M. Holtzman (2020). "Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors." *Neuropsychopharmacology* **45**(1): 104-120.

[0055] **FIGURE 43** provides a hand-held controller for adjusting parameters of the stimulus delivered by an operably coupled stimulus apparatus, in accordance with some embodiments. The features and advantages of the present solution will become more apparent from the detailed description set forth below when taken in conjunction with the drawings, in which like reference characters identify corresponding elements throughout. In the drawings, like reference numbers generally indicate like elements.

[0056] **FIGURE 44** provides the results on matter volume change from baseline (%) for treatment and control groups who received 40Hz gamma sensory stimulation therapy and sham sensory stimulation therapy, respectively, for a 6-month period. The dark gray boxes correspond to the Treatment group participants, and the light gray boxes correspond to the Placebo group participants. Error bars indicate standard error (SE).

[0057] **FIGURE 45** provides the T1-weighted image to T2-weighted images (T1w/T2w) ratio change in white matter (% change from baseline) for Placebo group participants (light gray) and Treatment group participants (dark gray) after receiving sham and 40Hz gamma sensory stimulation therapy, respectively, for a 6-month period.

[0058] **FIGURES 46A and 46B** provides measurements of volume change in white matter structures as a percent change relative to baseline. The Treatment group participants are indicated by dark gray, and the Placebo group participants' results are indicated in light gray. **FIGURE 46A** provides the results for entorhinal region, left cingulate lobe, parstriangularis region, cuneus region, lateral occipital region, postcentral region, left occipital lobe, left frontal lobe, left parietal lobe, occipital lobe, left temporal lobe and caudal middle frontal region (sorted in ascending order by p value) for the treatment group after 6 months of treatment. **FIGURE 46B** provides the results for the precentral region, paracentral region, lingual region, fusiform region, frontal lobe, rostral anterior cingulate region, inferior temporal region, right occipital lobe, parietal lobe, rostral middle frontal, precuneus region, medial orbitofrontal region and temporal lobe (sorted in ascending order by p value).

[0059] **FIGURES 47A and 47B** provides the T1w/T2w ratio change in white matter structures (% change from baseline) for Placebo and Treatment group participants after receiving sham and 40Hz gamma sensory stimulation therapy, respectively, for a 6-month period favors the treatment group. **FIGURE 47A** provides the results for the entorhinal region, parstriangularis region, postcentral

region, left parietal lobe, lateral occipital region, paracentral region, rostral middle frontal region, supramarginal region, precentral region, parietal lobe, right occipital lobe, fusiform region, occipital lobe, left frontal lobe, cuneus region, precuneus region, inferior parietal region, frontal lobe, lingual region, left occipital lobe, left temporal lobe, right parietal lobe and parsorbitalis region, with white matter structures sorted in ascending order by p value. **FIGURE 47B** provides the results for the right frontal lobe, caudal middle frontal region, rostral anterior cingulate region, superior frontal region, temporal lobe, medial orbitofrontal region, posterior cingulate region, superior parietal region, left cingulate lobe, superior temporal region, cingulate lobe and temporal pole region, with white matter structures sorted in ascending order by p value.

[0060] FIGURE 48 is a block diagram depicting a system for selecting dosing parameters of stimulation signals to induce synchronized neural oscillations in the brain of a subject in accordance with an embodiment.

[0061] FIGURE 49 is a block diagram of a subject profile that can be included in the system shown in **FIG. 26** in accordance with an embodiment.

[0062] FIGURE 50 is a graphical representation of adjusting a therapy session based on feedback collected during the therapy session.

[0063] FIGURE 51A is a flow diagram of a method for selecting dosing parameters of stimulation signals to induce synchronized neural oscillations in the brain of a subject in accordance with an embodiment.

[0064] FIGURE 51B is a flow diagram of a method for conducting a therapy session in accordance with an embodiment.

[0065] FIGURE 51C is a flow diagram of a method for counteracting distractions while applying a neural stimulus in accordance with an embodiment.

[0066] FIGURE 52 is a block diagram depicting a system for providing assessments for neural stimulation, in accordance with an embodiment.

[0067] FIGURE 53 is a block diagram depicting a system for providing assessments for neural stimulation on a subject in response to stimulation, in accordance with an embodiment.

[0068] FIGURE 54 is a flow diagram depicting a method of providing assessments for neural stimulation on a subject in response to stimulation.

[0069] FIGURE 55 is a flow diagram depicting a method of providing assessments for neural stimulation on a subject in response to stimulation.

[0070] FIGURE 56 is a flow diagram depicting a method of providing assessments for neural stimulation on a subject in response to iterative stimulation.

[0071] FIGURE 57 is a flow diagram depicting a method for generating therapy regimens based on comparison of assessments for different stimulation modalities.

[0072] **FIGURE 58** illustrates graphs depicting frequency-domain measurements of various states of neural stimulation, in accordance with an embodiment.

[0073] **FIGURE 59** is a flow diagram illustrating a method of sensing neural oscillations induced by an external stimulus and subject attentiveness during application of the external stimuli, in accordance with an embodiment.

[0074] **FIGURE 60** is a flow diagram of a method for evaluating neural responses to different stimulation modalities for subjects, in accordance with an embodiment.

[0075] **FIGURE 61** shows an embodiment of an illustrative portable system (Combinatorial Neurostimulation System).

[0076] **FIGURE 62** is a rendering of an embodiment of a controller of the portable system (Combinatorial Neurostimulation System).

[0077] **FIGURE 63** illustratively depicts a process for a personalized and patient-specific therapeutic use of the Combinatorial Neurostimulation System any embodiment of the device described herein. A physician prescribes at-home therapeutic Combinatorial Neurostimulation System settings for a patient, which include adjusting any parameters of which the device is configured to emit a visual stimulus or an auditory stimulus to the eyes and ears of the patient. The physician confirms that patient's neurological response to by cortical EEG recordings in order to identify the optimal stimulation frequency of the visual stimulus and the auditory stimulus. The patient then uses the device at home with the settings prescribed by the physician. The patient's adherence to using the device as prescribed is monitored throughout the course of treatment.

[0078] **FIGURE 64** depicts an embodiment of the portable system (Combinatorial Neurostimulation System) having a hand-held controller, headphones for delivering the auditory stimulation, and eyeglasses for visual stimulation. The Combinatorial Neurostimulation System device setting encryption, enhanced device connectivity with daily upload of device usage and actigraphy data. The patient can use an actigraphy watch for generating and tracking the patient's actigraphy data. The Combinatorial Neurostimulation System can also interface with an electronic tablet for, as a nonlimiting example, integrating patient surveys and cognitive and linguistic home assessments. The Combinatorial Neurostimulation System automatically generated daily reports to track treatment and patient activities to measure adherence to the prescribed treatment regimen. The daily reports can also include information and/or data to detect baseline response evaluation and re-assessment. Any embodiments of the portable system (Combinatorial Neurostimulation System) described herein can be used for the treatment of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

[0079] **FIGURE 65** depicts an embodiment of a portable system as described herein (Combinatorial Neurostimulation System). The Combinatorial Neurostimulation System integrated data flow is used to monitor and support adherence to the prescribed neural stimulation treatment regimen by the patient.

[0080] **FIGURE 66** depicts an embodiment of a portable system as described herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device with integrated stimulation eyeglasses and stimulation headphones. The stimulation eyeglasses can include transparent Ganz frames, so that the patient can engage in routine daily activities during the prescribed neural stimulation treatment regimen. The Combinatorial Neurostimulation System has accessibility updates, wireless and Bluetooth connectivity capabilities.

[0081] **FIGURE 67** depicts an embodiment of a portable system as described herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device with integrated stimulation eyeglasses and stimulation headphones. Each headphone of the single headset device possesses a connector configured to fasten to a detachable headband via a removable-attachment mechanism. **FIGURE 67** depicts a “female” connector in the housing of each headphone for attaching to a detachable headband equipped with “male” connectors positioned at each end (*see also* **FIGURE 70**).

[0082] **FIGURE 68** depicts an embodiment of a portable system as disclosed herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device with integrated stimulation eyeglasses and stimulation headphones having user control hardware structurally and functionally integrated into the device. The external housing of a headphone speaker includes a button control for turning on or off the emission of the auditory stimulus from the device. The button user control hardware can have the shape of a circle, a rhombus, a triangle, a parallelogram, or any other known regular or irregular shape.

[0083] **FIGURE 69** depicts an embodiment of a portable system as disclosed herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device with integrated stimulation eyeglasses and stimulation headphones having user control hardware structurally and functionally integrated into the device. The frame of the eyeglasses houses a button switch control for adjusting the brightness of the visual stimulus. The button switch control integrated in the frame has functions to: (1) increase light intensity of the visual stimulus, decrease light intensity of the visual stimulus, (3) turn on or activate emission of the visual stimulus, and (4) turn off or stop emission of the visual stimulus. The external housing of a headphone speaker includes a horizontal button switch control for adjusting the volume of the auditory stimulus emitted by the device. The button switch control has a position setting to: (1) increase the volume of the auditory stimulus, (2) decrease volume of the auditory stimulus, (3)

turn on or activate emission of the auditory stimulus, and (4) turn off or stop emission of the auditory stimulus. Any of the button switch user control hardware can be oriented vertically or horizontally.

[0084] FIGURE 70 depicts an embodiment of a portable system as disclosed herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device with integrated stimulation eyeglasses and stimulation headphones having user control hardware structurally and functionally integrated into the device as described in **FIGURE 69**. This embodiment of the single headset device further includes a detachable headband, which can be inserted into the housing of each headphone speaker. The detachable headband can be made of a malleable or flexible material. The headband can also comprise a synthetic material or a natural material. The detachable headband has an elongated shape and is configured to have an adjustable length to achieve a secure fit on a user's head. A "male" connecting member is affixed to each end of the detachable headband and is configured to fasten to a "female" connecting member that is housed within the slit on each headphone housing (see **FIGURE 67**). As depicted on the right, the material of the headband can be affixed or joined by any structural, physical, or chemical means to a second material as a means to achieve greater user comfort or accommodate any aspect of user wearability (*e.g.*, head size, head shape). The second material can be a soft fabric or material.

[0085] FIGURE 71 depicts another embodiment of a portable system as disclosed herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device with integrated stimulation eyeglasses and stimulation headphones having user control hardware structurally and functionally integrated into the single headset device as described in **FIGURE 69**. The detachable headband can be made of a rigid or semi-rigid material, such as a metal or plastic, to limit malleability and to substantially preserve the general shape and arch of the detachable headband of the single headset device, regardless of whether a user is wearing the single headset device. The headband can also comprise a synthetic material or a natural material. As depicted, the detachable headband is configured to have an adjustable length to achieve a secure fit on a user's head and to position the headphones over each ear of the user. As depicted, each end of the primary rigid material of the detachable headband is molded into a connecting member, such as a "male" or "female" connecting member, for the purpose of fastening to a complementary connecting member that is housed on each headphone housing (*e.g.*, a "female" or "male" connecting member). In some cases, the connecting members at each end of the detachable headband can be made of a metal that magnetically connects to the housing of or a component within each headphone. In some cases, the As depicted on the right, the material of the headband can be affixed or joined by any structural, physical, or chemical means to a second

material as a means to achieve greater user comfort or accommodate any aspect of user wearability (e.g., head size, head shape). The second material can be a soft fabric or material. Additionally, the single headset device can have vertically oriented user button, switch, or button switch controllers to enhance the user experience.

[0086] FIGURE 72 depicts an embodiment of portable system as disclosed herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset device e, a hand-held controller, and a charging station that can recharge the rechargeable battery of the single headset device for continued use of the Combinatorial Neurostimulation System. The charging station can be powered via a direct wired connection to an electrical power supply. The hand-held controller can transmit wireless commands to the single headset device to activate or de-activate emission of the visual stimulation or the auditory stimulation from the eyeglasses or headphones of the single headset device. The hand-held controller can also adjust the brightness of the light stimulus or the volume of the sound stimulus emitted from the single headset device.

[0087] FIGURE 73 depicts another embodiment of a portable system as disclosed herein (Combinatorial Neurostimulation System). This embodiment depicts a single headset, a hand-held controller, and a charging station that can recharge the rechargeable battery of the single headset device for continued use of the Combinatorial Neurostimulation System. As previously described, the charging station can be powered via a direct wired connection to an electrical power supply. The hand-held controller can transmit wireless commands to the single headset device to activate or de-activate emission of the visual stimulation or the auditory stimulation from the eyeglasses or headphones of the single headset device. The hand-held controller can also adjust the brightness of the light stimulus or the volume of the sound stimulus emitted from the single headset device via switches, buttons, or button switch mechanisms. The hand-held controller can also be equipped with a digital display to indicate the assigned user settings (e.g., brightness, volume, stimulus emission activation, stimulus emission de-activation, treatment duration, time remaining of a current treatment session). The digital display can be configured to display settings or information as numeric and/or alphabetic characters (as shown), as a percentage of a maximal value, or as a digital scale indicating an adjustable row of digital dots or shapes or, alternatively, an adjustable length of a digital line.

[0088] FIGURE 74 depicts an embodiment of a charging station of a portable system as disclosed herein (Combinatorial Neurostimulation System). In addition to the characteristics described in **FIGURE 72** and **FIGURE 73**, the charging station can also have wireless connection capabilities, including establishing a connection to a Wi-Fi or Bluetooth™ device. The charging station can also include a charging pin housing. The charging station can be equipped with a “locate” button which, when pressed, triggers emission of a sound alert from the single headset

device to aid the user in identifying the current location of the single headset device paired with the user's Combinatorial Neurostimulation System. As depicted, the charging station can also be equipped with a digital display to indicate current settings of the single headset device or other component of the Combinatorial Neurostimulation System settings (e.g., light stimulus brightness, sound stimulus volume, stimulus emission activation, stimulus emission de-activation, treatment duration, time remaining of a current treatment session, charging status of the single headset device, estimation of time remaining for single headset device to be fully charged). The digital display on the charging station can be configured to display settings or information as numeric and/or alphabetic characters (as shown), as a percentage of a maximal value, or as a digital scale indicating an adjustable row of digital dots or shapes or, alternatively, an adjustable length of a digital line.

[0089] FIGURE 75A-75D provide exemplary embodiments of hand-held controllers for systems provided herein. **FIG. 75A** provides one embodiment with a volume display at the top, a pause/play button below, and brightness (right) and volume (left) up/down toggles below the pause/play button. **FIG. 75B** shows an embodiment of a hand-held controller with a brightness level indicated at the top, a pause/play button below, and volume (left) and brightness (right) up/down toggles below the pause/play button. **FIG. 75C** provides an embodiment of a hand-held controller with a timer indicated at the top, a pause/play button below, and volume (left) and brightness (right) up/down toggles below the pause/play button. **FIG. 75D** provides a smaller, condensed version of a remote, with the pause play button directly between the volume (left) and brightness panels (right). In **FIG. 75D**, there are small lights at the top of the hand-held controller, which extend upward from the volume and brightness button panels, respectively. In this exemplary embodiment, these number of lights indicate a level of brightness (right) or volume (left). For example, four lights on the left side of the remote would be a lower volume than five lights on the left side of the hand-held controller. Four lights on the right side of the hand-held controller indicate a lower brightness than five lights on the right side of the hand-held controller.

[0090] FIGURE 76 depicts an empty case for a portable system as disclosed herein (or Combinatorial Neurostimulation System). This embodiment has on-ear headphones and wearable glasses as provided herein. The center of the case has a button with Bluetooth capabilities. The case can fit the portable, wearable system and a remote control for the system.

[0091] FIGURE 77 depicts a case for a portable system as disclosed herein. This embodiment has on-ear headphones and wearable glasses as provided herein. As shown in **FIG. 77**, the case is holding the portable, wearable system comprising the glasses with on-ear headphones and a remote control for the system.

[0092] **FIGURE 78** depicts details of an exemplary embodiment of a portable system as provided herein. The top panel provides a portable system comprising glasses with a light source in the rim of the glasses and off-ear speakers. The temple arms of the glasses are folded at the rims and enclosed in an open case.

[0093] **FIGURE 79** depicts a front view of an exemplary embodiment of a portable system as provided herein. As shown in **FIG. 79**, the portable systems comprise glasses, with foldable temple arms **8002**. An off-ear speaker **8001** is built into the temple arms **8002** of the glasses, proximal to the temple tips **8006**.

[0094] **FIGURE 80** depicts a rear-facing view of an exemplary embodiment of a portable systems as provided herein. As shown in **FIG. 80**, the portable systems provide glasses, with foldable temple arms **8002**. A hinge **8005** is provided for folding the temple arms. An off-ear speaker **8001** is built into the temple arm of the glasses, proximal to the temple tips **8006**. A play/pause button **8004** is located on the top of the temple arms.

[0095] **FIGURES 81A-B** depict corpus callosum area and group level changes in the brains of subjects administered stimulation using a portable system via methods as disclosed herein versus control subjects.

[0096] **FIGURES 82A-F** depict corpus callosum subregion area and group level changes in the brains of subjects administered stimulation using a portable system via methods as disclosed herein versus control subjects.

[0097] The features and advantages of the present solution will become more apparent from the detailed description set forth below when taken in conjunction with the drawings, in which like reference characters identify corresponding elements throughout. In the drawings, like reference numbers generally indicate like elements.

DETAILED DESCRIPTION

[0098] Devices, systems, and methods of the present disclosure are directed to neurostimulation via neural, visual, auditory, haptic stimulation, or any combination thereof. Neural, visual, auditory, or haptic stimulation, including neural, visual, auditory, or haptic signals, or any combination thereof can affect frequencies of neural oscillations. The neural, visual, auditory, or haptic stimulation can elicit brainwave effects via neural, visual, auditory, or haptic input, or any combination thereof. Devices, systems, and methods disclosed herein can adjust, control, or otherwise manage the frequency of the neural, visual, auditory, or haptic stimulation, or any combination thereof, to provide beneficial effects to one or more cognitive states or cognitive functions of a subject, such as beneficial effects within a brain region or the immune system, while mitigating or preventing adverse consequences of a cognitive state or cognitive function.

For example, devices, systems, and methods of the present technology can treat, prevent, protect against, or otherwise affect diseases or conditions such as dementia or Alzheimer's Disease.

[0099] External signals, e.g., stimuli, such as visual signals, audio signals or haptic signals, can be observed or perceived by the brain. The brain, in response to perceiving the signals, can adjust, manage, or control the frequency of neural oscillations within a region or regions of the brain. This stimulation can result in repeated activation of portions of the brain which are known to process input, such as the visual or auditory cortex. For example, visual signals having a predetermined modulation frequency and perceived by the visual cortex or other brain regions can trigger neural activity in the brain to cause a predetermined or resulting frequency of neural oscillations. The frequency of neural oscillations can be affected by or correspond to the modulation frequency of the signals. Thus, devices, systems, and methods of the present disclosure can induce brainwave oscillations via neural, visual, auditory, or haptic stimulation, or any combination thereof.

[0100] Devices, systems, and methods of the present disclosure can induce brainwave oscillations using a non-invasive external stimulus, such as a visual, auditory, or haptic stimulus, or any combination thereof, including stimuli such as visual, visual, audio, or haptic signals forming visual, acoustic, or vibratory pulses emitted at a predetermined modulation frequency to synchronize electrical activity among groups of neurons based on the modulation frequency of the visual, audio, or haptic signals. Brainwave oscillations can be observed based on the aggregate frequency of oscillations produced by the synchronous electrical activity in ensembles of cortical neurons which the visual, acoustic, or haptic vibratory pulses can adjust to synchronize with frequency of the acoustic or haptic vibratory pulses.

[0101] The present disclosure provides devices, and systems for stimulation via neural, visual, auditory, or haptic stimulation, or any combination thereof. In some embodiments, the system comprises a portable neurostimulation system comprising stimulus emitting components. In some embodiments, the stimulus emitting components comprise a visual source, an audio source, a haptic source, or a combination thereof. In some embodiments, a portable system comprises a visual source and an audio source that are operatively connected and comprise a single headset device wherein said device comprises one or more rotatable elements. A rotatable element as described herein may comprise one module of the device that rotates relative to an axis of another module of the device. The rotatable element may comprise an auditory module that rotates relative to a visual module of the device. The rotatable element may comprise a visual module that rotates relative to an auditory module of the device. A rotatable element as described herein may be as depicted in any one of FIGS. 66-73. In some embodiments, a portable system

comprises a visual source and an audio source that are operatively connected and comprise a single headset device wherein said visual source is rotatable about said audio source.

[0102] In some embodiments, a portable system comprises a visual source, wherein the visual source comprises glasses. The visual source can comprise a lens that is opaque, or not opaque, e.g., a translucent lens. In some embodiments, a device or system, e.g., a portable system or single headset device as disclosed herein provides a visual stimulus to a subject using a visual source with an opaque or transparent lens. In some embodiments, a portable system comprises an audio source, wherein the audio source comprises headphones. In some embodiments, the audio source comprises supra-aural headphones. The visual source and the audio source can be operatively connected as a single headset device that can be worn by a subject. The single headset device can be a wireless device. The portable system can comprise a haptic source. In some embodiments, a haptic source comprises wireless bone conduction headphones, wireless bone conduction protheses, or wireless bone conduction hearing aid devices. In some embodiments, a portable system comprises a single headset device comprising a visual source, an audio source, and a haptic source, wherein the visual source is rotatable about the audio source.

[0103] The devices or systems can be configured to emit a neural, visual, auditory, or haptic stimulus, or any combination thereof. In some embodiments, the stimulus comprises a gamma frequency. In some embodiments, the gamma frequency is about 20 Hertz (Hz) to about 140 Hz, about 30 Hz to about 60 Hz, about 40 Hz to about 60 Hz, about 35 Hz to about 45 Hz, or about 40 Hz.

I. Portable Systems

[0104] In some embodiments, disclosed herein are portable systems capable of delivering a stimulus to a subject. In some embodiments, a portable system includes one or more stimulus emitting components comprising one or more visual, audio, or haptic sources, or any combination thereof. In some embodiments, a portable system comprises a single headset device comprising one or more visual, audio, or haptic sources, capable of transmitting a visual, audio, and/or haptic stimulus, or any combination thereof. In some embodiments, a single headset device comprises an audio source operatively connected to a visual source, and/or a haptic source, wherein the visual source is rotatable about said audio source and wherein said single headset device is capable of being worn by a subject. In some embodiments, a portable system can further comprise a hand-held controller capable of receiving and transmitting a signal dictating a dosing parameter corresponding to a frequency of said visual stimulus, a duration of said visual stimulus, a brightness of said visual stimulus, a color of said visual stimulus, a

duration of said audio or haptic stimulus, an intensity of said audio or haptic stimulus, a frequency of said audio or haptic stimulus, or any combination thereof.

[0105] In some embodiments, a portable system further comprises a processor, a memory device, and a feedback sensor.

[0106] In some embodiments, a portable system as described herein is referred to as a Combinatorial Neurostimulation System.

[0107] In some embodiments, a portable system as disclosed herein comprises a Neural Stimulation System (NSS) as disclosed herein, and/or comprises a component of an NSS as disclosed herein, or can be configured to implement a method of an NSS as disclosed herein.

A. Stimulus Emitting Components

[0108] In some embodiments, a portable system comprises one or more stimulus emitting components, wherein the stimulus emitting components comprises a visual source, an audio source, and/or a haptic source, or any combination thereof.

i. Visual Source

[0109] In some embodiments, the stimulus emitting component comprises a visual source. In some embodiments, said visual source comprises a pair of glasses worn by the subject with a visual source capable of providing a visual stimulus. The visual source can comprise a lens, e.g., a translucent lens. In some embodiments, a visual source as disclosed herein provides a visual stimulus to a subject using a visual source with an opaque or transparent lens. In some embodiments, a visual source comprises a portable system visual source. In some embodiments, the glasses comprise one or more lenses. In some embodiments, the lenses comprise transparent lenses. In some embodiments, a lens comprises a transmittance of about 0% to about 100%. In some embodiments, the visual source is operatively coupled to one or more processors.

[0110] In some embodiments, a portable system visual source comprises a frame that can be designed and constructed to be placed or positioned on a subject's head. The frame can be configured to be worn by the person. The frame can be designed and constructed to stay in place. The frame can be configured to be worn and stay in place as a person sits, stands, walks, runs, or lays down flat. In some embodiments, a portable system visual source comprises a visual source operatively connected to one or more processors that can be configured on the frame to project light pulses towards the person's eyes in various positions. In some embodiments, the visual source can be configured to project light pulses towards the person's eyes if their eyelids are closed such that the light pulse penetrates the eyelid to be perceived by the retina. The frame can include a bridge. The frame can include one or more eye wires coupled to the bridge. The bridge

can be positioned in between the eye wires. The frame can include one or more temples extending from the one or more eye wires. In some embodiments, the portable system visual source can include or hold a lens. In some embodiments, the portable system visual source can include or hold a solid material or cover. The lens, solid material, or cover can be transparent, semi-transparent, opaque, or completely block out external light.

[0111] One or more visual sources can be positioned on or adjacent to the eye wire, lens or other solid material, or bridge. For example, a visual source can be positioned in the middle of the eye wire on a solid material in order to transmit light pulses into the direct visual field. In some embodiments, a visual source can be positioned at a corner of the eye wire, such as a corner of the eye wire coupled to the temple, in order to transmit light pulses towards a peripheral field.

[0112] The portable system visual source can perform visual stimulation via a single eye or both eyes. For example, the portable system visual source can direct light pulses to a single eye or both eyes. The visual signaling component can include a single visual source configured and positioned to direct light pulses to a first eye. The visual signaling component can further include a light blocking component that keeps out or blocks the light pulses generated from the visual source from entering a second eye. The visual signaling component can block or prevent light from entering the second eye during the brain stimulation process.

[0113] In some embodiments, the visual source can alternatively transmit or direct light pulses to the first eye and the second eye. For example, the visual source can direct light pulses to the first eye for a first time interval. The visual source can direct light pulses to the second eye for a second time interval. The first time interval and the second time interval can be a same time interval, overlapping time intervals, mutually exclusive time intervals, or subsequent time intervals.

[0114] The lens can include electrochromic glass or plastic. Electrochromic glass or plastic can change from light to dark (e.g., clear to opaque) in response to an electrical voltage or current. Electrochromic glass or plastic can include metal-oxide coatings that are deposited on the glass or plastic, multiple layers, and lithium ions that travel between two electrodes between a layer to lighten or darken the lens.

[0115] In some embodiments, a portable system visual source can include a tablet computing visual source or other computing visual source having a display screen.

[0116] In some embodiments, the visual source can display a pattern of light. The light can flicker, toggle or switch between two or more patterns to generate flashes of light or light pulses. Patterns can include, for example, alternating checkerboard patterns. The pattern can include symbols, characters, or images that can be toggled or adjusted from one state to another state. For example, the color of a character or text relative to a background color can be inverted to cause a

switch between a first state and a second state. Inverting a foreground color and background color at a predetermined frequency can generate light pulses by way of indicating visual changes that can facilitate adjusting or managing a frequency of neural oscillations.

[0117] In some embodiments, the visual source can instruct or cause a visual stimulus to flicker, toggle, or switch between images configured to stimulate specific or predetermined portions of the brain or a specific cortex. The presentation, form, color, motion and other aspects of the light or an image based stimuli can dictate which cortex or cortices are recruited to process the stimuli. The visual source can stimulate discrete portions of the cortex by modulating the presentation of the stimuli to target specific or general regions of interest. The relative position in the field of view, the color of the input, or the motion and speed of the light stimuli can dictate which region of the cortex is stimulated. For example, the brain can include at least two portions that process predetermined types of visual stimuli: the primary visual cortex on the left side of the brain, and the calcarine fissure on the right side of the brain. Each of these two portions can have one or more multiple sub-portions that process predetermined types of visual stimuli. For example, the calcarine fissure can include a sub-portion referred to as area V5 that can include neurons that respond strongly to motion but cannot register stationary objects. Subjects with damage to area V5 can have motion blindness, but otherwise normal vision. In another example, the primary visual cortex can include a sub-portion referred to as area V4 that can include neurons that are specialized for color perception. Subjects with damage to area V4 can have color blindness and only perceive objects in shades of gray. In another example, the primary visual cortex can include a sub-portion referred to as area V1 that includes neurons that respond strongly to contrast edges and helps segment the image into separate objects. Thus, the visual source can instruct or cause a visual stimulus to form a type of still image or video, or generate a flicker, or toggle between images that configured to stimulate specific or predetermined portions of the brain or a specific cortex. For example, the visual source can generate images of human faces to stimulate a fusiform face area, which can facilitate brain stimulation for subjects having prosopagnosia or face blindness. In some embodiments, the visual source can generate images of faces flickering to target this area of the subject's brain. In another example, the visual source can generate images that include edges or line drawings to stimulate neurons of the primary visual cortex that respond strongly to contrast edges.

[0118] The portable system visual source can include, access, interface with, or otherwise communicate with at least one visual source. The visual source can be designed and constructed to measure or verify an environmental variable (e.g., light intensity, timing, incident light, ambient light, eye lid status, etc.) to adjust a parameter associated with the visual signal, such as a frequency, amplitude, wavelength, intensity pattern or other parameter of the visual signal, or

any combination thereof. The visual source can automatically vary a parameter of the visual signal based on profile information or feedback. The visual source can receive the feedback information from a feedback monitor. The visual source can receive instructions or information from a side effects management module. The visual source can receive profile information from a profile manager. The visual source can include an LED.

[0119] The portable system visual source can include, access, interface with, or otherwise communicate with at least one unwanted frequency filtering module. The unwanted frequency filtering module can be designed and constructed to block, mitigate, reduce, or otherwise filter out frequencies of visual signals that are undesired to prevent or reduce an amount of such visual signals from being perceived by the brain. The unwanted frequency filtering module can interface, instruct, control, or otherwise communicate with a filtering component to cause the filtering component to block, attenuate, or otherwise reduce the effect of the unwanted frequency on the neural oscillations.

[0120] The portable system visual source can include, access, interface with, or otherwise communicate with at least one profile manager. The profile manager can be designed or constructed to store, update, retrieve or otherwise manage information associated with one or more subjects associated with the portable system. Profile information can include, for example, historical treatment information, historical brain stimulation information, dosing information, parameters of light waves, feedback, physiological information, environmental information, or other data associated with the systems and methods of brain stimulation.

[0121] The portable system visual source can include, access, interface with, or otherwise communicate with at least one side effects management module. The side effects management module can be designed and constructed to provide information to the visual source to change one or more parameter of the visual signal in order to reduce a side effect. Side effects can include, for example, nausea, migraines, fatigue, seizures, eye strain, or loss of sight.

[0122] The side effects management module can automatically instruct a component of the portable system visual source to alter or change a parameter of the visual signal. The side effects management module can be configured with predetermined thresholds to reduce side effects. For example, the side effects management module can be configured with a maximum duration of a pulse train, maximum intensity of light waves, maximum amplitude, maximum duty cycle of a pulse train (e.g., the pulse width multiplied by the frequency of the pulse train), maximum number of treatments for brainwave stimulation in a time period (e.g., 1 hour, 2 hours, 12 hours, or 24 hours).

[0123] The side effects management module can cause a change in the parameter of the visual signal in response to feedback information. The side effect management module can receive

feedback from the feedback monitor. The side effects management module can determine to adjust a parameter of the visual signal based on the feedback. The side effects management module can compare the feedback with a threshold to determine to adjust the parameter of the visual signal.

[0124] The side effects management module can be configured with or include a policy engine that applies a policy or a rule to the current visual signal and feedback to determine an adjustment to the visual signal. For example, if feedback indicates that a patient receiving visual signals has a heart rate or pulse rate above a threshold, the side effects management module can turn off the pulse train until the pulse rate stabilizes to a value below the threshold, or below a second threshold that is lower than the threshold.

[0125] The portable system visual source can include, access, interface with, or otherwise communicate with at least one feedback monitor. The feedback monitor can be designed and constructed to receive feedback information from a feedback component. The feedback component can include, for example, a feedback sensor such as a temperature sensor, heart or pulse rate monitor, physiological sensor, ambient light sensor, ambient temperature sensor, sleep status via actigraphy, blood pressure monitor, respiratory rate monitor, brain wave sensor, EEG probe, electrooculography (“EOG”) probes configured to measure the corneo-retinal standing potential that exists between the front and the back of the human eye, accelerometer, gyroscope, motion detector, proximity sensor, camera, microphone, or photo detector, or any combination thereof.

[0126] In some embodiments, a computing visual source can include the feedback component or feedback sensor. For example, the feedback sensor can be placed on a tablet and can include a front-facing camera that can capture images of a person viewing the visual source.

[0127] The feedback sensor can interact with or communicate with portable system visual source. For example, the feedback sensor can provide detected feedback information or data to the portable system visual source. The feedback sensor can provide data to the portable system visual source in real-time, for example as the feedback sensor detects or senses or information. The feedback sensor can provide the feedback information to the portable system visual source based on a time interval, such as 1 minute, 2 minutes, 5 minutes, 10 minutes, hourly, 2 hours, 4 hours, 12 hours, or 24 hours. The feedback sensor can provide the feedback information to the portable system visual source responsive to a condition or event, such as a feedback measurement exceeding a threshold or falling below a threshold. The feedback sensor can provide feedback information responsive to a change in a feedback parameter. In some embodiments, the portable system visual source can ping, query, or send a request to the feedback sensor for information, and the feedback sensor can provide the feedback information

in response to the ping, request, or query. Feedback sensors can include, for example, EEG probes that detect brain wave activity.

[0128] The feedback monitor can detect, receive, obtain, or otherwise identify feedback information from the one or more feedback sensors. The feedback monitor can provide the feedback information to one or more component of the portable system visual source for further processing or storage. For example, the profile manager can update profile data structure stored in data repository with the feedback information. Profile manager can associate the feedback information with an identifier of the patient or person undergoing the visual brain stimulation, as well as a time stamp and date stamp corresponding to receipt or detection of the feedback information. The identifier can be indicative of an activity of a subject, a physiological or physical condition of a subject, or a mental condition of a subject. The identifier can also be indicative of a disease, disorder, or condition.

[0129] The feedback monitor can detect symptoms of a neurological disease or disorder. For the example, the feedback monitor can be used to evaluate changes in fine motor skills over time or changes in voice pitch or tone. The profile manager can update profile data structure with the feedback information. The profile data structure can be used to assess whether a person is at risk of developing a neurological disorder, whether a person has a neurological disorder, or progression of symptoms of a neurological disorder.

[0130] The feedback monitor can determine a level of attention. The level of attention can refer to the focus provided to the light pulses used for brain stimulation. The feedback monitor can determine the level of attention using various hardware and software techniques. The feedback monitor can assign a score to the level of attention (e.g., 1 to 10 with 1 being low attention and 10 being high attention, or vice versa, 1 to 100 with 1 being low attention and 100 being high attention, or vice versa, 0 to 1 with 0 being low attention and 1 being high attention, or vice versa), categorize the level of attention (e.g., low, medium, high), grade the attention (e.g., A, B, C, D, or F), or otherwise provide an indication of a level of attention.

[0131] In some cases, the feedback monitor can track a person's eye movement to identify a level of attention. The feedback monitor can interface with a feedback component that includes an eye-tracker. The feedback monitor can detect and record eye movement of the person and analyze the recorded eye movement to determine an attention span or level of attention. The feedback monitor can measure eye gaze which can indicate or provide information related to covert attention. For example, the feedback monitor can be configured with electro-oculography ("EOG") to measure the skin electric potential around the eye, which can indicate a direction the eye faces relative to the head. In some embodiments, the EOG can include a system or visual source to stabilize the head so it cannot move in order to determine the direction of the eye

relative to the head. In some embodiments, the EOG can include or interface with a head tracker system to determine the position of the heads, and then determine the direction of the eye relative to the head.

[0132] In some embodiments, the feedback monitor and feedback component can determine or track the direction of the eye or eye movement using video detection of the pupil or corneal reflection. For example, the feedback component can include one or more camera or video camera. The feedback component can include an infra-red source that sends light pulses towards the eyes. The light can be reflected by the eye. The feedback component can detect the position of the reflection. The feedback component can capture or record the position of the reflection. The feedback component can perform image processing on the reflection to determine or compute the direction of the eye or gaze direction of the eye.

[0133] The feedback monitor can compare the eye direction or movement to historical eye direction or movement of the same person, nominal eye movement, or other historical eye movement information to determine a level of attention. For example, if the eye is focused on the light pulses during the pulse train, then the feedback monitor can determine that the level of attention is high. If the feedback monitor determines that the eye moved away from the pulse train for 25% of the pulse train, then the feedback monitor can determine that the level of attention is medium. If the feedback monitor determines that the eye movement occurred for more than 50% of the pulse train or the eye was not focused on the pulse train for greater than 50%, then the feedback monitor can determine that the level of attention is low.

[0134] In some embodiments, the portable system visual source can include a filter to control the spectral range of the light emitted from the visual source. In some embodiments, the visual source includes a light reactive material affecting the light emitted, such as a polarizer, filter, prism or a photochromic material, or electrochromic glass or plastic. The filtering component can receive instructions from the unwanted frequency filtering module to block or attenuate one or more frequencies of light.

[0135] The filtering component can include an optical filter that can selectively transmit light in a particular range of wavelengths or colors, while blocking one or more other ranges of wavelengths or colors. The optical filter can modify the magnitude or phase of the incoming light wave for a range of wavelengths. The optical filter can include an absorptive filter, or an interference or dichroic filter. An absorptive filter can take energy of a photon to transform the electromagnetic energy of a light wave into internal energy of the absorber (e.g., thermal energy). The reduction in intensity of a light wave propagating through a medium by absorption of a part of its photons can be referred to as attenuation.

[0136] An interference filter or dichroic filter can include an optical filter that reflects one or more spectral bands of light, while transmitting other spectral bands of light. An interference filter or dichroic filter can have a nearly zero coefficient of absorption for one or more wavelengths. Interference filters can be high-pass, low-pass, bandpass, or band-rejection. An interference filter can include one or more thin layers of a dielectric material or metallic material having different refractive indices.

1. Visual Stimulus

[0137] In some embodiments, a portable system visual source is configured to generate a visual stimulus such as such as a light pulse or flash of light. In some embodiments, the visual stimulus comprises a light pulse or flash of light with amplitude or intensity, a frequency, a pulse rate, a tone, a signal delay, an offset, a duration, or any combination thereof. In some embodiments, the visual source comprises a light emitting diode (LED) capable of producing a light pulse or flash of light.

[0138] In some embodiments, the visual stimulus comprises one or more light waves. In some embodiments, the visual stimulus is perceptible to the subject. In some embodiments, the visual stimulus is imperceptible to the subject. In some embodiments, the visual stimulus comprises a frequency from about 0 Hz to about 50 kHz. In some embodiments, the visual stimulus comprises a frequency from about 20 Hz to about 20 kHz.

[0139] In some embodiments, the visual stimulus comprises a frequency capable of modulating a gamma waveform in a brain region of the subject. In some embodiments, the frequency capable of modulating a gamma waveform in the subject comprises a waveform of .1 Hz, 1 Hz, 5 Hz, 10 Hz, 20 Hz, 25 Hz, 30 Hz, 31 Hz, 32 Hz, 33 Hz, 34 Hz, 35 Hz, 36 Hz, 37 Hz, 38 Hz, 39 Hz, 40 Hz, 41 Hz, 42 Hz, 43 Hz, 44 Hz, 45 Hz, 46 Hz, 47 Hz, 48 Hz, 49 Hz, 50 Hz, 60 Hz, 70 Hz, 80 Hz, 90 Hz, 100 Hz, 150 Hz, 200 Hz, 250 Hz, 300 Hz, 400 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4,000 Hz, 5000 Hz, 6,000 Hz, 7,000 Hz, 8,000 Hz, 9,000 Hz, or 10,000 Hz.

[0140] The visual stimulus can be turned on and off based on a predetermined or fixed pulse rate interval, such as every 0.025 seconds, to provide a pulse repetition frequency of 40 Hz. The visual source can be turned on and off to provide a pulse repetition frequency in the range of about 20 Hertz (Hz) to about 140 Hz, about 30 Hz to about 60 Hz, about 40 Hz to about 60 Hz, about 35 Hz to about 45 Hz, or about 40 Hz, in accordance with methods disclosed herein.

[0141] In some embodiments, the present disclosure describes systems and devices for providing a gamma-oscillation inducing waveform that is imperceptible to a subject. In some cases, a display device can be configured to output the gamma oscillation inducing waveform. In some cases, a stimulation source can be configured to be operatively configured to another device, such

that the stimulation source outputs the gamma oscillation inducing waveform in association with the output of the device. In some cases, a device can comprise a filter, wherein the filter is capable of masking one or more waveforms of a waveform source such that a subject using the filter receives a gamma oscillation inducing waveform. In some cases, a device can comprise a cover, wherein the cover is configured to add a gamma-oscillation inducing waveform to one or more waveforms of a waveform source such that a subject using the cover receives a gamma oscillation inducing waveform.

ii. Audio Source

[0142] Devices and systems as disclosed herein may comprise an audio source. By way of example, a portable system audio source can comprise headphones worn by a subject. In some embodiments, the headphones can be worn about the head of a subject. The headphones can comprise wireless over-ear headphones or wireless in-ear headphones suitable for delivering an auditory stimulus to the subject.

[0143] In some embodiments, wireless headphones can include, for example, circumaural headphones (e.g., full size/over-ear headphones) that include circular or ellipsoid earpads that are designed and constructed to seal against the head to attenuate external noise. Circumaural headphones can facilitate providing an immersive auditory brainwave wave stimulation experience, while reducing external distractions. In some embodiments, headphones can include supra-aural headphones, which include pads that press against the ears rather than around them. Supra-aural headphones can provide less attenuation of external noise.

[0144] Both circumaural headphones and supra-aural headphones can have an open back, closed back, or semi-open back. An open back can leak more sound and allow more ambient sounds to enter, but can provide a more natural or speaker-like sound. Closed back headphones can block more of the ambient noise as compared to open back headphones, thus providing a more immersive auditory brainwave stimulation experience while reducing external distractions.

[0145] In some embodiments, headphones include ear-fitting headphones, such as earphones or in-ear headphones. Earphones (or earbuds) can refer to small headphones that are fitted directly in the outer ear, facing but not inserted in the ear canal. In-ear headphones (or in-ear monitors or canalphones) can refer to small headphones that can be designed and constructed for insertion into the ear canal. In-ear headphones engage the ear canal and can block out more ambient noise as compared to earphones, thus providing a more immersive auditory brainwave stimulation experience. In-ear headphones can include ear canal plugs made or formed from one or more material, such as silicone rubber, elastomer, or foam. In some embodiments, in-ear headphones can include custom-made castings of the ear canal to create custom-molded plugs that provide

added comfort and noise isolation to the subject, thereby further improving the immersion of a subject.

[0146] In some embodiments, a portable system audio source comprises a signal emitter. In some embodiments, a signal emitter includes a speaker, wherein the speaker can include one or more types of speaker hardware, components, or technology to generate an auditory stimulus such as an audio tone, beep, or click disclosed herein.

[0147] The speaker can include a diaphragm to produce sound. The speaker can include a moving-iron loudspeaker that uses a stationary coil to vibrate a magnetized piece of metal. The speaker can include a piezoelectric speaker. A piezoelectric speaker can use the piezoelectric effect to generate sound by applying a voltage to a piezoelectric material to generate motion, which is converted into audible sound using diaphragms and resonators.

[0148] The speaker can include various other types of hardware or technology, such as magnetostatic loudspeakers, magnetostrictive speakers, electrostatic loudspeakers, a ribbon speaker, planar magnetic loudspeakers, bending wave loudspeakers, coaxial drivers, horn loudspeakers, Heil air motion transducers, or transparent ionic conduction speaker.

[0149] In some embodiments, the speaker may not include a diaphragm. For example, the speaker can be a plasma arc speaker that uses electrical plasma as a radiating element. The speaker can be a thermoacoustic speaker that uses carbon nanotube thin film. The speaker can be a rotary woofer that includes a fan with blades that constantly change their pitch.

[0150] In some embodiments, the portable system audio source comprises one or more microphones. The microphones can be used to detect sound. A microphone can be integrated with a speaker. The microphone can provide feedback information to an audio source or system as disclosed herein. The microphone can provide feedback to a component of the speaker to cause the speaker to adjust a parameter of an auditory stimulus.

[0151] The microphone can include a transducer that converts sound into an electrical signal. The microphone can use electromagnetic induction, capacitance change, or piezoelectricity to produce the electrical signal from air pressure variations. In some embodiments, the microphone can include or be connected to a pre-amplifier to amplify the signal before it is recorded or processed. The microphone can include one or more type of microphone, including, for example, a condenser microphone, RF condenser microphone, electret condenser, dynamic microphone, moving-coil microphone, ribbon microphone, carbon microphone, piezoelectric microphone, crystal microphone, fiber optic microphone, laser microphone, liquid or water microphone, microelectromechanical systems ("MEMS") microphone, or speakers as microphones.

[0152] In some embodiments, a portable system audio source comprises one or more feedback components. The feedback component can include or interface with the microphone to obtain,

identify, or receive sound. The feedback component can obtain ambient noise. The feedback component can obtain sound from the speakers to facilitate the audio source adjusting a characteristic of the auditory stimulus generated by the speaker. The microphone can receive voice input from a subject, such as audio commands, instructions, requests, feedback information, or responses to survey questions.

[0153] In some embodiments, a portable system audio source also includes at least one memory for storing processor executable instructions and at least one processor communicatively connected to the audio source and the at least one memory. Upon execution of the processor executable instructions, the at least one processor can control the audio source such that device emits the auditory stimulus at a frequency that activates neural, visual, oscillations, *e.g.*, gamma oscillations, in a brain region of the subject corresponding to the audio frequency generated by the audio source. In some embodiments, the at least one processor can control the audio source such that the device actuates the auditory stimulus at the frequency that activates neural, visual, oscillations, *e.g.*, gamma oscillations, in at least one of the auditory cortex and the hippocampus at the frequency corresponding to the audio frequency generated by the audio source.

[0154] In some embodiments, the audio source includes a data interface that enables data communication between the audio source and an external control device or system. The external device can be external device such as a fitting system, PDA, computer, mobile phone, or any other suitable device. Preferably, the interface allows two-way or bidirectional communication. That is, interface data can be sent from both the audio source and the external device. For example, in one embodiment, the interface can be adapted to receive control signals from the external device for generating an auditory stimulus at predetermined frequencies, and receive control settings for the audio source for storing in the memory unit. In some embodiments, however, the interface is a one-way interface, allowing only data to be forwarded from the external device to the audio source. In other embodiments, communication is a one-way interface with data being forwarded from the audio source to any type of receiving device. The data can include measured control signals or any type of status information or other suitable data. This information can be used to merely monitor the audio source or be used with a control device that can be a separate device or be integrated into the audio source or be any other suitable device.

[0155] In some embodiments, the processor is configured to receive an indication of a physiological, cognitive, neural, visual, auditory, or physical assessment, or any combination thereof of the subject wearing the audio source. In some embodiments, when the processor receives the indication of the physiological, cognitive, neural, visual, auditory, or physical assessment, or any combination thereof of the subject, the processor instructs the stimulus emitter to emit the auditory stimulus. In some embodiments, the physical assessment of the subject

comprises ascertaining at least one of the subject's: compliance with proper use and positioning of the system, eye status, alert or sleep status, or environment and surroundings. In some embodiments, the physical assessment of the subject is performed to determine hearing of the subject. the indication of the physiological, cognitive, neural, visual, , or physical assessment, or any combination thereof of the subject comprises a biosignal. In some embodiments, the biosignal comprises an electroencephalography (EEG).

[0156] In some embodiments, the cognitive assessment of the subject is obtained through questions posed to the subject, activities and tasks performed by the subject in response to a prompt, or behaviors exhibited by the subject.

[0157] In some embodiments, an audio source as disclosed herein is provided with or operatively connected to a computer system as disclosed herein. The computer system can communicate with one or more remote computer systems through the network. For instance, the computer system can communicate with a remote computer system of a user. Examples of remote computer systems include personal computers (e.g., portable PC), slate or tablet PC's (e.g., Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (e.g., Apple® iPhone, Android-enabled device, Blackberry®), or personal digital assistants. The user can access the computer system via the network. In some embodiments, the computer systems are programmed to implement the function of an audio source, such as implementing an auditory stimulus delivered to a subject by the audio source as described herein.

1.Auditory Stimulus

[0158] In some embodiments, a portable system audio source is configured to generate an auditory stimulus such as an audio tone, a beep, a click, or a similar audio stimulus, or any combination thereof. In some embodiments, the auditory stimulus comprises a sound with amplitude or intensity, a frequency, a pulse rate, a tone, a signal delay, an offset, a duration, a sinusoidal grating, a dynamic sound, a perceived direction of motion, or any combination thereof.

[0159] In some embodiments, the auditory stimulus comprises one or more acoustic waves. In some embodiments, the sound comprises an ultrasound or an infrasound. In some embodiments, the sound comprises a tone or frequency perceptible to the subject. In some embodiments, the sound comprises a tone or frequency imperceptible to the subject. In some embodiments, the sound comprises an acoustic frequency from about 0 Hz to about 50 kHz. In some embodiments, the sound comprises an acoustic frequency from about 20 Hz to about 20 kHz. In some embodiments, the sound comprises an acoustic frequency from about 8 Hz to about 12 kHz. In some embodiments, the sound comprises an acoustic frequency of 10 kHz.

[0160] In some embodiments, the dynamic sound comprises a tone or acoustic frequency perceptible to the subject. In some embodiments, the dynamic sound comprises a tone or acoustic frequency imperceptible to the subject. In some embodiments, the dynamic sound comprises an acoustic frequency from about 20 Hz to about 20 kHz. In some embodiments, the auditory stimulus comprises an acoustic frequency capable of modulating a gamma waveform in the subject. In some embodiments, the acoustic frequency capable of modulating a gamma waveform in the subject comprises an acoustic waveform of .1 Hz, 1 Hz, 5 Hz, 10 Hz, 20 Hz, 25 Hz, 30 Hz, 31 Hz, 32 Hz, 33 Hz, 34 Hz, 35 Hz, 36 Hz, 37 Hz, 38 Hz, 39 Hz, 40 Hz, 41 Hz, 42 Hz, 43 Hz, 44 Hz, 45 Hz, 46 Hz, 47 Hz, 48 Hz, 49 Hz, 50 Hz, 60 Hz, 70 Hz, 80 Hz, 90 Hz, 100 Hz, 150 Hz, 200 Hz, 250 Hz, 300 Hz, 400 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4,000 Hz, 5000 Hz, 6,000 Hz, 7,000 Hz, 8,000 Hz, 9,000 Hz, or 10,000 Hz.

[0161] The auditory stimulus can be turned on and off based on a predetermined or fixed pulse rate interval, such as every 0.025 seconds, to provide a pulse repetition frequency of 40 Hz. The audio source can be turned on and off to provide a pulse repetition frequency in the range of about 20 Hertz (Hz) to about 140 Hz, about 30 Hz to about 60 Hz, about 40 Hz to about 60 Hz, about 35 Hz to about 45 Hz, or about 40 Hz, in accordance with methods disclosed herein.

iii. Haptic Source

[0162] In a fully functional human hearing anatomy, the outer ear comprises an auricle and an ear canal. A sound wave or acoustic pressure is collected by the auricle and channeled into and through the ear canal. Disposed across the distal end of the ear canal is a tympanic membrane which vibrates in response to acoustic wave. This vibration is coupled to the oval window or fenestra ovalis through three bones of middle ear, collectively referred to as the ossicles and comprising the malleus, the incus, and the stapes. The ossicles of the middle ear serve to filter and amplify an acoustic wave, causing the oval window to vibrate. Such vibration sets up waves of fluid motion within the cochlea. Such fluid motion, in turn, activates hair cells that line the inside of cochlea. Activation of the hair cells causes appropriate nerve impulses to be transferred through the spiral ganglion cells and auditory nerve to the brain, where they are perceived as sound. In some embodiments, such as in damaged or dysfunctional hearing, this process is disrupted. A haptic source, such as a wireless bone conduction device, works by transmitting vibrations through the bones of the skull to the inner ear's cochlea, bypassing the outer and middle ear. In some embodiments, a haptic source can improve hearing perception, such as in damaged or dysfunctional hearing and can be useful in activating neural, visual, oscillations, *e.g.*, gamma oscillations, in a brain region of a subject corresponding to the haptic frequency generated by the haptic device.

[0163] By way of example, a portable system can comprise a haptic source. The haptic source can comprise headphones worn about the head of a subject. The wireless headphones can comprise wireless bone conduction headphones suitable for delivering a haptic vibration gamma stimulus to the subject. The wireless bone conduction headphones can include, for example, circumaural headphones (e.g., full size/over-ear headphones) designed to sit above the ear of a user. The haptic source can be integrated into the audio source, i.e., wherein the haptic source located within an audio source as disclosed herein.

[0164] In some embodiments, bone conduction headphones include ear-fitting headphones, such as earphones or in-ear headphones. Earphones (or earbuds) can refer to small headphones that are fitted directly in the outer ear, facing but not inserted in the ear canal. In-ear headphones (or in-ear monitors or canalphones) can refer to small headphones that can be designed and constructed for insertion into the ear canal. In-ear headphones engage the ear canal and can block out more ambient noise as compared to earphones, thus providing a more immersive auditory brainwave stimulation experience. In-ear headphones can include ear canal plugs made or formed from one or more material, such as silicone rubber, elastomer, or foam. In some embodiments, in-ear headphones can include custom-made castings of the ear canal to create custom-molded plugs that provide added comfort and noise isolation to the subject, thereby further improving the immersion of a subject during the non-invasive stimulation .

[0165] In some embodiments, the haptic device can include an implanted bone conduction prosthesis, or a bone conduction hearing aid device.

1. Haptic Stimulus

[0166] In some embodiments, a haptic source is configured to generate a haptic stimulus such as a vibration, or a similar haptic stimulus. In some embodiments, the haptic stimulus can include any means that induces the perception of vibration through touch. In some embodiments, a haptic stimulus can be any stimulus that activates the somatosensory system.

[0167] In some embodiments, the frequency of the haptic stimulus comprises a haptic stimulus of 1 Hertz (Hz), 1 Hz, 5 Hz, 10 Hz, 20 Hz, 25 Hz, 30 Hz, 31 Hz, 32 Hz, 33 Hz, 34 Hz, 35 Hz, 36 Hz, 37 Hz, 38 Hz, 39 Hz, 40 Hz, 41 Hz, 42 Hz, 43 Hz, 44 Hz, 45 Hz, 46 Hz, 47 Hz, 48 Hz, 49 Hz, 50 Hz, 60 Hz, 70 Hz, 80 Hz, 90 Hz, 100 Hz, 150 Hz, 200 Hz, 250 Hz, 300 Hz, 400 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4,000 Hz, 5000 Hz, 6,000 Hz, 7,000 Hz, 8,000 Hz, 9,000 Hz, or 10,000 Hz.

[0168] In some embodiments, the haptic stimulus can be turned on and off based on a predetermined or fixed pulse rate interval, such as every 0.025 seconds, to provide a pulse repetition frequency of 40 Hz. The haptic source can be turned on and off to provide a pulse

repetition frequency in the range of 20 Hertz (Hz) to about 140 Hz, about 30 Hz to about 60 Hz, about 40 Hz to about 60 Hz, about 35 Hz to about 45 Hz, or about 40 Hz, in accordance with methods disclosed herein.

B. Additional Portable System Components

i. Single Headset Device

[0169] In some embodiments, a portable system as disclosed herein comprises a single headset device. In some embodiments, the single headset device comprises a visual, audio, or haptic source, or any combination thereof as described herein. In some embodiments, the single headset device comprises an audio source and a visual source, wherein the visual source is rotatable about the audio source. In some embodiments, a module of any device or system as disclosed herein is rotatable about an axis of another module of the device or system. For instance, a visual module may be rotatable about an auditory module of a device or system as disclosed herein. In some embodiments, the single headset device comprises an audio source comprising headphones, and a visual source comprising glasses wherein the glasses are rotatable about the headphones, e.g., as shown and described in **FIGs. 66-73**.

[0170] In some embodiments, the single headset device comprises an audio source and a visual source, wherein the visual source is rotatable about the audio source, wherein the visual source is rotatable by about 0 degrees to about 360 degrees about the audio source. In some embodiments, the visual source is rotatable by about 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, or 360 degrees about the audio source. In some embodiments, the visual source is rotatable by more than 360 degrees about the audio source.

[0171] In some embodiments, a portable system as disclosed herein comprises a single headset device wherein the single headset device comprises a visual source and an audio source, wherein the visual source is rotatable about the audio source and audio source comprises a headband, e.g., as shown and described in **FIGs. 70 and 71**. In some embodiments the headband comprises a detachable headband.

ii. Processor, Memory, and Feedback Sensor

[0172] In some embodiments, a portable system also includes at least one memory for storing processor executable instructions and at least one processor communicatively connected one or more additional component of the portable system. In some embodiments, a portable system also includes at least one memory for storing processor executable instructions and at least one processor communicatively connected to a stimulus emitting component of the portable system

and the at least one memory. Upon execution of the processor executable instructions, the at least one processor may control the portable system such that system emits a stimulus at a frequency that activates neural oscillations, *e.g.*, gamma oscillations, in a brain region of the subject corresponding to the frequency generated by the stimulus emitting component.

[0173] In some embodiments, the portable system includes a data interface that enables data communication between the system and an external control device or system. The external device may be external device such as a fitting system, PDA, computer, mobile phone, or any other suitable device. Preferably, the interface allows two-way or bidirectional communication. That is, interface data may be sent from both the open view visual stimulation device and the external device. For example, in one embodiment, the interface may be adapted to receive control signals from the external device for generating a visual stimulus at predetermined frequencies, and receive control settings for the portable system for storing in the memory unit. In some embodiments, however, the interface is a one-way interface, allowing only data to be forwarded from the external device to the portable system. In other embodiments, communication is a one-way interface with data being forwarded from the open view visual stimulation device to any type of receiving device. The data may include measured control signals or any type of status information or other suitable data. This information may be used to merely monitor the portable system or be used with a control device that may be a separate device or be integrated into the portable system or any other suitable device.

[0174] In some embodiments, the processor is configured to receive an indication of a physiological, cognitive, neural, visual, or physical assessment of the subject wearing portable system, *e.g.*, as a single headset device embodiment. In some embodiments, when the processor receives the indication of the physiological, cognitive, neural, visual, or physical assessment of the subject, the processor instructs the stimulus emitting component to emit a visual, auditory, and/or haptic stimulus, or any combination thereof. In some embodiments, the physical assessment of the subject comprises ascertaining at least one of the subject's: compliance with proper use and positioning of the system, eye status, alert or sleep status, or environment and surroundings. In some embodiments, the physical assessment of the subject is performed to determine hearing of the subject. the indication of the physiological, cognitive, neural, visual, or physical assessment of the subject comprises a biosignal. In some embodiments, the biosignal comprises an electroencephalography (EEG).

[0175] In some embodiments, the cognitive assessment of the subject is obtained through questions posed to the subject, activities and tasks performed by the subject in response to a prompt, or behaviors exhibited by the subject.

[0176] In some embodiments, a portable system as disclosed herein is provided with or operatively connected to a computer system as disclosed herein. The computer system can communicate with one or more remote computer systems through the network. For instance, the computer system can communicate with a remote computer system of a user. Examples of remote computer systems include personal computers (e.g., portable PC), slate or tablet PC's (e.g., Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (e.g., Apple® iPhone, Android-enabled device, Blackberry®), or personal digital assistants. The user can access the computer system via the network. In some embodiments, the computer systems are programmed to implement the function of a portable system, such as implementing a stimulus delivered to a subject by the portable system as described herein.

[0177] In some embodiments, a portable system comprises one or more feedback components. The feedback component can include or interface with the microphone to obtain, identify, or receive sound. The feedback component can obtain ambient noise. The feedback component can obtain sound from the speakers to facilitate the audio device adjusting a characteristic of the auditory stimulus generated by the speaker. The microphone can receive voice input from a subject, such as audio commands, instructions, requests, feedback information, or responses to survey questions.

iii. Hand-held Controller

[0178] In some embodiments, the portable system further comprises a hand-held controller. In some embodiments, said hand-held controller receives and transmits a signal dictating a dosing parameter corresponding to a frequency, a duration, a brightness, or a color of said visual stimulus, or a combination thereof, or a duration, an intensity, or a frequency of said audio stimuli, or a combination thereof, or a duration, frequency, intensity, or combination thereof of said haptic stimulus. In some embodiments, said hand-held controller further comprises an independent power supply comprising batteries or a rechargeable battery.

[0179] In some embodiments, the hand-held controller further comprises adjustable inputs for said single headset device, said audio source, said haptic source, and/or said visual source, wherein said adjustable inputs for said audio source comprise an adjustable volume input, and said adjustable inputs for said visual source comprise an adjustable brightness input and wherein said adjustable input for said single headset device comprises an input for powering on and powering off said single headset device, or for pausing said visual, haptic, or audio stimulus. In some embodiments, said hand-held controller comprises a device as shown and described in **FIGs. 72, FIG. 73, FIG. 75A, FIG. 75B, FIG. 75C, or FIG. 75D.**

iv. Neural Stimulation System (NSS)

[0180] In some embodiments, disclosed herein is a neural stimulation system. In some cases, a portable system or single headset device as disclosed herein comprises a neural stimulation system as disclosed herein. In some embodiments, a portable system or single headset device comprises a visual source, an audio source, and/or a haptic source as disclosed herein, wherein the visual, audio, or haptic source comprises an NSS as disclosed herein. The following describe illustrative embodiments, of a NSS that can be integrated into a portable system or single headset device as disclosed herein.

[0181] **FIG. 1** is a block diagram depicting a system to perform visual brain stimulation in accordance with an embodiment. The system 100 can include a neural stimulation system (“NSS”) 105. The NSS 105 can be referred to as visual NSS 105 or NSS 105. In some embodiments, the visual NSS or NSS comprise a visual source, audio source, or a haptic source as described herein and can be included in a portable system as disclosed herein, wherein the visual source, audio source, or haptic source is configured to deliver a visual, auditory, or haptic stimulus, or a combination thereof. In brief overview, the NSS 105 can include, access, interface with, or otherwise communicate with one or more of a light generation module 110, light adjustment module 115, unwanted frequency filtering module 120, profile manager 125, side effects management module 130, feedback monitor 135, data repository 140, visual signaling component 150, filtering component 155, or feedback component 160. The light generation module 110, light adjustment module 115, unwanted frequency filtering module 120, profile manager 125, side effects management module 130, feedback monitor 135, visual signaling component 150, filtering component 155, or feedback component 160 can each include at least one processing unit or other logic device such as programmable logic array engine, or module configured to communicate with the database repository 150. The light generation module 110, light adjustment module 115, unwanted frequency filtering module 120, profile manager 125, side effects management module 130, feedback monitor 135, visual signaling component 150, filtering component 155, or feedback component 160 can be separate components, a single component, or part of the NSS 105. The system 100 and its components, such as the NSS 105, can include hardware elements, such as one or more processors, logic devices, or circuits. The system 100 and its components, such as the NSS 105, can include one or more hardware or interface component depicted in system 700 in FIGs. 7A and 7B. For example, a component of system 100 can include or execute on one or more processors 721, access storage 728 or memory 722, and communicate via network interface 718.

[0182] Still referring to **FIG. 1**, and in further detail, the NSS 105 can include at least one light generation module 110. The light generation module 110 can be designed and constructed to

interface with a visual signaling component 150 to provide instructions or otherwise cause or facilitate the generation of a visual signal, such as a light pulse or flash of light, having one or more predetermined parameter. The light generation module 110 can include hardware or software to receive and process instructions or data packets from one or more module or component of the NSS 105. The light generation module 110 can generate instructions to cause the visual signaling component 150 to generate a visual signal. The light generation module 110 can control or enable the visual signaling component 150 to generate the visual signal having one or more predetermined parameters.

[0183] The light generation module 110 can be communicatively coupled to the visual signaling component 150. The light generation module 110 can communicate with the visual signaling component 150 via a circuit, electrical wire, data port, network port, power wire, ground, electrical contacts or pins. The light generation module 110 can wirelessly communicate with the visual signaling component 150 using one or more wireless protocols such as Bluetooth, Bluetooth Low Energy, Zigbee, Z-Wave, IEEE 802.11, WIFI, 3G, 4G, LTE, near field communications (“NFC”), or other short, medium or long range communication protocols, etc. The light generation module 110 can include or access network interface 718 to communicate wirelessly or over a wire with the visual signaling component 150.

[0184] The light generation module 110 can interface, control, or otherwise manage various types of visual signaling components 150 in order to cause the visual signaling component 150 to generate, block, control, or otherwise provide the visual signal having one or more predetermined parameters. The light generation module 110 can include a driver configured to drive a light source of the visual signaling component 150. For example, the light source can include a light emitting diode (“LED”), and the light generation module 110 can include an LED driver, chip, microcontroller, operational amplifiers, transistors, resistors, or diodes configured to drive the LED light source by providing electricity or power having certain voltage and current characteristics.

[0185] In some embodiments, the light generation module 110 can instruct the visual signaling component, e.g., the visual source, 150 to provide a visual signal that include a light wave 200 as depicted in **FIG. 2A**. The light wave 200 can include or be formed of electromagnetic waves. The electromagnetic waves of the light wave can have respective amplitudes and travel orthogonal to one another as depicted by the amplitude of the electric field 205 versus time and the amplitude of the magnetic field 210 versus time. The light wave 200 can have a wavelength 215. The light wave can also have a frequency. The product of the wavelength 215 and the frequency can be the speed of the light wave. For example, the speed of the light wave can be approximately 299,792,458 meters per second in a vacuum.

[0186] The light generation module 110 can instruct the visual signaling component 150 to generate light waves having one or more predetermined wavelength or intensity. The wavelength of the light wave can correspond to the visible spectrum, ultraviolet spectrum, infrared spectrum, or some other wavelength of light. For example, the wavelength of the light wave within the visible spectrum range can range from 390 to 700 nanometers (“nm”). Within the visible spectrum, the light generation module 110 can further specify one or more wavelengths corresponding to one or more colors. For example, the light generation module 110 can instruct the visual signaling component 150 to generate visual signals comprising one or more light waves having one or more wavelength corresponding to one or more of ultra-violet (e.g., 10-380 nm); violet (e.g., 380-450 nm), blue (e.g., 450-495 nm), green (e.g., 495-570 nm), yellow (e.g., 570-590 nm), orange (e.g., 590-620 nm), red (e.g., 620-750 nm); or infrared (e.g., 750 -1000000 nm). The wavelength can range from 10 nm to 100 micrometers. In some embodiments, the wavelength can be in the range of 380 to 750 nm.

[0187] The light generation module 110 can determine to provide visual signals that include light pulses. The light generation module 110 can instruct or otherwise cause the visual signaling component 150 to generate light pulses. A light pulse can refer to a burst of light waves. For example, **FIG. 2B** illustrates a burst of a light wave. The burst of light wave can refer to a burst of an electric field 250 generated by the light wave. The burst of the electric field 250 of the light wave can be referred to as a light pulse or a flash of light. For example, a light source that is intermittently turned on and off can create bursts, flashes or pulses of light.

[0188] **FIG. 2C** illustrates pulses of light 235a-c in accordance with an embodiment. The light pulses 235a-c can be illustrated via a graph in the frequency spectrum where the y-axis represents frequency of the light wave (e.g., the speed of the light wave divided by the wavelength) and the x-axis represents time. The visual signal can include modulations of light wave between a frequency of F_a and frequency different from F_a . For example, the NSS 105 can modulate a light wave between a frequency in the visible spectrum, such as F_a , and a frequency outside the visible spectrum. The NSS 105 can modulate the light wave between two or more frequencies, between an on state and an off state, or between a high power state and a low power state.

[0189] In some cases, the frequency of the light wave used to generate the light pulse can be constant at F_a , thereby generating a square wave in the frequency spectrum. In some embodiments, each of the three pulses 235a-c can include light waves having a same frequency F_a .

[0190] The width of each of the light pulses (e.g., the duration of the burst of the light wave) can correspond to a pulse width 230a. The pulse width 230a can refer to the length or duration of the burst. The pulse width 230a can be measured in units of time or distance. In some embodiments,

the pulses 235a-c can include light waves having different frequencies from one another. In some embodiments, the pulses 235a-c can have different pulse widths 230a from one another, as illustrated in **FIG. 2D**. For example, a first pulse 235d of **FIG. 2D** can have a pulse width 230a, while a second pulse 235e has a second pulse width 230b that is greater than the first pulse width 230a. A third pulse 235f can have a third pulse width 230c that is less than the second pulse width 230b. The third pulse width 230c can also be less than the first pulse width 230a. While the pulse widths 230a-c of the pulses 235d-f of the pulse train can vary, the light generation module 110 can maintain a constant pulse rate interval 240 for the pulse train.

[0191] The pulses 235a-c can form a pulse train having a pulse rate interval 240. The pulse rate interval 240 can be quantified using units of time. The pulse rate interval 240 can be based on a frequency of the pulses of the pulse train 201. The frequency of the pulses of the pulse train 201 can be referred to as a modulation frequency. For example, the light generation module 110 can provide a pulse train 201 with a predetermined frequency corresponding to gamma activity, such as 40 Hz. To do so, the light generation module 110 can determine the pulse rate interval 240 by taking the multiplicative inverse (or reciprocal) of the frequency (e.g., 1 divided by the predetermined frequency for the pulse train). For example, the light generation module 110 can take the multiplicative inverse of 40 Hz by dividing 1 by 40 Hz to determine the pulse rate interval 240 as .025 seconds. The pulse rate interval 240 can remain constant throughout the pulse train. In some embodiments, the pulse rate interval 240 can vary throughout the pulse train or from one pulse train to a subsequent pulse train. In some embodiments, the number of pulses transmitted during a second can be fixed, while the pulse rate interval 240 varies.

[0192] In some embodiments, the light generation module 110 can generate a light pulse having a light wave that varies in frequency. For example, the light generation module 110 can generate up-chirp pulses where the frequency of the light wave of the light pulse increases from the beginning of the pulse to the end of the pulse as illustrated in **FIG. 2E**. For example, the frequency of a light wave at the beginning of pulse 235g can be F_a . The frequency of the light wave of the pulse 235g can increase from F_a to F_b in the middle of the pulse 235g, and then to a maximum of F_c at the end of the pulse 235g. Thus, the frequency of the light wave used to generate the pulse 235g can range from F_a to F_c . The frequency can increase linearly, exponentially, or based on some other rate or curve.

[0193] The light generation module 110 can generate down-chirp pulses, as illustrated in **FIG. 2F**, where the frequency of the light wave of the light pulse decreases from the beginning of the pulse to the end of the pulse. For example, the frequency of a light wave at the beginning of pulse 235j can be F_d . The frequency of the light wave of the pulse 235j can decrease from F_d to F_e in the middle of the pulse 235j, and then to a minimum of F_f at the end of the pulse 235j. Thus, the

frequency of the light wave used to generate the pulse 235j can range from F_d to F_f . The frequency can decrease linearly, exponentially, or based on some other rate or curve.

[0194] A visual signaling component 150 can be designed and constructed to generate the light pulses responsive to instructions from the light generation module 110. The instructions can include, for example, parameters of the light pulse such as a frequency or wavelength of the light wave, intensity, duration of the pulse, frequency of the pulse train, pulse rate interval, or duration of the pulse train (e.g., a number of pulses in the pulse train or the length of time to transmit a pulse train having a predetermined frequency). The light pulse can be perceived, observed, or otherwise identified by the brain via ocular means such as eyes. The light pulses can be transmitted to the eye via direct visual field or peripheral visual field.

[0195] FIG. 3A illustrates a horizontal direct visual field 310 and a horizontal peripheral visual field. FIG. 3B illustrates a vertical direct visual field 320 and a vertical peripheral visual field 325. FIG. 3C illustrates degrees of direct visual fields and peripheral visual fields, including relative distances at which visual signals might be perceived in the different visual fields. The visual signaling component 150 can include a light source 305. The light source 305 can be positioned to transmit light pulses into the direct visual field 310 or 320 of a person's eyes. The NSS 105 can be configured to transmit light pulses into the direct visual field 310 or 320 because this can facilitate brain entrainment as the person can pay more attention to the light pulses. The level of attention can be quantitatively measured directly in the brain, indirectly through the person's eye behavior, or by active feedback (e.g., mouse tracking).

[0196] The light source 305 can be positioned to transmit light pulses into a peripheral visual field 315 or 325 of a person's eyes. For example, the NSS 105 can transmit light pulses into the peripheral visual field 315 or 325 as these light pulses can be less distracting to the person who might be performing other tasks, such as reading, walking, driving, etc. Thus, the NSS 105 can provide subtle, on-going visual brain stimulation by transmitting light pulses via the peripheral visual field.

[0197] In some embodiments, the light source 305 can be head-worn, while in other embodiments the light source 305 can be held by a subject's hands, placed on a stand, hung from a ceiling, or connected to a chair or otherwise positioned to direct light towards the direct or peripheral visual fields. For example, a chair or externally supported system can include or position the light source 305 to provide the visual input while maintaining a fixed/pre-specified relationship between the subject's visual field and the visual stimulus. The system can provide an immersive experience. For example, the system can include an opaque or partially opaque dome that includes the light source. The dome can be positioned over the subject's head while the subject

sits or reclines in chair. The dome can cover portions of the subject's visual field, thereby reducing external distractions and facilitating entrainment of regions of the brain.

[0198] The light source 305 can include any type of light source or light emitting device. The light source can include a coherent light source, such as a laser. The light source 305 can include a light emitting diode (LED), Organic LED, fluorescent light source, incandescent light, or any other light emitting device. The light source can include a lamp, light bulb, or one or more light emitting diodes of various colors (e.g., white, red, green, blue). In some embodiments, the light source includes a semiconductor light emitting device, such as a light emitting diode of any spectral or wavelength range. In some embodiments, the light source 305 includes a broadband lamp or a broadband light source. In some embodiments, the light source includes a black light. In some embodiments, light source 305 includes a hollow cathode lamp, a fluorescent tube light source, a neon lamp, an argon lamp, a plasma lamp, a xenon flash lamp, a mercury lamp, a metal halide lamp, or a sulfur lamp. In some embodiments, the light source 305 includes a laser, or a laser diode. In some embodiments, light source 305 includes an OLED, PHOLED, QDLED, or any other variation of a light source utilizing an organic material. In some embodiments, light source 305 includes a monochromatic light source. In some embodiments, light source 305 includes a polychromatic light source. In some embodiments, the light source 305 includes a light source emitting light partially in the spectral range of ultraviolet light. In some embodiments, light source 305 includes a device, product or a material emitting light partially in the spectral range of visible light. In some embodiments, light source 305 is a device, product or a material partially emanating or emitting light in the spectral range of the infrared light. In some embodiments, light source 305 includes a device, product or a material emanating or emitting light in the visible spectral range. In some embodiments, light source 305 includes a light guide, an optical fiber or a waveguide through which light is emitted from the light source.

[0199] In some embodiments, light source 305 includes one or more mirrors for reflecting or redirecting of light. For example, the mirrors can reflect or redirect light towards the direct visual field 310 or 320, or the peripheral visual field 315 or 325. The light source 305 can include or interact with microelectromechanical devices ("MEMS"). The light source 305 can include or interact with a digital light projector ("DLP"). In some embodiments, the light source 305 can include ambient light or sunlight. The ambient light or sunlight can be focused by one or more optical lenses and directed towards the direct visual field or peripheral field. The ambient light or sunlight can be directed by one or more mirrors towards the directed visual field or peripheral visual field.

[0200] In cases where the light source is ambient light, the ambient light is not positioned but the ambient light can enter the eye via a direct visual field or peripheral visual field. In some

embodiments, the light source 305 can be positioned to direct light pulses towards the direct visual field or peripheral field. For example, one or more light sources 305 can be attached, affixed, coupled, mechanically coupled, or otherwise provided with a frame 400 as illustrated in **FIG. 4A**. In some embodiments, the visual signaling component 150 can include the frame 400. Additional details of the operation of the NSS 105 in conjunction with the frame 400 including one or more light sources 305 are provided below, in the section labelled as “NSS Operating With A Frame”. Thus, the light source can include any type of light source such as an optical light source, mechanical light source, or chemical light source. The light source can include any material or object that is reflective or opaque that can generate, emit, or reflect oscillating patterns of light, such as a fan rotating in front of a light, or bubbles. In some embodiments, the light source can include optical illusions that are invisible, physiological phenomena that are within the eye (e.g., pressing the eyeball), or chemicals applied to the eye.

1. Systems and Devices Configured for Neural Stimulation via Visual Stimulation

[0201] Referring now to **FIG. 4A**, the frame 400 can be designed and constructed to be placed or positioned on a person's head. The frame 400 can be configured to be worn by the person. The frame 400 can be designed and constructed to stay in place. The frame 400 can be configured to be worn and stay in place as a person sits, stands, walks, runs, or lays down flat. The light source 305 can be configured on the frame 400 to project light pulses towards the person's eyes during these various positions. In some embodiments, the light source 305 can be configured to project light pulses towards the person's eyes if their eyelids are closed such that the light pulse penetrates the eyelid to be perceived by the retina. The frame 400 can include a bridge 420. The frame 400 can include one or more eye wires 415 coupled to the bridge 420. The bridge 420 can be positioned in between the eye wires 415. The frame 400 can include one or more temples extending from the one or more eye wires 415. In some embodiments, the eye wires 415 can include or hold a lens 425. In some embodiments, the eye wires 415 can include or hold a solid material 425 or cover 425. The lens, solid material, or cover 425 can be transparent, semi-transparent, opaque, or completely block out external light.

[0202] One or more light sources 305 can be positioned on or adjacent to the eye wire 415, lens or other solid material 425, or bridge 420. For example, a light source 305 can be positioned in the middle of the eye wire 415 on a solid material 425 in order to transmit light pulses into the direct visual field. In some embodiments, a light source 305 can be positioned at a corner of the eye wire 415, such as a corner of the eye wire 415 coupled to the temple 410, in order to transmit light pulses towards a peripheral field.

[0203] The NSS 105 can perform visual brain stimulation via a single eye or both eyes. For example, the NSS 105 can direct light pulses to a single eye or both eyes. The NSS 105 can interface with a visual signaling component 150 that includes a frame 400 and two eye wires 415. However, the visual signaling component 150 can include a single light source 305 configured and positioned to direct light pulses to a first eye. The visual signaling component 150 can further include a light blocking component that keeps out or blocks the light pulses generated from the light source 305 from entering a second eye. The visual signaling component 150 can block or prevent light from entering the second eye during the brain entrainment process.

[0204] In some embodiments, the visual signaling component 150 can alternatively transmit or direct light pulses to the first eye and the second eye. For example, the visual signaling component 150 can direct light pulses to the first eye for a first time interval. The visual signaling component 150 can direct light pulses to the second eye for a second time interval. The first time interval and the second time interval can be a same time interval, overlapping time intervals, mutually exclusive time intervals, or subsequent time intervals.

[0205] FIG. 4B illustrates a frame 400 comprising a set of shutters 435 that can block at least a portion of light that enters through the eye wire 415. The set of shutters 435 can intermittently block ambient light or sunlight that enters through the eye wire 415. The set of shutters 435 can open to allow light to enter through the eye wire 415, and close to at least partially block light that enters through the eye wire 415. Additional details of the operation of the NSS 105 in conjunction with the frame 400 including one or more shutters 430 are provided below, in the section labelled as “NSS Operating With A Frame”.

[0206] The set of shutters 435 can include one or more shutter 430 that is opened and closed by one or more actuator. The shutter 430 can be formed from one or more materials. The shutter 430 can include one or more materials. The shutter 430 can include or be formed from materials that are capable of at least partially blocking or attenuating light.

[0207] The frame 400 can include one or more actuators configured to at least partially open or close the set of shutters 435 or an individual shutter 430. The frame 400 can include one or more types of actuators to open and close the shutters 435. For example, the actuator can include a mechanically driven actuator. The actuator can include a magnetically driven actuator. The actuator can include a pneumatic actuator. The actuator can include a hydraulic actuator. The actuator can include a piezoelectric actuator. The actuator can include a micro-electromechanical systems (“MEMS”).

[0208] The set of shutters 435 can include one or more shutter 430 that is opened and closed via electrical or chemical techniques. For example, the shutter 430 or set of shutters 435 can be formed from one or more chemicals. The shutter 430 or set of shutters can include one or more

chemicals. The shutter 430 or set of shutters 435 can include or be formed from chemicals that are capable of at least partially blocking or attenuating light.

[0209] For example, the shutter 430 or set of shutters 435 can include photochromic lenses configured to filter, attenuate or block light. The photochromic lenses can automatically darken when exposed to sunlight. The photochromic lens can include molecules that are configured to darken the lens. The molecules can be activated by light waves, such as ultraviolet radiation or other light wavelengths. Thus, the photochromic molecules can be configured to darken the lens in response to a predetermined wavelength of light.

[0210] The shutter 430 or set of shutters 435 can include electrochromic glass or plastic. Electrochromic glass or plastic can change from light to dark (e.g., clear to opaque) in response to an electrical voltage or current. Electrochromic glass or plastic can include metal-oxide coatings that are deposited on the glass or plastic, multiple layers, and lithium ions that travel between two electrodes between a layer to lighten or darken the glass.

[0211] The shutter 430 or set of shutters 435 can include micro shutters. Micro shutters can include tiny windows that measure 100 by 200 microns. The micro shutters can be arrayed in the eye frame 415 in a waffle-like grid. The individual micro shutters can be opened or closed by an actuator. The actuator can include a magnetic arm that sweeps past the micro shutter to open or close the micro shutter. An open micro shutter can allow light to enter through the eye frame 415, while a closed micro shutter can block, attenuate, or filter the light.

[0212] The NSS 105 can drive the actuator to open and close one or more shutters 430 or the set of shutters 435 at a predetermined frequency such as 40 Hz. By opening and closing the shutter 430 at the predetermined frequency, the shutter 430 can allow flashes of light to pass through the eye wire 415 at the predetermined frequency. Thus, the frame 400 including a set of shutters 435 may not include or use separate light source coupled to the frame 400, such as a light source 305 coupled to frame 400 depicted in **FIG. 4A**.

[0213] In some embodiments, the visual signaling component 150 or light source 305 can refer to or be included in a virtual reality headset 401, as depicted in **FIG. 4C**. For example, the virtual reality headset 401 can be designed and constructed to receive a light source 305. The light source 305 can include a computing device having a display device, such as a smartphone or mobile telecommunications device. The virtual reality headset 401 can include a cover 440 that opens to receive the light source 305. The cover 440 can close to lock or hold the light source 305 in place. When closed, the cover 440 and case 450 and 445 can form an enclosure for the light source 305. This enclosure can provide an immersive experience that minimize or eliminates unwanted visual distractions. The virtual reality headset can provide an environment to maximize brainwave entrainment. The virtual reality headset can provide an augmented reality

experience. In some embodiments, the light source 305 can form an image on another surface such that the image is reflected off the surface and towards a subject's eye (e.g., a heads up display that overlays on the screen a flickering object or an augmented portion of reality). Additional details of the operation of the NSS 105 in conjunction with the virtual reality headset 401 are provided below.

[0214] The virtual reality headset 401 includes straps 455 and 460 configured to secure the virtual reality headset 401 to a person's head. The virtual reality headset 401 can be secured via straps 455 and 460 such to minimize movement of the headset 401 worn during physical activity, such as walking or running. The virtual reality headset 401 can include a skull cap formed from 460 or 455.

[0215] The feedback sensor 605 can include an electrode, dry electrode, gel electrode, saline soaked electrode, or adhesive-based electrodes.

[0216] FIGs. 5A-5D illustrate embodiments of the visual signaling component 150 that can include a tablet computing device 500 or other computing device 500 having a display screen 305 as the light source 305. The visual signaling component 150 can transmit light pulses, light flashes, or patterns of light via the display screen 305 or light source 305.

[0217] FIG. 5A illustrates a display screen 305 or light source 305 that transmits light. The light source 305 can transmit light comprising a wavelength in the visible spectrum. The NSS 105 can instruct the visual signaling component 150 to transmit light via the light source 305. The NSS 105 can instruct the visual signaling component 150 to transmit flashes of light or light pulses having a predetermined pulse rate interval. For example, **FIG. 5B** illustrates the light source 305 turned off or disabled such that the light source does not emit light, or emits a minimal or reduced amount of light. The visual signaling component 150 can cause the tablet computing device 500 to enable (e.g., **FIG. 5A**) and disable (e.g., **FIG. 5B**) the light source 305 such that flashes of light have a predetermined frequency, such as 40 Hz. The visual signaling component 150 can toggle or switch the light source 305 between two or more states to generate flashes of light or light pulses with the predetermined frequency.

[0218] In some embodiments, the light generation module 110 can instruct or cause the visual signaling component 150 to display a pattern of light via display device 305 or light source 305, as depicted in **FIGs. 5C and 5D**. The light generation module 110 can cause the visual signaling component 150 can flicker, toggle or switch between two or more patterns to generate flashes of light or light pulses. Patterns can include, for example, alternating checkerboard patterns 510 and 515. The pattern can include symbols, characters, or images that can be toggled or adjusted from one state to another state. For example, the color of a character or text relative to a background color can be inverted to cause a switch between a first state 510 and a second state 515. Inverting

a foreground color and background color at a predetermined frequency can generate light pulses by way of indicating visual changes that can facilitate adjusting or managing a frequency of neural oscillations. Additional details of the operation of the NSS 105 in conjunction with the tablet 500 are provided below, in the section labeled as “NSS Operating With a Tablet”.

[0219] In some embodiments, the light generation module 110 can instruct or cause the visual signaling component 150 to flicker, toggle, or switch between images configured to stimulate specific or predetermined portions of the brain or a specific cortex. The presentation, form, color, motion and other aspects of the light or an image based stimuli can dictate which cortex or cortices are recruited to process the stimuli. The visual signaling component 150 can stimulate discrete portions of the cortex by modulating the presentation of the stimuli to target specific or general regions of interest. The relative position in the field of view, the color of the input, or the motion and speed of the light stimuli can dictate which region of the cortex is stimulated.

[0220] For example, the brain can include at least two portions that process predetermined types of visual stimuli: the primary visual cortex on the left side of the brain, and the calcarine fissure on the right side of the brain. Each of these two portions can have one or more multiple sub-portions that process predetermined types of visual stimuli. For example, the calcarine fissure can include a sub-portion referred to as area V5 that can include neurons that respond strongly to motion but may not register stationary objects. Subjects with damage to area V5 can have motion blindness, but otherwise normal vision. In another example, the primary visual cortex can include a sub-portion referred to as area V4 that can include neurons that are specialized for color perception. Subjects with damage to area V4 can have color blindness and only perceive objects in shades of gray. In another example, the primary visual cortex can include a sub-portion referred to as area V1 that includes neurons that respond strongly to contrast edges and helps segment the image into separate objects.

[0221] Thus, the light generation module 110 can instruct or cause the visual signaling component 150 to form a type of still image or video, or generate a flicker, or toggle between images that configured to stimulate specific or predetermined portions of the brain or a specific cortex. For example, the light generation module 110 can instruct or cause the visual signaling component 150 to generate images of human faces to stimulate a fusiform face area, which can facilitate brain entrainment for subjects having prosopagnosia or face blindness. The light generation module 110 can instruct or cause the visual signaling component 150 to generate images of faces flickering to target this area of the subject's brain. In another example, the light generation module 110 can instruct the visual signaling component 150 to generate images that include edges or line drawings to stimulate neurons of the primary visual cortex that respond strongly to contrast edges.

[0222] The NSS 105 can include, access, interface with, or otherwise communicate with at least one light adjustment module 115. The light adjustment module 115 can be designed and constructed to measure or verify an environmental variable (e.g., light intensity, timing, incident light, ambient light, eye lid status, etc.) to adjust a parameter associated with the visual signal, such as a frequency, amplitude, wavelength, intensity pattern or other parameter of the visual signal. The light adjustment module 115 can automatically vary a parameter of the visual signal based on profile information or feedback. The light adjustment module 115 can receive the feedback information from the feedback monitor 135. The light adjustment module 115 can receive instructions or information from a side effects management module 130. The light adjustment module 115 can receive profile information from profile manager 125.

[0223] The NSS 105 can include, access, interface with, or otherwise communicate with at least one unwanted frequency filtering module 120. The unwanted frequency filtering module 120 can be designed and constructed to block, mitigate, reduce, or otherwise filter out frequencies of visual signals that are undesired to prevent or reduce an amount of such visual signals from being perceived by the brain. The unwanted frequency filtering module 120 can interface, instruct, control, or otherwise communicate with a filtering component 155 to cause the filtering component 155 to block, attenuate, or otherwise reduce the effect of the unwanted frequency on the neural oscillations.

[0224] The NSS 105 can include, access, interface with, or otherwise communicate with at least one profile manager 125. The profile manager 125 can be designed or constructed to store, update, retrieve or otherwise manage information associated with one or more subjects associated with the visual brain entrainment. Profile information can include, for example, historical treatment information, historical brain entrainment information, dosing information, parameters of light waves, feedback, physiological information, environmental information, or other data associated with the systems and methods of brain entrainment.

[0225] The NSS 105 can include, access, interface with, or otherwise communicate with at least one side effects management module 130. The side effects management module 130 can be designed and constructed to provide information to the light adjustment module 115 or the light generation module 110 to change one or more parameter of the visual signal in order to reduce a side effect. Side effects can include, for example, nausea, migraines, fatigue, seizures, eye strain, or loss of sight.

[0226] The side effects management module 130 can automatically instruct a component of the NSS 105 to alter or change a parameter of the visual signal. The side effects management module 130 can be configured with predetermined thresholds to reduce side effects. For example, the side effects management module 130 can be configured with a maximum duration of a pulse

train, maximum intensity of light waves, maximum amplitude, maximum duty cycle of a pulse train (e.g., the pulse width multiplied by the frequency of the pulse train), maximum number of treatments for brainwave entrainment in a time period (e.g., 1 hour, 2 hours, 12 hours, or 24 hours).

[0227] The side effects management module 130 can cause a change in the parameter of the visual signal in response to feedback information. The side effect management module 130 can receive feedback from the feedback monitor 135. The side effects management module 130 can determine to adjust a parameter of the visual signal based on the feedback. The side effects management module 130 can compare the feedback with a threshold to determine to adjust the parameter of the visual signal.

[0228] The side effects management module 130 can be configured with or include a policy engine that applies a policy or a rule to the current visual signal and feedback to determine an adjustment to the visual signal. For example, if feedback indicates that a patient receiving visual signals has a heart rate or pulse rate above a threshold, the side effects management module 130 can turn off the pulse train until the pulse rate stabilizes to a value below the threshold, or below a second threshold that is lower than the threshold.

[0229] The NSS 105 can include, access, interface with, or otherwise communicate with at least one feedback monitor 135. The feedback monitor can be designed and constructed to receive feedback information from a feedback component 160. Feedback component 160 can include, for example, a feedback sensor 605 such as a temperature sensor, heart or pulse rate monitor, physiological sensor, ambient light sensor, ambient temperature sensor, sleep status via actigraphy, blood pressure monitor, respiratory rate monitor, brain wave sensor, EEG probe, electrooculography (“EOG”) probes configured to measure the corneo-retinal standing potential that exists between the front and the back of the human eye, accelerometer, gyroscope, motion detector, proximity sensor, camera, microphone, or photo detector.

[0230] In some embodiments, a computing device 500 can include the feedback component 160 or feedback sensor 605, as depicted in FIGS. 5C and 5D. For example, the feedback sensor on tablet 500 can include a front-facing camera that can capture images of a person viewing the light source 305.

[0231] FIG. 6A depicts one or more feedback sensors 605 provided on a frame 400. In some embodiments, a frame 400 can include one or feedback sensors 605 provided on a portion of the frame, such as the bridge 420 or portion of the eye wire 415. The feedback sensor 605 can be provided with or coupled to the light source 305. The feedback sensor 605 can be separate from the light source 305.

[0232] The feedback sensor 605 can interact with or communicate with NSS 105. For example, the feedback sensor 605 can provide detected feedback information or data to the NSS 105 (e.g., feedback monitor 135). The feedback sensor 605 can provide data to the NSS 105 in real-time, for example as the feedback sensor 605 detects or senses or information. The feedback sensor 605 can provide the feedback information to the NSS 105 based on a time interval, such as 1 minute, 2 minutes, 5 minutes, 10 minutes, hourly, 2 hours, 4 hours, 12 hours, or 24 hours. The feedback sensor 605 can provide the feedback information to the NSS 105 responsive to a condition or event, such as a feedback measurement exceeding a threshold or falling below a threshold. The feedback sensor 605 can provide feedback information responsive to a change in a feedback parameter. In some embodiments, the NSS 105 can ping, query, or send a request to the feedback sensor 605 for information, and the feedback sensor 605 can provide the feedback information in response to the ping, request, or query.

[0233] **FIG. 6B** illustrates feedback sensors 605 placed or positioned at, on, or near a person's head. Feedback sensors 605 can include, for example, EEG probes that detect brain wave activity.

[0234] The feedback monitor 135 can detect, receive, obtain, or otherwise identify feedback information from the one or more feedback sensors 605. The feedback monitor 135 can provide the feedback information to one or more component of the NSS 105 for further processing or storage. For example, the profile manager 125 can update profile data structure 145 stored in data repository 140 with the feedback information. Profile manager 125 can associate the feedback information with an identifier of the patient or person undergoing the visual brain stimulation, as well as a time stamp and date stamp corresponding to receipt or detection of the feedback information. The identifier can be indicative of an activity of a subject, a physiological or physical condition of a subject, or a mental condition of a subject. The identifier can also be indicative of a disease, disorder, or condition.

[0235] The feedback monitor 135 can detect symptoms of a neurological disease or disorder. For the example, the feedback monitor can be used to evaluate changes in fine motor skills over time or changes in voice pitch or tone. The profile manager 125 can update profile data structure with the feedback information. The profile data structure can be used to assess whether a person is at risk of developing a neurological disorder, whether a person has a neurological disorder, or progression of symptoms of a neurological disorder.

[0236] The feedback monitor 135 can determine a level of attention. The level of attention can refer to the focus provided to the light pulses used for brain stimulation. The feedback monitor 135 can determine the level of attention using various hardware and software techniques. The feedback monitor 135 can assign a score to the level of attention (e.g., 1 to 10 with 1 being low

attention and 10 being high attention, or vice versa, 1 to 100 with 1 being low attention and 100 being high attention, or vice versa, 0 to 1 with 0 being low attention and 1 being high attention, or vice versa), categorize the level of attention (e.g., low, medium, high), grade the attention (e.g., A, B, C, D, or F), or otherwise provide an indication of a level of attention.

[0237] In some cases, the feedback monitor 135 can track a person's eye movement to identify a level of attention. The feedback monitor 135 can interface with a feedback component 160 that includes an eye-tracker. The feedback monitor 135 (e.g., via feedback component 160) can detect and record eye movement of the person and analyze the recorded eye movement to determine an attention span or level of attention. The feedback monitor 135 can measure eye gaze which can indicate or provide information related to covert attention. For example, the feedback monitor 135 (e.g., via feedback component 160) can be configured with electro-oculography ("EOG") to measure the skin electric potential around the eye, which can indicate a direction the eye faces relative to the head. In some embodiments, the EOG can include a system or device to stabilize the head so it cannot move in order to determine the direction of the eye relative to the head. In some embodiments, the EOG can include or interface with a head tracker system to determine the position of the heads, and then determine the direction of the eye relative to the head.

[0238] In some embodiments, the feedback monitor 135 and feedback component 160 can determine or track the direction of the eye or eye movement using video detection of the pupil or corneal reflection. For example, the feedback component 160 can include one or more camera or video camera. The feedback component 160 can include an infra-red source that sends light pulses towards the eyes. The light can be reflected by the eye. The feedback component 160 can detect the position of the reflection. The feedback component 160 can capture or record the position of the reflection. The feedback component 160 can perform image processing on the reflection to determine or compute the direction of the eye or gaze direction of the eye.

[0239] The feedback monitor 135 can compare the eye direction or movement to historical eye direction or movement of the same person, nominal eye movement, or other historical eye movement information to determine a level of attention. For example, if the eye is focused on the light pulses during the pulse train, then the feedback monitor 135 can determine that the level of attention is high. If the feedback monitor 135 determines that the eye moved away from the pulse train for 25% of the pulse train, then the feedback monitor 135 can determine that the level of attention is medium. If the feedback monitor 135 determines that the eye movement occurred for more than 50% of the pulse train or the eye was not focused on the pulse train for greater than 50%, then the feedback monitor 135 can determine that the level of attention is low.

[0240] In some embodiments, the system 100 can include a filter (e.g., filtering component 155) to control the spectral range of the light emitted from the light source. In some embodiments,

light source includes a light reactive material affecting the light emitted, such as a polarizer, filter, prism or a photochromic material, or electrochromic glass or plastic. The filtering component 155 can receive instructions from the unwanted frequency filtering module 120 to block or attenuate one or more frequencies of light.

[0241] The filtering component 155 can include an optical filter that can selectively transmit light in a particular range of wavelengths or colors, while blocking one or more other ranges of wavelengths or colors. The optical filter can modify the magnitude or phase of the incoming light wave for a range of wavelengths. The optical filter can include an absorptive filter, or an interference or dichroic filter. An absorptive filter can take energy of a photon to transform the electromagnetic energy of a light wave into internal energy of the absorber (e.g., thermal energy). The reduction in intensity of a light wave propagating through a medium by absorption of a part of its photons can be referred to as attenuation.

[0242] An interference filter or dichroic filter can include an optical filter that reflects one or more spectral bands of light, while transmitting other spectral bands of light. An interference filter or dichroic filter can have a nearly zero coefficient of absorption for one or more wavelengths. Interference filters can be high-pass, low-pass, bandpass, or band-rejection. An interference filter can include one or more thin layers of a dielectric material or metallic material having different refractive indices.

[0243] In an illustrative implementation, the NSS 105 can interface with a visual signaling component 150, a filtering component 155, and a feedback component 160. The visual signaling component 150 can include hardware or devices, such as glass frames 400 and one or more light sources 305. The filtering component 155 can include hardware or devices, such as a feedback sensor 605. The filtering component 155 can include hardware, materials or chemicals, such as a polarizing lens, shutters, electrochromic materials or photochromic materials.

2. Systems and Devices Configured for Neural Stimulation via Auditory Stimulation

[0244] FIG. 12A illustrates a system for auditory stimulation in accordance with an embodiment. The system 1200 can include one or more speakers 1205. The system 1200 can include one or more microphones. In some embodiments, the system can include both speakers 1205 and microphones 1210. In some embodiments, the system 1200 includes speakers 1205 and may not include microphones 1210. In some embodiments, the system 1200 includes microphones 1210 and may not include speakers 1210.

[0245] The speakers 1205 can be integrated with the audio signaling component 950. The audio signaling component 950 can include speakers 1205. The speakers 1205 can interact or

communicate with audio signaling component 950. For example, the audio signaling component 950 can instruct the speaker 1205 to generate sound.

[0246] The microphones 1210 can be integrated with the feedback component 960. The feedback component 960 can include microphones 1210. The microphones 1210 can interact or communicate with feedback component 960. For example, the feedback component 960 can receive information, data or signals from microphone 1210.

[0247] In some embodiments, the speaker 1205 and the microphone 1210 can be integrated together or a same device. For example, the speaker 1205 can be configured to function as the microphone 1210. The NSS 905 can toggle the speaker 1205 from a speaker mode to a microphone mode.

[0248] In some embodiments, the system 1200 can include a single speaker 1205 positioned at one of the ears of the subject. In some embodiments, the system 1200 can include two speakers. A first speaker of the two speakers can be positioned at a first ear, and the second speaker of the two speakers can be positioned at the second ear. In some embodiments, additional speakers can be positioned in front of the subject's head, or behind the subject's head. In some embodiments, one or more microphones 1210 can be positioned at one or both ears, in front of the subject's head, or behind the subject's head.

[0249] The speaker 1205 can include a dynamic cone speaker configured to produce sound from an electrical signal. The speaker 1205 can include a full-range driver to produce acoustic waves with frequencies over some or all of the audible range (e.g., 60 Hz to 20,000 Hz). The speaker 1205 can include a driver to produce acoustic waves with frequencies outside the audible range, such as 0 to 60 Hz, or in the ultrasonic range such as 20 kHz to 4 GHz. The speaker 1205 can include one or more transducers or drivers to produce sounds at varying portions of the audible frequency range. For example, the speaker 1205 can include tweeters for high range frequencies (e.g., 2,000 Hz to 20,000 Hz), mid-range drivers for middle frequencies (e.g., 250 Hz to 2000 Hz), or woofers for low frequencies (e.g., 60 Hz to 250 Hz).

[0250] The speaker 1205 can include one or more types of speaker hardware, components or technology to produce sound. For example, the speaker 1205 can include a diaphragm to produce sound. The speaker 1205 can include a moving-iron loudspeaker that uses a stationary coil to vibrate a magnetized piece of metal. The speaker 1205 can include a piezoelectric speaker. A piezoelectric speaker can use the piezoelectric effect to generate sound by applying a voltage to a piezoelectric material to generate motion, which is converted into audible sound using diaphragms and resonators.

[0251] The speaker 1205 can include various other types of hardware or technology, such as magnetostatic loudspeakers, magnetostrictive speakers, electrostatic loudspeakers, a ribbon

speaker, planar magnetic loudspeakers, bending wave loudspeakers, coaxial drivers, horn loudspeakers, Heil air motion transducers, or transparent ionic conduction speaker.

[0252] In some cases, the speaker 1205 may not include a diaphragm. For example, the speaker 1205 can be a plasma arc speaker that uses electrical plasma as a radiating element. The speaker 1205 can be a thermoacoustic speaker that uses carbon nanotube thin film. The speaker 1205 can be a rotary woofer that includes a fan with blades that constantly change their pitch.

[0253] In some embodiments, the speaker 1205 can include a headphone or a pair of headphones, ear speakers, earphones, or earbuds. Headphones can be relatively small speakers as compared to loudspeakers. Headphones can be designed and constructed to be placed in the ear, around the ear, or otherwise at or near the ear. Headphones can include electroacoustic transducers that convert an electrical signal to a corresponding sound in the subject's ear. In some embodiments, the headphones 1205 can include or interface with a headphone amplifier, such as an integrated amplifier or a standalone unit.

[0254] In some embodiments, the speaker 1205 can include headphones that can include an air jet that pushes air into the auditory canal, pushing the tympanum in a manner similar to that of a sound wave. The compression and rarefaction of the tympanic membrane through bursts of air (with or without any discernible sound) can control frequencies of neural oscillations similar to auditory signals. For example, the speaker 1205 can include air jets or a device that resembles in-ear headphones that either push, pull or both push and pull air into and out of the ear canal in order to compress or pull the tympanic membrane to affect the frequencies of neural oscillations. The NSS 905 can instruct, configure or cause the air jets to generate bursts of air at a predetermined frequency.

[0255] In some embodiments, the headphones can connect to the audio signaling component 950 via a wired or wireless connection. In some embodiments, the audio signaling component 950 can include the headphones. In some embodiments, the headphones 1205 can interface with one or more components of the NSS 905 via a wired or wireless connection. In some embodiments, the headphones 1205 can include one or more components of the NSS 905 or system 100, such as the audio generation module 910, audio adjustment module 915, unwanted frequency filtering module 920, profile manager 925, side effects management module 930, feedback monitor 935, audio signaling component 950, filtering component 955, or feedback component 960.

[0256] The speaker 1205 can include or be integrated into various types of headphones. For example, the headphones can include, for example, circumaural headphones (e.g., full size headphones) that include circular or ellipsoid earpads that are designed and constructed to seal against the head to attenuate external noise. Circumaural headphones can facilitate providing an immersive auditory brainwave stimulation experience, while reducing external distractions.

In some embodiments, headphones can include supra-aural headphones, which include pads that press against the ears rather than around them. Supra-aural headphones can provide less attenuation of external noise.

[0257] Both circumaural headphones and supra-aural headphones can have an open back, closed back, or semi open back. An open back leaks more sound and allows more ambient sounds to enter, but provides a more natural or speaker-like sound. Closed back headphones block more of the ambient noise as compared to open back headphones, thus providing a more immersive auditory brainwave stimulation experience while reducing external distractions.

[0258] In some embodiments, headphones can include ear-fitting headphones, such as earphones or in-ear headphones. Earphones (or earbuds) can refer to small headphones that are fitted directly in the outer ear, facing but not inserted in the ear canal. Earphones, however, provide minimal acoustic isolation and allow ambient noise to enter. In-ear headphones (or in-ear monitors or canalphones) can refer to small headphones that can be designed and constructed for insertion into the ear canal. In-ear headphones engage the ear canal and can block out more ambient noise as compared to earphones, thus providing a more immersive auditory brainwave stimulation experience. In-ear headphones can include ear canal plugs made or formed from one or more material, such as silicone rubber, elastomer, or foam. In some embodiments, in-ear headphones can include custom-made castings of the ear canal to create custom-molded plugs that provide added comfort and noise isolation to the subject, thereby further improving the immersiveness of the auditory brainwave stimulation experience.

[0259] In some embodiments, one or more microphones 1210 can be used to detect sound. A microphone 1210 can be integrated with a speaker 1205. The microphone 1210 can provide feedback information to the NSS 905 or other component of system 100. The microphone 1210 can provide feedback to a component of the speaker 1205 to cause the speaker 1205 to adjust a parameter of audio signal.

[0260] The microphone 1210 can include a transducer that converts sound into an electrical signal. The Microphone 1210 can use electromagnetic induction, capacitance change, or piezoelectricity to produce the electrical signal from air pressure variations. In some cases, the microphone 1210 can include or be connected to a pre-amplifier to amplify the signal before it is recorded or processed. The microphone 1210 can include one or more type of microphone, including, for example, a condenser microphone, RF condenser microphone, electret condenser, dynamic microphone, moving-coil microphone, ribbon microphone, carbon microphone, piezoelectric microphone, crystal microphone, fiber optic microphone, laser microphone, liquid or water microphone, microelectromechanical systems (“MEMS”) microphone, or speakers as microphones.

[0261] The feedback component 960 can include or interface with the microphone 1210 to obtain, identify, or receive sound. The feedback component 960 can obtain ambient noise. The feedback component 960 can obtain sound from the speakers 1205 to facilitate the NSS 905 adjusting a characteristic of the audio signal generated by the speaker 1205. The microphone 1210 can receive voice input from the subject, such as audio commands, instructions, requests, feedback information, or responses to survey questions.

[0262] In some embodiments, one or more speakers 1205 can be integrated with one or more microphones 1210. For example, the speaker 1205 and microphone 1210 can form a headset, be placed in a single enclosure, or can even be the same device since the speaker 1205 and the microphone 1210 can be structurally designed to toggle between a sound generation mode and a sound reception mode.

[0263] **FIG. 12B** illustrates a system configuration for auditory brain entrainment in accordance with an embodiment. The system 1200 can include at least one speaker 1205. The system 1200 can include at least microphone 1210. The system 1200 can include at least one active noise cancellation component 1215. The system 1200 can include at least one feedback sensor 1225. The system 1200 can include or interface with the NSS 905. The system 1200 can include or interface with an audio player 1220.

[0264] The system 1200 can include a first speaker 1205 positioned at a first ear. The system 1200 can include a second speaker 1205 positioned at a second ear. The system 1200 can include a first active noise cancellation component 1215 communicatively coupled with the first microphone 1210. The system 1200 can include a second active noise cancellation component 1215 communicatively coupled with the second microphone 1210. In some cases, the active noise cancellation component 1215 can communicate with both the first speaker 1205 and the second speaker 1205, or both the first microphone 1210 and the second microphone 1210. The system 1200 can include a first microphone 1210 communicatively coupled with the active noise cancellation component 1215. The system 1200 can include a second microphone 1210 communicatively coupled with the active noise cancellation component 1215. In some embodiments, each of the microphone 1210, speaker 1205 and active noise cancellation component can communicate or interface with the NSS 905. In some embodiments, the system 1200 can include a feedback sensor 1225 and a second feedback sensor 1225 communicatively coupled to the NSS 905, the speaker 1205, microphone 1210, or active noise cancellation component 1215.

[0265] In operation, and in some embodiments, the audio player 1220 can play a musical track. The audio player 1220 can provide the audio signal corresponding to the musical track via a wired or wireless connection to the first and second speakers 1205. In some embodiments, the

NSS 905 can intercept the audio signal from the audio player. For example, the NSS 905 can receive the digital or analog audio signal from the audio player 1220. The NSS 905 can be intermediary to the audio player 1220 and a speaker 1205. The NSS 905 can analyze the audio signal corresponding to the music in order to embed an auditory brainwave stimulation signal. For example, the NSS 905 can adjust the volume of the auditory signal from the audio player 1220 to generate acoustic pulses having a pulse rate interval as depicted in **FIG. 11C**. In some embodiments, the NSS 905 can use a binaural beats technique to provide different auditory signals to the first and second speakers that, when perceived by the brain, is combined to have the desired stimulation frequency.

[0266] In some embodiments, the NSS 905 can adjust for any latency between first and second speakers 1205 such that the brain perceives the audio signals at the same or substantially same time (e.g., within 1 milliseconds, 2 milliseconds, 5 milliseconds, or 10 milliseconds). The NSS 905 can buffer the audio signals to account for latency such that audio signals are transmitted from the speakers at the same time.

[0267] In some embodiments, the NSS 905 may not be intermediary to the audio player 1220 and the speaker. For example, the NSS 905 can receive the musical track from a digital music repository. The NSS 905 can manipulate or modify the musical track to embed acoustic pulses in accordance with the desired PRI. The NSS 905 can then provide the modified musical track to the audio player 1220 to provide the modified audio signal to the speaker 1205.

[0268] In some embodiments, an active noise cancellation component 1215 can receive ambient noise information from the microphone 1210, identify unwanted frequencies or noise, and generate an inverted phase waveform to cancel out or attenuate the unwanted waveforms. In some embodiments, the system 1200 can include an additional speaker that generates the noise canceling waveform provided by the noise cancellation component 1215. The noise cancellation component 1215 can include the additional speaker.

[0269] The feedback sensor 1225 of the system 1200 can detect feedback information, such as environmental parameters or physiological conditions. The feedback sensor 1225 can provide the feedback information to NSS 905. The NSS 905 can adjust or change the audio signal based on the feedback information. For example, the NSS 905 can determine that a pulse rate of the subject exceeds a predetermined threshold, and then lower the volume of the audio signal. The NSS 905 can detect that the volume of the auditory signal exceeds a threshold, and decrease the amplitude. The NSS 905 can determine that the pulse rate interval is below a threshold, which can indicate that a subject is losing focus or not paying a satisfactory level of attention to the audio signal, and the NSS 905 can increase the amplitude of the audio signal or change the tone or music track. In some embodiments, the NSS 905 can vary the tone or the music track based on

a time interval. Varying the tone or the music track can cause the subject to pay a greater level of attention to the auditory stimulation, which can facilitate brainwave entrainment.

[0270] In some embodiments, the NSS 905 can receive neural oscillation information from EEG probes 1225, and adjust the auditory stimulation based on the EEG information. For example, the NSS 905 can determine, from the probe information, that neurons are oscillating at an undesired frequency. The NSS 905 can then identify the corresponding undesired frequency in ambient noise using the microphone 1210. The NSS 905 can then instruct the active noise cancellation component 1215 to cancel out the waveforms corresponding to the ambient noise having the undesired frequency.

[0271] In some embodiments, the NSS 905 can enable a passive noise filter. A pass noise filter can include a circuit having one or more of a resistor, capacitor or an inductor that filters out undesired frequencies of noise. In some cases, a passive filter can include a sound insulating material, sound proofing material, or sound absorbing material.

[0272] **FIG. 4C** illustrates a system configuration for auditory brain entrainment in accordance with an embodiment. The system 401 can provide auditory brainwave stimulation using ambient noise source 1230. For example, system 401 can include the microphone 1210 that detects the ambient noise 1230. The microphone 1210 can provide the detected ambient noise to NSS 905. The NSS 905 can modify the ambient noise 1230 before providing it to the first speaker 1205 or the second speaker 1205. In some embodiments, the system 401 can be integrated or interface with a hearing aid device. A hearing aid can be a device designed to improve hearing.

[0273] The NSS 905 can increase or decrease the amplitude of the ambient noise 1230 to generate acoustic bursts having the desired pulse rate interval. The NSS 905 can provide the modified audio signals to the first and second speakers 1205 to facilitate auditory brainwave entrainment.

[0274] In some embodiments, the NSS 905 can overlay a click train, tones, or other acoustic pulses over the ambient noise 1230. For example, the NSS 905 can receive the ambient noise information from the microphone 1210, apply an auditory stimulation signal to the ambient noise information, and then present the combined ambient noise information and auditory stimulation signal to the first and second speakers 1205. In some cases, the NSS 905 can filter out unwanted frequencies in the ambient noise 1230 prior to providing the auditory stimulation signal to the speakers 1205.

[0275] Thus, using the ambient noise 1230 as part of the auditory stimulation, a subject can observe the surroundings or carry on with their daily activities while receiving auditory stimulation to facilitate brainwave entrainment.

[0276] FIG. 13 illustrates a system configuration for auditory brain entrainment in accordance with an embodiment. The system 1300 can provide auditory stimulation for brainwave entrainment using a room environment. The system 1300 can include one or more speakers. The system 1300 can include a surround sound system. For example, the system 1300 includes a left speaker 1310, right speaker 1315, center speaker 1305, right surround speaker 1325, and left surround speaker 1330. System 1300 can include a sub-woofer 1320. The system 1300 can include the microphone 1210. The system 1300 can include or refer to a 5.1 surround system. In some embodiments, the system 1300 can have 1, 2, 3, 4, 5, 6, 7 or more speakers.

[0277] When providing auditory stimulation using a surround system, the NSS 905 can provide the same or different audio signals to each of the speakers in the system 1300. The NSS 905 can modify or adjust audio signals provided to one or more of the speakers in system 1300 in order to facilitate brainwave entrainment. For example, the NSS 905 can receive feedback from microphone 1210 and modify, manipulate or otherwise adjust the audio signal to optimize the auditory stimulation provided to a subject located at a position in the room that corresponds to the location of the microphone 1210. The NSS 905 can optimize or improve the auditory stimulation perceived at the location corresponding to microphone 1210 by analyzing the acoustic beams or waves generated by the speakers that propagate towards the microphone 1210.

[0278] The NSS 905 can be configured with information about the design and construction of each speaker. For example, speaker 1305 can generate sound in a direction that has an angle of 1335; speaker 1310 can generate sound that travels in a direction having an angle of 1340; speaker 1315 can generate sound that travels in a direction having an angle of 1345; speaker 1325 can generate sound that travels in a direction having an angle of 1355; and speaker 1330 can generate sound that travels in a direction having an angle of 1350. These angles can be the optimal or predetermined angles for each of the speakers. These angles can refer to the optimal angle of each speaker such that a person positioned at location corresponding to microphone 1210 can receive the optimum auditory stimulation. Thus, the speakers in system 1300 can be oriented to transmit auditory stimulation towards the subject.

[0279] In some embodiments, the NSS 905 can enable or disable one or more speakers. In some embodiments, the NSS 905 can increase or decrease the volume of the speakers to facilitate brainwave entrainment. The NSS 905 can intercept musical tracks, television audio, movie audio, internet audio, audio output from a set top box, or other audio source. The NSS 905 can adjust or manipulate the received audio, and transmit the adjusted audio signals to the speakers in system 1300 to induce brainwave entrainment.

[0280] FIG. 14 illustrates feedback sensors 1405 placed or positioned at, on, or near a person's head. Feedback sensors 1405 can include, for example, EEG probes that detect brain wave activity.

[0281] The feedback monitor 935 can detect, receive, obtain, or otherwise identify feedback information from the one or more feedback sensors 1405. The feedback monitor 935 can provide the feedback information to one or more component of the NSS 905 for further processing or storage. For example, the profile manager 925 can update profile data structure 945 stored in data repository 940 with the feedback information. Profile manager 925 can associate the feedback information with an identifier of the patient or person undergoing the auditory brain stimulation, as well as a time stamp and date stamp corresponding to receipt or detection of the feedback information.

[0282] The feedback monitor 935 can determine a level of attention. The level of attention can refer to the focus provided to the acoustic pulses used for brain stimulation. The feedback monitor 935 can determine the level of attention using various hardware and software techniques. The feedback monitor 935 can assign a score to the level of attention (e.g., 1 to 10 with 1 being low attention and 10 being high attention, or vice versa, 1 to 100 with 1 being low attention and 100 being high attention, or vice versa, 0 to 1 with 0 being low attention and 1 being high attention, or vice versa), categorize the level of attention (e.g., low, medium, high), grade the attention (e.g., A, B, C, D, or F), or otherwise provide an indication of a level of attention.

[0283] In some cases, the feedback monitor 935 can track a person's eye movement to identify a level of attention. The feedback monitor 935 can interface with a feedback component 960 that includes an eye-tracker. The feedback monitor 935 (e.g., via feedback component 960) can detect and record eye movement of the person and analyze the recorded eye movement to determine an attention span or level of attention. The feedback monitor 935 can measure eye gaze which can indicate or provide information related to covert attention. For example, the feedback monitor 935 (e.g., via feedback component 960) can be configured with electro-oculography ("EOG") to measure the skin electric potential around the eye, which can indicate a direction the eye faces relative to the head. In some embodiments, the EOG can include a system or device to stabilize the head so it cannot move in order to determine the direction of the eye relative to the head. In some embodiments, the EOG can include or interface with a head tracker system to determine the position of the heads, and then determine the direction of the eye relative to the head.

[0284] In some embodiments, the feedback monitor 935 and feedback component 960 can determine a level of attention the subject is paying to the auditory stimulation based on eye movement. For example, increased eye movement can indicate that the subject is focusing on visual stimuli, as opposed to the auditory stimulation. To determine the level of attention the

subject is paying to visual stimuli as opposed to the auditory stimulation, the feedback monitor 935 and feedback component 960 can determine or track the direction of the eye or eye movement using video detection of the pupil or corneal reflection. For example, the feedback component 960 can include one or more camera or video camera. The feedback component 960 can include an infra-red source that sends light pulses towards the eyes. The light can be reflected by the eye. The feedback component 960 can detect the position of the reflection. The feedback component 960 can capture or record the position of the reflection. The feedback component 960 can perform image processing on the reflection to determine or compute the direction of the eye or gaze direction of the eye.

[0285] The feedback monitor 935 can compare the eye direction or movement to historical eye direction or movement of the same person, nominal eye movement, or other historical eye movement information to determine a level of attention. For example, the feedback monitor 935 can determine a historical amount of eye movement during historical auditory stimulation sessions. The feedback monitor 935 can compare the current eye movement with the historical eye movement to identify a deviation. The NSS 905 can determine, based on the comparison, an increase in eye movement and further determine that the subject is paying less attention to the current auditory stimulation based on the increase in eye movement. In response to detecting the decrease in attention, the feedback monitor 935 can instruct the audio adjustment module 915 to change a parameter of the audio signal to capture the subject's attention. The audio adjustment module 915 can change the volume, tone, pitch, or music track to capture the subject's attention or increase the level of attention the subject is paying to the auditory stimulation. Upon changing the audio signal, the NSS 905 can continue to monitor the level of attention. For example, upon changing the audio signal, the NSS 905 can detect a decrease in eye movement which can indicate an increase in a level of attention provided to the audio signal.

[0286] The feedback sensor 1405 can interact with or communicate with NSS 905. For example, the feedback sensor 1405 can provide detected feedback information or data to the NSS 905 (e.g., feedback monitor 935). The feedback sensor 1405 can provide data to the NSS 905 in real-time, for example as the feedback sensor 1405 detects or senses or information. The feedback sensor 1405 can provide the feedback information to the NSS 905 based on a time interval, such as 1 minute, 2 minutes, 5 minutes, 10 minutes, hourly, 2 hours, 4 hours, 12 hours, or 24 hours. The feedback sensor 1405 can provide the feedback information to the NSS 905 responsive to a condition or event, such as a feedback measurement exceeding a threshold or falling below a threshold. The feedback sensor 1405 can provide feedback information responsive to a change in a feedback parameter. In some embodiments, the NSS 905 can ping, query, or send a request to

the feedback sensor 1405 for information, and the feedback sensor 1405 can provide the feedback information in response to the ping, request, or query.

3. Computing Environment

[0287] In some embodiments, a portable system or single headset device as disclosed herein can comprise a computing system and/or a computing device. In some embodiments, a portable system as disclosed herein can comprise an NSS as disclosed herein, wherein the NSS comprises a computing system.

[0288] **FIGs. 7A** and **7B** depict block diagrams of a computing device 700. As shown in **FIGs. 7A** and **7B**, each computing device 700 includes a central processing unit 721, and a main memory unit 722. As shown in **FIG. 7A**, a computing device 700 can include a storage device 728, an installation device 716, a network interface 718, an I/O controller 723, display devices 724a-724n, a keyboard 726 and a pointing device 727, e.g., a mouse. The storage device 728 can include, without limitation, an operating system, software, and software of a neural stimulation system (“NSS”) 701. The NSS 701 can include or refer to one or more of NSS 105, NSS 905, or NSOS 1605. As shown in **FIG. 7B**, each computing device 700 can also include additional optional elements, e.g., a memory port 703, a bridge 770, one or more input/output devices 730a-730n (generally referred to using reference numeral 730), and a cache memory 740 in communication with the central processing unit 721.

[0289] The central processing unit 721 is any logic circuitry that responds to and processes instructions fetched from the main memory unit 722. In many embodiments, the central processing unit 721 is provided by a microprocessor unit, e.g.: those manufactured by Intel Corporation of Mountain View, California; those manufactured by Motorola Corporation of Schaumburg, Illinois; the ARM processor (from, e.g., ARM Holdings and manufactured by ST, TI, ATMEL, etc.) and TEGRA system on a chip (SoC) manufactured by Nvidia of Santa Clara, California; the POWER7 processor, those manufactured by International Business Machines of White Plains, New York; or those manufactured by Advanced Micro Devices of Sunnyvale, California; or field programmable gate arrays (“FPGAs”) from Altera in San Jose, CA, Intel Corporation, Xilinx in San Jose, CA, or MicroSemi in Aliso Viejo, CA, etc. The computing device 700 can be based on any of these processors, or any other processor capable of operating as described herein. The central processing unit 721 can utilize instruction level parallelism, thread level parallelism, different levels of cache, and multi-core processors. A multi-core processor can include two or more processing units on a single computing component. Examples of multi-core processors include the AMD PHENOM IIX2, INTEL CORE i5 and INTEL CORE i7.

[0290] Main memory unit 722 can include one or more memory chips capable of storing data and allowing any storage location to be directly accessed by the microprocessor 721. Main memory unit 722 can be volatile and faster than storage 728 memory. Main memory units 722 can be Dynamic random access memory (DRAM) or any variants, including static random access memory (SRAM), Burst SRAM or SynchBurst SRAM (BSRAM), Fast Page Mode DRAM (FPM DRAM), Enhanced DRAM (EDRAM), Extended Data Output RAM (EDO RAM), Extended Data Output DRAM (EDO DRAM), Burst Extended Data Output DRAM (BEDO DRAM), Single Data Rate Synchronous DRAM (SDR SDRAM), Double Data Rate SDRAM (DDR SDRAM), Direct Rambus DRAM (DRDRAM), or Extreme Data Rate DRAM (XDR DRAM). In some embodiments, the main memory 722 or the storage 728 can be non-volatile, e.g., non-volatile read access memory (NVRAM), flash memory non-volatile static RAM (nvSRAM), Ferroelectric RAM (FeRAM), Magnetoresistive RAM (MRAM), Phase-change memory (PRAM), conductive-bridging RAM (CBRAM), Silicon-Oxide-Nitride-Oxide-Silicon (SONOS), Resistive RAM (RRAM), Racetrack, Nano-RAM (NRAM), or Millipede memory. The main memory 722 can be based on any of the above described memory chips, or any other available memory chips capable of operating as described herein. In the embodiment shown in **FIG. 7A**, the processor 721 communicates with main memory 722 via a system bus 750 (described in more detail below). **FIG. 7B** depicts an embodiment of a computing device 700 in which the processor communicates directly with main memory 722 via a memory port 703. For example, in **FIG. 7B** the main memory 722 can be DRDRAM.

[0291] **FIG. 7B** depicts an embodiment in which the main processor 721 communicates directly with cache memory 740 via a secondary bus, sometimes referred to as a backside bus. In other embodiments, the main processor 721 communicates with cache memory 740 using the system bus 750. Cache memory 740 typically has a faster response time than main memory 722 and is typically provided by SRAM, BSRAM, or EDRAM. In the embodiment shown in **FIG. 7B**, the processor 721 communicates with various I/O devices 730 via a local system bus 750. Various buses can be used to connect the central processing unit 721 to any of the I/O devices 730, including a PCI bus, a PCI-X bus, or a PCI-Express bus, or a NuBus. For embodiments in which the I/O device is a video display 724, the processor 721 can use an Advanced Graphics Port (AGP) to communicate with the display 724 or the I/O controller 723 for the display 724. **FIG. 7B** depicts an embodiment of a computer 700 in which the main processor 721 communicates directly with I/O device 730b or other processors 721' via HYPERTRANSPORT, RAPIDIO, or INFINIBAND communications technology. **FIG. 7B** also depicts an embodiment in which local busses and direct communication are mixed: the processor 721 communicates with I/O device 730a using a local interconnect bus while communicating with I/O device 730b directly.

[0292] A wide variety of I/O devices 730a-730n can be present in the computing device 700. Input devices can include keyboards, mice, trackpads, trackballs, touchpads, touch mice, multi-touch touchpads and touch mice, microphones (analog or MEMS), multi-array microphones, drawing tablets, cameras, single-lens reflex camera (SLR), digital SLR (DSLR), CMOS sensors, CCDs, accelerometers, inertial measurement units, infrared optical sensors, pressure sensors, magnetometer sensors, angular rate sensors, depth sensors, proximity sensors, ambient light sensors, gyroscopic sensors, or other sensors. Output devices can include video displays, graphical displays, speakers, headphones, inkjet printers, laser printers, and 3D printers.

[0293] Devices 730a-730n can include a combination of multiple input or output devices, including, e.g., Microsoft KINECT, Nintendo Wiimote for the WII, Nintendo WII U GAMEPAD, or Apple IPHONE. Some devices 730a-730n allow gesture recognition inputs through combining some of the inputs and outputs. Some devices 730a-730n provides for facial recognition which can be utilized as an input for different purposes including authentication and other commands. Some devices 730a-730n provides for voice recognition and inputs, including, e.g., Microsoft KINECT, SIRI for IPHONE by Apple, Google Now or Google Voice Search.

[0294] Additional devices 730a-730n have both input and output capabilities, including, e.g., haptic feedback devices, touchscreen displays, or multi-touch displays. Touchscreen, multi-touch displays, touchpads, touch mice, or other touch sensing devices can use different technologies to sense touch, including, e.g., capacitive, surface capacitive, projected capacitive touch (PCT), in-cell capacitive, resistive, infrared, waveguide, dispersive signal touch (DST), in-cell optical, surface acoustic wave (SAW), bending wave touch (BWT), or force-based sensing technologies. Some multi-touch devices can allow two or more contact points with the surface, allowing advanced functionality including, e.g., pinch, spread, rotate, scroll, or other gestures. Some touchscreen devices, including, e.g., Microsoft PIXELSENSE or Multi-Touch Collaboration Wall, can have larger surfaces, such as on a table-top or on a wall, and can also interact with other electronic devices. Some I/O devices 730a-730n, display devices 724a-724n or group of devices can be augmented reality devices. The I/O devices can be controlled by an I/O controller 721 as shown in **FIG. 7A**. The I/O controller 721 can control one or more I/O devices, such as, e.g., a keyboard 126 and a pointing device 727, e.g., a mouse or optical pen. Furthermore, an I/O device can also provide storage and/or an installation medium 116 for the computing device 700. In still other embodiments, the computing device 700 can provide USB connections (not shown) to receive handheld USB storage devices. In further embodiments, an I/O device 730 can be a bridge between the system bus 750 and an external communication bus, e.g., a USB bus, a SCSI bus, a FireWire bus, an Ethernet bus, a Gigabit Ethernet bus, a Fibre Channel bus, or a Thunderbolt bus.

[0295] In some embodiments, display devices 724a-724n can be connected to I/O controller 721. Display devices can include, e.g., liquid crystal displays (LCD), thin film transistor LCD (TFT-LCD), blue phase LCD, electronic papers (e-ink) displays, flexible displays, light emitting diode displays (LED), digital light processing (DLP) displays, liquid crystal on silicon (LCOS) displays, organic light-emitting diode (OLED) displays, active-matrix organic light-emitting diode (AMOLED) displays, liquid crystal laser displays, time-multiplexed optical shutter (TMOS) displays, or 3D displays. Examples of 3D displays can use, e.g., stereoscopy, polarization filters, active shutters, or autostereoscopy. Display devices 724a-724n can also be a head-mounted display (HMD). In some embodiments, display devices 724a-724n or the corresponding I/O controllers 723 can be controlled through or have hardware support for OpenGL or DirectX API or other graphics libraries.

[0296] In some embodiments, the computing device 700 can include or connect to multiple display devices 724a-724n, which each can be of the same or different type and/or form. As such, any of the I/O devices 730a-730n and/or the I/O controller 723 can include any type and/or form of suitable hardware, software, or combination of hardware and software to support, enable or provide for the connection and use of multiple display devices 724a-724n by the computing device 700. For example, the computing device 700 can include any type and/or form of video adapter, video card, driver, and/or library to interface, communicate, connect or otherwise use the display devices 724a-724n. In one embodiment, a video adapter can include multiple connectors to interface to multiple display devices 724a-724n. In other embodiments, the computing device 700 can include multiple video adapters, with each video adapter connected to one or more of the display devices 724a-724n. In some embodiments, any portion of the operating system of the computing device 700 can be configured for using multiple displays 724a-724n. In other embodiments, one or more of the display devices 724a-724n can be provided by one or more other computing devices 700a or 700b connected to the computing device 700, via the network 140. In some embodiments, software can be designed and constructed to use another computer's display device as a second display device 724a for the computing device 700. For example, in one embodiment, an Apple iPad can connect to a computing device 700 and use the display of the device 700 as an additional display screen that can be used as an extended desktop.

[0297] Referring again to **FIG. 7A**, the computing device 700 can comprise a storage device 728 (e.g., one or more hard disk drives or redundant arrays of independent disks) for storing an operating system or other related software, and for storing application software programs such as any program related to the software for the NSS. Examples of storage device 728 include, e.g., hard disk drive (HDD); optical drive including CD drive, DVD drive, or BLU-RAY drive; solid-state drive (SSD); USB flash drive; or any other device suitable for storing data. Some storage

devices can include multiple volatile and non-volatile memories, including, e.g., solid state hybrid drives that combine hard disks with solid state cache. Some storage devices 728 can be non-volatile, mutable, or read-only. Some storage devices 728 can be internal and connect to the computing device 700 via a bus 750. Some storage devices 728 can be external and connect to the computing device 700 via a I/O device 730 that provides an external bus. Some storage devices 728 can connect to the computing device 700 via the network interface 718 over a network, including, e.g., the Remote Disk for MACBOOK AIR by Apple. Some client devices 700 may not require a non-volatile storage device 728 and can be thin clients or zero clients 202. Some storage devices 728 can also be used as an installation device 716, and can be suitable for installing software and programs. Additionally, the operating system and the software can be run from a bootable medium, for example, a bootable CD, e.g., KNOPPIX, a bootable CD for GNU/Linux that is available as a GNU/Linux distribution from knoppix.net.

[0298] Computing device 700 can also install software or application from an application distribution platform. Examples of application distribution platforms include the App Store for iOS provided by Apple, Inc., the Mac App Store provided by Apple, Inc., GOOGLE PLAY for Android OS provided by Google Inc., Chrome Webstore for CHROME OS provided by Google Inc., and Amazon Appstore for Android OS and KINDLE FIRE provided by Amazon.com, Inc.

[0299] Furthermore, the computing device 700 can include a network interface 718 to interface to the network 140 through a variety of connections including, but not limited to, standard telephone lines LAN or WAN links (e.g., 802.11, T1, T3, Gigabit Ethernet, Infiniband), broadband connections (e.g., ISDN, Frame Relay, ATM, Gigabit Ethernet, Ethernet-over-SONET, ADSL, VDSL, BPON, GPON, fiber optical including FiOS), wireless connections, or some combination of any or all of the above. Connections can be established using a variety of communication protocols (e.g., TCP/IP, Ethernet, ARCNET, SONET, SDH, Fiber Distributed Data Interface (FDDI), IEEE 802.11a/b/g/n/ac CDMA, GSM, WiMax and direct asynchronous connections). In one embodiment, the computing device 700 communicates with other computing devices 700' via any type and/or form of gateway or tunneling protocol e.g., Secure Socket Layer (SSL) or Transport Layer Security (TLS), or the Citrix Gateway Protocol manufactured by Citrix Systems, Inc. of Ft. Lauderdale, Florida. The network interface 118 can comprise a built-in network adapter, network interface card, PCMCIA network card, EXPRESSCARD network card, card bus network adapter, wireless network adapter, USB network adapter, modem or any other device suitable for interfacing the computing device 700 to any type of network capable of communication and performing the operations described herein.

[0300] A computing device 700 of the sort depicted in **FIG. 7A** can operate under the control of an operating system, which controls scheduling of tasks and access to system resources. The

computing device 700 can be running any operating system such as any of the versions of the MICROSOFT WINDOWS operating systems, the different releases of the Unix and Linux operating systems, any version of the MAC OS for Macintosh computers, any embedded operating system, any real-time operating system, any open source operating system, any proprietary operating system, any operating systems for mobile computing devices, or any other operating system capable of running on the computing device and performing the operations described herein. Typical operating systems include, but are not limited to: WINDOWS 7000, WINDOWS Server 2012, WINDOWS CE, WINDOWS Phone, WINDOWS XP, WINDOWS VISTA, and WINDOWS 7, WINDOWS RT, and WINDOWS 8 all of which are manufactured by Microsoft Corporation of Redmond, Washington; MAC OS and iOS, manufactured by Apple, Inc. of Cupertino, California; and Linux, a freely-available operating system, e.g., Linux Mint distribution (“distro”) or Ubuntu, distributed by Canonical Ltd. of London, United Kingdom; or Unix or other Unix-like derivative operating systems; and Android, designed by Google, of Mountain View, California, among others. Some operating systems, including, e.g., the CHROME OS by Google, can be used on zero clients or thin clients, including, e.g., CHROMEBOOKS.

[0301] The computer system 700 can be any workstation, telephone, desktop computer, laptop or notebook computer, netbook, ULTRABOOK, tablet, server, handheld computer, mobile telephone, smartphone or other portable telecommunications device, media playing device, a gaming system, mobile computing device, or any other type and/or form of computing, telecommunications or media device that is capable of communication. The computer system 700 has sufficient processor power and memory capacity to perform the operations described herein. In some embodiments, the computing device 700 can have different processors, operating systems, and input devices consistent with the device. The Samsung GALAXY smartphones, e.g., operate under the control of Android operating system developed by Google, Inc. GALAXY smartphones receive input via a touch interface.

[0302] In some embodiments, the computing device 700 is a gaming system. For example, the computer system 700 can comprise a PLAYSTATION 3, or PERSONAL PLAYSTATION PORTABLE (PSP), or a PLAYSTATION VITA device manufactured by the Sony Corporation of Tokyo, Japan, a NINTENDO DS, NINTENDO 3DS, NINTENDO WII, or a NINTENDO WII U device manufactured by Nintendo Co., Ltd., of Kyoto, Japan, or an XBOX 360 device manufactured by the Microsoft Corporation of Redmond, Washington, or an OCULUS RIFT or OCULUS VR device manufactured BY OCULUS VR, LLC of Menlo Park, California.

[0303] In some embodiments, the computing device 700 is a digital audio player such as the Apple IPOD, IPOD Touch, and IPOD NANO lines of devices, manufactured by Apple Computer

of Cupertino, California. Some digital audio players can have other functionality, including, e.g., a gaming system or any functionality made available by an application from a digital application distribution platform. For example, the IPOD Touch can access the Apple App Store. In some embodiments, the computing device 700 is a portable media player or digital audio player supporting file formats including, but not limited to, MP3, WAV, M4A/AAC, WMA Protected AAC, AIFF, Audible audiobook, Apple Lossless audio file formats and .mov, .m4v, and .mp4 MPEG-4 (H.264/MPEG-4 AVC) video file formats.

[0304] In some embodiments, the computing device 700 is a tablet e.g., the IPAD line of devices by Apple; GALAXY TAB family of devices by Samsung; or KINDLE FIRE, by Amazon.com, Inc. of Seattle, Washington. In other embodiments, the computing device 700 is an eBook reader, e.g., the KINDLE family of devices by Amazon.com, or NOOK family of devices by Barnes & Noble, Inc. of New York City, New York.

[0305] In some embodiments, the communications device 700 includes a combination of devices, e.g., a smartphone combined with a digital audio player or portable media player. For example, one of these embodiments is a smartphone, e.g., the IPHONE family of smartphones manufactured by Apple, Inc.; a Samsung GALAXY family of smartphones manufactured by Samsung, Inc.; or a Motorola DROID family of smartphones. In yet another embodiment, the communications device 700 is a laptop or desktop computer equipped with a web browser and a microphone and speaker system, e.g., a telephony headset. In these embodiments, the communications devices 700 are web-enabled and can receive and initiate phone calls. In some embodiments, a laptop or desktop computer is also equipped with a webcam or other video capture device that enables video chat and video call.

[0306] In some embodiments, the status of one or more machines 700 in the network are monitored, generally as part of network management. In one of these embodiments, the status of a machine can include an identification of load information (e.g., the number of processes on the machine, CPU and memory utilization), of port information (e.g., the number of available communication ports and the port addresses), or of session status (e.g., the duration and type of processes, and whether a process is active or idle). In another of these embodiments, this information can be identified by a plurality of metrics, and the plurality of metrics can be applied at least in part towards decisions in load distribution, network traffic management, and network failure recovery as well as any aspects of operations of the present solution described herein. Aspects of the operating environments and components described above will become apparent in the context of the systems and methods disclosed herein.

v. Computing Devices and Systems for Portable Systems

[0307] The present disclosure provides computer systems that are programmed to implement systems, devices and methods of the disclosure. The computer system can be an electronic device of a user or a computer system that is remotely located with respect to the electronic device. The electronic device can be a mobile electronic device.

[0308] The computer system includes a central processing unit (CPU, also “processor” and “computer processor” herein), which can be a single core or multi core processor, or a plurality of processors for parallel processing. The computer system also includes memory or memory location (e.g., random-access memory, read-only memory, flash memory), electronic storage unit (e.g., hard disk), communication interface (e.g., network adapter) for communicating with one or more other systems, and peripheral devices, such as cache, other memory, data storage or electronic display adapters. The memory, storage unit, interface, and peripheral devices are in communication with the CPU through a communication bus, such as a motherboard. The storage unit can be a data storage unit (or data repository) for storing data. The computer system can be operatively coupled to a computer network (“network”) with the aid of the communication interface. The network can be the Internet, an internet or extranet, or an intranet or extranet that is in communication with the Internet. In some embodiments, the network is a telecommunication or data network. The network can include one or more computer servers, which can enable distributed computing, such as cloud computing. In some embodiments, the network, with the aid of the computer system, can implement a peer-to-peer network, which may enable devices coupled to the computer system to behave as a client or a server.

[0309] The CPU can execute a sequence of machine-readable instructions, which can be embodied in a program or software. The instructions may be stored in a memory location, such as the memory. The instructions can be directed to the CPU, which can subsequently program or otherwise configure the CPU to implement methods of the present disclosure. Examples of operations performed by the CPU can include fetch, decode, execute, and writeback.

[0310] The CPU can be part of a circuit, such as an integrated circuit. One or more other components of the system can be included in the circuit. In some embodiments, the circuit is an application specific integrated circuit (ASIC).

[0311] The storage unit can store files, such as drivers, libraries, and saved programs. The storage unit can store user data, e.g., user preferences and user programs. The computer system In some embodiments can include one or more additional data storage units that are external to the computer system, such as located on a remote server that is in communication with the computer system through an intranet or the Internet.

[0312] The computer system can communicate with one or more remote computer systems through the network. For instance, the computer system can communicate with a remote

computer system of a user. Examples of remote computer systems include personal computers (e.g., portable PC), slate or tablet PC's (e.g., Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (e.g., Apple® iPhone, Android-enabled device, Blackberry®), or personal digital assistants. The user can access the computer system via the network.

[0313] Methods as described herein can be implemented by way of machine (e.g., computer processor) executable code stored on an electronic storage location of the computer system, such as, for example, on the memory or electronic storage unit. The machine executable or machine-readable code can be provided in the form of software. During use, the code can be executed by the processor. In some embodiments, the code can be retrieved from the storage unit and stored on the memory for ready access by the processor. In some situations, the electronic storage unit can be precluded, and machine-executable instructions are stored on memory.

[0314] The code can be pre-compiled and configured for use with a machine having a processor adapted to execute the code, or can be compiled during runtime. The code can be supplied in a programming language that can be selected to enable the code to execute in a pre-compiled or as-compiled fashion.

[0315] Aspects of the systems and methods provided herein, such as the computer system, can be embodied in programming. Various aspects of the technology may be thought of as “products” or “articles of manufacture” typically in the form of machine (or processor) executable code or associated data that is carried on or embodied in a type of machine readable medium. Machine-executable code can be stored on an electronic storage unit, such as memory (e.g., read-only memory, random-access memory, flash memory) or a hard disk. “Storage” type media can include any or all of the tangible memory of the computers, processors or the like, or associated modules thereof, such as various semiconductor memories, tape drives, disk drives and the like, which may provide non-transitory storage at any time for the software programming. All or portions of the software may at times be communicated through the Internet or various other telecommunication networks. Such communications, for example, may enable loading of the software from one computer or processor into another, for example, from a management server or host computer into the computer platform of an application server. Thus, another type of media that may bear the software elements includes optical, electrical, and electromagnetic waves, such as used across physical interfaces between local devices, through wired and optical landline networks and over various air-links. The physical elements that carry such waves, such as wired or wireless links, optical links or the like, also may be considered as media bearing the software. As used herein, unless restricted to non-transitory, tangible “storage” media, terms such as computer or machine “readable medium” refer to any medium that participates in providing instructions to a processor for execution.

[0316] Hence, a machine readable medium, such as computer-executable code, may take many forms, including but not limited to, a tangible storage medium, a carrier wave medium or physical transmission medium. Non-volatile storage media include, for example, optical or magnetic disks, such as any of the storage devices in any computer(s) or the like, such as may be used to implement the databases, etc., as shown in the drawings. Volatile storage media include dynamic memory, such as main memory of such a computer platform. Tangible transmission media include coaxial cables; copper wire and fiber optics, including the wires that comprise a bus within a computer system. Carrier-wave transmission media may take the form of electric or electromagnetic signals, or acoustic or light waves such as those generated during radio frequency (RF) and infrared (IR) data communications. Common forms of computer-readable media therefore include for example: a floppy disk, a flexible disk, hard disk, magnetic tape, any other magnetic medium, a CD-ROM, DVD or DVD-ROM, any other optical medium, punch cards paper tape, any other physical storage medium with patterns of holes, a RAM, a ROM, a PROM and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave transporting data or instructions, cables or links transporting such a carrier wave, or any other medium from which a computer may read programming code or data. Many of these forms of computer readable media may be involved in carrying one or more sequences of one or more instructions to a processor for execution.

[0317] The computer system can include or be in communication with an electronic display that comprises a user interface (UI). Examples of UI's include, without limitation, a graphical user interface (GUI) and web-based user interface.

[0318] Methods and systems of the present disclosure can be implemented by way of one or more algorithms. An algorithm can be implemented by way of software upon execution by the central processing unit.

II. Methods of Using Portable System or Devices as disclosed herein

A. Methods of Using Portable Systems or Devices as Disclosed Herein

[0319] In some embodiments, methods of using a device, e.g., a single headset device, or portable system as disclosed herein are provided below.

[0320] In some embodiments, the method comprises administering to a subject a visual, auditory, or haptic stimulus, or a combination thereof generated by a device or portable system as disclosed herein. In some embodiments, the stimulation induces neural, visual, oscillations in a brain region of the subject, wherein the frequency of the induced neural, visual, oscillations corresponds to the frequency of the haptic stimulus that is administered to the subject.

[0321] In some embodiments, the stimulus is administered at a frequency of 1 Hertz (Hz), 2 Hz, 5 Hz, 10 Hz, 20 Hz, 25 Hz, 30 Hz, 31 Hz, 32 Hz, 33 Hz, 34 Hz, 35 Hz, 36 Hz, 37 Hz, 38 Hz, 39 Hz, 40 Hz, 41 Hz, 42 Hz, 43 Hz, 44 Hz, 45 Hz, 46 Hz, 47 Hz, 48 Hz, 49 Hz, 50 Hz, 60 Hz, 70 Hz, 80 Hz, 90 Hz, 100 Hz, 150 Hz, 200 Hz, 250 Hz, 300 Hz, 400 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4,000 Hz, 5000 Hz, 6,000 Hz, 7,000 Hz, 8,000 Hz, 9,000 Hz, or 10,000 Hz.

[0322] In some embodiments, the stimulus is administered at a frequency of about 20 Hertz (Hz) to about 140 Hz, about 30 Hz to about 60 Hz, about 40 Hz to about 60 Hz, about 35 Hz to about 45 Hz, or about 40 Hz. In some embodiments, the stimulus is administered at a gamma frequency. In some embodiments, administration of the gamma frequency results in the induction of synchronized gamma oscillations within a brain region of the subject.

i. Stimulus Exposure, Session duration, Session frequency, and Regimen

Duration

[0323] In some embodiments, administering the stimulus comprises a stimulus exposure. In some embodiments, the stimulus exposure comprises a session duration, a session frequency, a regimen duration, or a combination thereof. In some embodiments, the stimulus exposure may comprise more than one regimen duration. In some embodiments, administering may be performed continuously for a session duration. In some embodiments, the session duration may be between 10 minutes and 2 hours. In some embodiments, the session duration may be at least 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 minutes. In some embodiments, the session duration may be at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours. In some embodiments, the session duration may be at least 1, 2, 3, 4, 5, 6, or 7 days. In some embodiments, the session duration may be at most 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 minutes. In some embodiments, the session duration may be at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours. In some embodiments, the session duration may be at most 1, 2, 3, 4, 5, 6, or 7 days.

[0324] In some embodiments, the session frequency may occur at least once, at least twice, at least 3 times, at least 4 times, or at least 5 times per day. In some embodiments, the session frequency may occur at least once, at least twice, at least 3 times, at least 4 times, at least 5 times, at least 6 times, or at least 7 times per week. In some embodiments, the session frequency may occur at least once, at least twice, at least 3 times, at least 4 times, or at least 5 times, at least 8 times, at least 10 times, at least 20 times, at least 28 times, at least 30 times, or at least 31 times per month. In some embodiments, the session frequency may occur at least once, at least twice, at least 3 times, at least 4 times, or at least 5 times, at least 10 times, at least 20 times, at least 30 times, at least 50 times, at least 100 times, at least 150 times, at least 200 times, at least 300

times, at least 365 times, at least 400 times, at least 500 times, at least 600 times, at least 700 times, at least 800 times, at least 900 times, or at least one thousand times per year.

[0325] The regimen duration refers to the length of time over which all session durations and session frequencies for the administering of the non-invasive stimulus occur. For example, a regimen duration can refer to a total length of an experimental study period, a total length of a therapeutic treatment, or a total length of a diagnostic period. In some embodiments, the regimen duration comprises at least one day, at least one week, at least one month, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least one year, at least 2 years, at least 3 years, at least 4 years, at least 5 years, at least 10 years, at least 15 years, or at least 20 years. In some embodiments, the regimen duration comprises the remainder of the life expectancy of the subject. In some embodiments, the regimen duration comprises the remainder of the subject's life.

[0326] In some embodiments, the regimen duration and session frequency comprises about once a day for 6 months. In some embodiments, the regimen duration and session frequency comprises at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a day. In some embodiments, the regimen duration and session frequency comprises at most about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a day.

ii. Methods of Verifying Administration of a Stimulus

[0327] In some embodiments, the administration of a stimulus to a subject is confirmed or verified within the subject by evaluating and measuring the stimulus. In some embodiments, the stimulus is measured in the brain of the subject. In some embodiments, a stimulus is measured in at least one, at least two, at least three, at least 4, at least 5, at least 8, at least 10, at least 15, at least 20 specific brain regions of the subject. In some embodiments, a stimulus is measured simultaneously in at least one, at least two, at least three, at least 4, at least 5, at least 8, at least 10, at least 15, at least 20 specific brain regions of the subject.

[0328] In some embodiments, the measuring comprises analyzing the brain or a specific brain region of the subject. In some embodiments, the measuring comprises analyzing the stimulus in the brain or a specific brain region of the subject.

[0329] In some embodiments, the specific brain region comprises an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof.

[0330] In some embodiments, the measuring comprises neuroimaging. In some embodiments, the measuring comprises neuroimaging of the brain of the subject. In some embodiments, the

measuring comprises neuroimaging of the whole brain of the subject. In some embodiments, the measuring comprises neuroimaging of the specific brain regions of the subject. In some embodiments, the measuring comprises neuroimaging of an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof.

[0331] In some embodiments, the measuring comprises neuroimaging techniques. In some embodiments, the neuroimaging comprises magnetic resonance imaging (MRI), computer tomography, positron emission tomography (PET) imaging, diffusion-weighted MRI imaging, or any combination thereof in a brain region of a subject, wherein a brain region an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof.

iii. Closed Loop Therapy

[0332] In some embodiments, the present disclosure provides methods of administering a closed-loop therapy to a subject with a system or device as disclosed herein. For example, in some embodiments, a subject may be monitored during a therapy session using a variety of sensors, such as ECG sensors, heart rate sensors, or galvanic skin response sensors, or a combination thereof, and the dosing parameters for the session may be updated in real time based on the outputs of the sensors. Such a therapy session can be referred to as a closed loop therapy session.

FIG. 50 is a graphical representation of adjusting a therapy session based on feedback collected during the therapy session, i.e., a closed loop therapy session. A graph 2805 shows a series of scheduled stimulation pulses included in a single therapy session along a time axis. As shown, the pulses occur during intervals labeled as T1, T2, T3, T4, T5, and T6. In this example, the intervals T5 and T6 do not include any scheduled stimulation pulses. It should be understood that the graph 2805 may represent pulses of any modality (e.g., visual stimulation pulses or auditory stimulation pulses). It should also be understood that the amplitude of the pulses, the duration of the pulse intervals, and the frequency of the pulses is illustrative only, and that in some implementations, these factors may be varied without departing from the scope of this disclosure.

[0333] A graph 2810 shows the attention level of the subject over time. Higher values indicate that the subject is more attentive, and lower values indicate that the subject is less attentive. In some implementations, subject attention level may be correlated with quality of a therapy

session, such as when the subject's attention is required for the stimulation pulses to be delivered effectively. For example, if the stimulation pulses are delivered via a video display screen, it may be necessary for the subject to focus his or her attention on the video display screen in order to receive the benefit of the stimulation pulses. Thus, the graph 2810 includes a threshold L for user attention level. In this example, it can be assumed that the user's attention level must be greater than or equal to the threshold L in order for the therapy to be effectively delivered. As shown in the graph 2810, the subject's attention level varies over time, and is sometimes below the threshold L. If the subject's attention level is below the threshold L during any of the pulse intervals, the subject may not receive the benefit of the pulses delivered during those intervals.

[0334] In some implementations, the subject's attention level can be monitored by a sensor. For example, one or more camera sensors can be configured to track the subject's eyes to determine whether they are aligned in a particular orientation that allows the subject to perceive the stimulation pulses (e.g., whether the subject's eyes are focused on a video screen that delivers the stimulation pulses). During time periods in which the subject's eyes are appropriately focused, the subject's attention level may be recorded as relatively high (e.g., above the threshold L). During time periods in which the subject's eyes are not appropriately focused, the subject's attention level may be recorded as relatively low (e.g., below the threshold L).

[0335] The graphs 2815, 2820, and 2825 show adjusted stimulation pulses that may be delivered to the subject based on the attention level of the subject over time.

[0336] Referring now to the graph 2815, two additional stimulation pulses are delivered to the subject during intervals T5 and T6, which originally did not include any scheduled pulses as shown in the graph 2805. In some implementations, the additional pulses delivered during the intervals T5 and T6 can be useful because the subject's attention level was below the threshold L for portions of the time periods during which the scheduled pulses were delivered (i.e., intervals T2 and T4). Because the subject may not receive the benefits of the pulses delivered during the intervals T2 and T4 as a result of the relatively low attention level during portions of these intervals, the overall effect of the therapy session may be reduced. Thus, the additional pulses delivered during the intervals T5 and T6 can be administered to compensate for the subject's low attention level during some of the scheduled pulses.

[0337] The graph 2820 shows stimulation pulses that are intended to refocus the subject's attention when it appears that the subject's attention level may be below the threshold L during certain time intervals. For example, the subject's attention level falls at the end of the interval T2. Thus, the graph 2820 includes a pulse that occurs just before the beginning of the interval T3, which is intended to recapture the subject's attention so that the subject's attention level will be above the threshold L during the interval T3. As shown in the graph 2810, the subject's attention

level increases just before the beginning of the interval T3 as a result of the pulse shown on the left-hand side of the graph 2820. Before the time period T4, the subject's attention level again drops below the threshold L. As a result, the graph 2820 shows a second pulse that occurs before the interval T4 in order to refocus the subject's attention. However, the second pulse shown in the graph 2820 appears to be ineffective, as the subject's attention level does not rise above the threshold L for the beginning of the interval T4. It should be understood that the modality associated with the graph 2820 need not be the same as the modality associated with the graph 2805. For example, the scheduled pulses shown in the graph 2805 may be visual stimulation pulses, and the pulses shown in the graph 2820 may be auditory pulses that are intended to remind the subject to refocus his attention appropriately.

[0338] The graph 2825 shows adjusted stimulation pulses that are intended to combat the subject's inattention during certain time intervals. For example, the subject's attention level drops at the end of the interval T2. As a result, the graph 2825 includes a pulse that occurs simultaneous with the subject's attention dropping during the interval T2, and continues until the end of the interval T2. It should be noted that the amplitude of the adjusted pulses shown in the graph 2825 is larger than the amplitude of the scheduled pulses shown in the graph 2805. Such a larger amplitude can serve to refocus the subject's attention, or can be used to increase the [0339] effectiveness of pulses that the user is not sufficiently focused on. In some implementations, the larger amplitude of the pulses shown in the graph 2825 may correspond to a brighter visual stimulation signal or a louder auditory stimulation signal, relative to the signals used to generate the scheduled pulses shown in the graph 2805. As shown in the graph 2825, a second adjusted pulse having a high amplitude occurs during the beginning of the interval T4, when the subject's attention level is relatively low. However, when the subject's attention level changes to exceed the threshold level L towards the end of the time interval T4, the adjusted pulse is terminated, as it is no longer necessary.

[0340] In some implementations, adjusted pulses different from those shown in **FIG. 28** may be used. Furthermore, adjusted pulses may be delivered to the subject in other scenarios not illustrated in **FIG. 50**. In some implementations, adjusted pulses may be delivered in order to increase the subject's comfort level during a therapy session. For example, if sensor data (e.g., heart rate sensor data or galvanic skin response sensor data) indicates that the subject is experiencing stress during a therapy session, and adjusted pulse having an amplitude lower than that of a scheduled pulse may be delivered to the subject, in order to reduce the discomforting effect that the scheduled pulses may have on the subject.

iv. Additional Methods

[0341] In some embodiments, the present disclosure provides devices, systems and methods for improving one or more patient outcomes or treating a disease. The device or system may comprise any device or system as disclosed herein. In some embodiments, the gamma oscillation inducing waveform is delivered through one or more of: visual stimulus, auditory stimulus, tactile stimulus, haptic stimulus, olfactory stimulus, or bone conduction, or a combination thereof. In some embodiments, combined audio-visual stimulus is delivered for an hour each day for a 3 to 6 month or longer period. In some embodiments, stimulus is delivered for two hours each day. In some embodiments, a stimulus is delivered for multiple periods over the course of a day. In some embodiments, combined audio-visual stimulus is delivered over an extended open-ended period of time. In some embodiments, stimulus is delivered in periods of varying durations. In some embodiments, the gamma oscillation inducing waveform is delivered at least in part through glasses, goggles, a mask, or other worn apparatus that can provide visual stimulus.

[0342] In some embodiments, the systems, devices, and methods for benefiting a cognitive state or function of a brain of a subject, comprises a portable system comprising a first stimulus emitting component comprising a visual source comprising a pair of glasses configured to project light pulses towards said subject's eyes, said light pulses having a frequency of about 30 Hz to about 60 Hz and producing a square-wave duty cycle of about 50%, wherein said pair of glasses comprises: a light emitting diode and a light emitting diode driver, said light emitting diode projecting said light pulses towards a screen which flickers at about 30 Hz to about 60 Hz and reflects said light pulses to redirect said light pulses towards said subject's eyes; and a display device configured to provide a visual stimulus to said subject and a second stimulus emitting component comprising an audio source comprising a set of supra-aural headphones, wherein said set of supra-aural headphones produces an auditory stimulus with a frequency of about 30 Hz to about 60 Hz and a duty cycle of 50% wherein said glasses and said supra-aural headphones are operatively configured to comprise a single headset device to be worn by said subject, and wherein use of said system promotes synchronized gamma oscillations in at least one brain region of said subject and causes an improvement in one or more cognitive functions of said subject's brain, thereby slowing progression of mild cognitive impairment or Alzheimer's disease in said subject.

[0343] In some embodiments, the systems, methods, and devices of the present disclosure can be implemented as shown and described in **FIG. 48- FIG. 61**.

[0344] In some embodiments, said portable system can be used as shown in **FIG. 63** which illustratively depicts a process for a personalized and patient-specific therapeutic use of a

portable system and/or any embodiment of a device described herein. In some embodiments, a physician prescribes at-home therapeutic portable system settings for a patient, which include adjusting any parameters of which the portable system is configured to emit a visual stimulus, a haptic stimulus, or an auditory stimulus to the eyes and ears, or brain of the patient. The physician can confirm that a patient's neurological response is elicited by analyzing cortical EEG recordings in order to identify the optimal stimulation frequency of the visual stimulus, haptic stimulus, or the auditory stimulus delivered by the portable system. The patient can then use the device at home with the settings prescribed by the physician. The patient's adherence to using the device as prescribed is monitored throughout the course of treatment.

[0345] In some embodiments, a rendering of an embodiment of a controller of the portable system (Combinatorial Neurostimulation System) is shown in **FIG. 62**.

[0346] In some embodiments, said portable system comprises a device as shown and described in **FIG. 64** and **FIG. 65**.

[0347] In some embodiments, a single headset device as disclosed herein comprises a device as shown and described in **FIG. 66–FIG. 80**.

[0348] In some embodiments, the portable system (or Combinatorial Neurostimulation System) further comprises a hand-held controller. In some embodiments, said portable system comprises a portable neurostimulation system. In some embodiments, said hand-held controller receives and transmits a signal dictating a dosing parameter corresponding to a frequency, a duration, a brightness, or a color of said visual stimulus, or a duration, an intensity, or a frequency of said audio stimuli. In some embodiments, said hand-held controller further comprises an independent power supply comprising batteries or a rechargeable battery.

[0349] In some embodiments, the hand-held controller further comprises adjustable inputs for said single headset device, said audio source, and said visual source, wherein said adjustable inputs for said audio source comprise an adjustable volume input, and said adjustable inputs for said visual source comprise an adjustable brightness input and wherein said adjustable input for said single headset device comprises an input for powering on and powering off said single headset device, or for pausing said visual or audio stimulus. In some embodiments, said hand-held controller comprises a device as shown and described in **FIG. 72, FIG. 73, FIG. 75A, FIG. 75B, FIG. 75C, or FIG. 75D**.

[0350] In some embodiments, said portable system is configured to induce gamma oscillation inducing waveforms in a subject.

[0351] In some embodiments, said portable system comprises a stimulus first stimulus emitting component comprising a visual source comprising a pair of glasses and a second stimulus

emitting component comprising an audio source comprising an audio speaker within the temple arm of the glasses, as shown and described in **FIG. 79** and **FIG. 80**.

[0352] In some embodiments, said supra-aural headphones of said portable system further comprise said adjustable inputs for said system, including said adjustable inputs for said visual source, said audio source, and said single headset device.

[0353] In some embodiments, the gamma oscillation inducing waveform is delivered by a visual stimulus through a visual source. In some embodiments, said visual source comprises a pair of glasses worn by the subject with illuminating elements on the interior providing a visual stimulus. In some embodiments, the gamma oscillation inducing waveform is delivered through supra-aural headphones or earbuds worn by the subject providing an auditory signal. In some embodiments, combined visual and auditory signals are provided by such supra-aural headphones and glasses worn together at the same time comprising said single headset device.

[0354] In some embodiments said single headset device comprises a neurostimulation device as disclosed and described herein.

[0355] In some embodiments, said gamma oscillation inducing waveform comprises a visual stimulus with a frequency of about 30 Hz to about 60 Hz and/or an auditory stimulus with a frequency of about 30 Hz to about 60 Hz.

[0356] In some embodiments, the gamma oscillation inducing waveform is delivered as vibrotactile stimulus via an article of clothing or body attachment. In some embodiments, such body attachment can include a device providing treatment for a condition of a user during sleep, such as a CPAP device. In some embodiments, the gamma oscillation inducing waveform can be delivered through the user's nostrils.

1. Program parameters and parameter values

[0357] In some embodiments, gamma oscillation inducing waveform parameters are configured with a stimulus frequency (e.g., f_s in **FIG. 31**) of about 30 Hz to about 60 Hz for both audio and visual signals. In some embodiments, audio and visual stimulus are offset relative to each other by a delay (e.g., t_d in **FIG. 31**). In an example embodiment, audio and visual signals are synchronized ($t_d = 0$ s).

[0358] In some embodiments, gamma oscillation inducing waveform parameters are configured with a variety of timing and intensity parameters. In an example embodiment, these parameters include those illustrated in **FIG. 31**. In some embodiments, these parameters are preconfigured; they can be adjusted at least in part by a third party such as a caregiver or healthcare provider. In some embodiments, one or more parameters of the stimulus can be adjusted responsive to measurements or analysis of one or more of: user context, measured parameters associated with

the user, observed or detected use of the stimulation device. In some embodiments, gamma oscillation inducing waveform are adjusted responsive to detected or analyzed symptom progression related to an affliction impacting cognitive function. Various frequencies and various intensities can be used as parameters for the gamma oscillation inducing waveform.

[0359] In some embodiments, one or more stimulus parameters are based at least partially on various clinical measures of cognitive function disclosed herein. In some embodiments, varying combinations stimulus parameters are used during different time periods and subsequent stimulus parameters are selected at least in part based on comparison of clinical measures of cognitive function among at least some of those periods. In some embodiments, stimulus parameters are selected to optimize, improve, and/or enhance sleep improvement as assessed at least in part by clinical measures of cognitive function.

[0360] In some embodiments, the present disclosure delivers about 30 Hz to about 60 Hz gamma oscillation inducing waveform as an auditory stimulus, a visual stimulus, or combined audio-visual stimulus. In some embodiments stimulus is delivered at one or more stimulus frequencies (e.g., fs in **FIG. 31**) in the approximate range of about 30 Hz to about 60 Hz In some embodiments, “gamma” can refer to frequencies in the range of 30-60Hz, 30-50Hz, 30-40Hz, or 35-45 Hz. In some embodiments, stimulus can be delivered based at least in part on a user’s detected, reported, or demographically or individually associated or dominant alpha wave frequency.

[0361] In some embodiments, specific parameters for a visual stimulus can include one or more of: stimulus frequency, intensity (brightness), hue, visual patterns, spatial frequency, contrast, and duty-cycle. In an exemplary embodiment, visual stimulus is provided at a stimulus frequency of 40 Hz, brightness between 0 $\mu\text{W}/\text{cm}^2$ to 1120 $\mu\text{W}/\text{cm}^2$, and 50% duty-cycle.

[0362] In some embodiments, gamma oscillation inducing waveform can be delivered as combined visual stimulus and auditory stimulus, delivered at about 35-45 Hz frequency. In some embodiments, visual stimulus and auditory stimulus can be synchronized to begin each cycle simultaneously. In some embodiments, the beginning of each auditory stimulus and visual stimulus cycle is offset by a configured amount of time. In some embodiments, visual and auditory signals are delivered at an intensity clearly recognized by subjects and adjusted to their tolerance level. In some embodiments, visual and auditory signals are delivered at an intensity imperceptible by subjects.

[0363] In some embodiments, at least some of the parameters or characteristics of the gamma oscillation inducing waveform administered to a subject correspond to those specified in one or more of US Patents US 10307611 B2, US 10293177 B2, or US 10279192 B2. In some embodiments, at least some of the parameters or characteristics of the gamma oscillation

inducing waveform administered to a subject correspond to those specified in one or more of US Patents US 10159816 B2 or US 10265497 B2.

[0364] In some embodiments, parameters of an auditory stimulus include one or more of: stimulus frequency, intensity (volume), and duty-cycle. In some embodiments, frequency is adjusted responsive to a subject's hearing characteristics, for example to frequencies that a subject is better at hearing. In an example embodiment, audio stimulus is provided at an audio tone frequency of 7,000 Hz, volume level between 0 dBA to 80 dBA, and 0.57% duty-cycle.

[0365] In some embodiments, gamma oscillation inducing waveform parameters are directed at evoking gamma wave oscillations in the nervous systems of human subjects. In some embodiments, the gamma oscillation inducing waveform parameters can be configured to induce beta waves in human subjects. In some embodiments, the gamma oscillation inducing waveform parameters can be configured to induce alpha waves in human subjects.

[0366] In some embodiments, light levels and hue can be adjusted to avoid fatiguing the subject. In some embodiments, light levels and hue can be adjusted to provide motivation to the subject. In some embodiments, light levels and hue can be adjusted to be imperceptible to the subject. In some embodiments, parameters to each ear or eye of the subject are adjusted in a similar manner. In some embodiments, parameters to each ear or eye of the subject are adjusted differently. In some embodiments, audio and visual parameters such as tone and hue are varied to provide engagement or motivation to the subject to continue applying the stimulus or monitoring. In some embodiments, audio and visual parameters such as tone and hue can be varied to be imperceptible to the subject.

[0367] The embodiments of the portable system described herein can allow for personalization and patient user-specific therapeutic treatment regimens, as prescribed and determined by a physician or healthcare provider. In some embodiments, the devices and systems provided herein allow for connectivity to patient and care partner support networks (e.g., online, phone, group, telemedicine, telehealth). In some embodiments, the portable system comprises feedback sensors. In some embodiments, the feedback sensors comprise a sensor configured to track the eyes of the user or patient, measure adherence to the prescribed stimulation treatment regimen, or the health status of the user or patient. In some embodiments, the feedback sensors are configured to determine if the eyes of the user or patient are open during the visual and auditory stimulation. In some embodiments, the health status of the user or patient comprises homeostatic eye movement to determine if the user or patient is experiencing a seizure or significant atypical or detrimental neurological event.

[0368] In some embodiments, the portable neurostimulation system comprises feedback loops configured to execute routines and adapt to patient-relevant biometric data for allowing the

portable neurostimulation device to establish a patient-specific or user-specific treatment regimen. In some embodiments, the portable neurostimulation system comprises feedback loops configured to automate transfer of data pertaining to or in the form of patient surveys, self-assessments, healthcare provider assessments, caregiver assessments, biometric data, actigraphy data, and/or treatment adherence between the portable neurostimulation system and a receiving device, data network, or cloud storage system for subsequent analysis. In some embodiments, the devices and systems described herein can be structurally and/or functionally integrated with third-party activity sensors or monitoring sensors. In some embodiments, the data obtained by the device sensors, feedback sensors, and feedback loops can be used to identify additional health or disease indications, including new biomarkers (e.g., changes in neurological activity, cognitive status, cognitive function, treatment adherence). In some embodiments, data analytics obtained via the portable system or devices associated therewith can be enhanced by artificial intelligence.

[0369] The portable system (or Combinatorial Neurostimulation System) described herein is a therapeutic sensory stimulation system that is a portable system, which, in some embodiments, includes a handheld controller, eyeglasses for visual stimulation, and headphones for auditory stimulation that work together to deliver precisely timed, non-invasive stimulation to induce steady-state gamma brainwave activity. In some embodiments, the eyeglasses and headphones are integrated into a single headset device.

[0370] In some embodiments, the visual stimulation generated by the portable system (or Combinatorial Neurostimulation System) comprises precisely timed flashes of visible white light from light-emitting diodes (LEDs), and the auditory stimulation comprises short-duration clicks. The stimuli typically occur at a pulse repetition frequency of about 20 Hz to about 60 Hz. The on-off periods of the visual stimulation are perceivable by the patient but not disruptive; an individual remains aware of their surroundings and can converse with a care partner during the use of the system. In some embodiments, the light pulses of the light-emitting diodes (LEDs) are emitted from the device or system in a manner that is in-phase with the emission of the short-duration clicks from the device or system. In some embodiments, the light pulses of the light-emitting diodes (LEDs) are emitted from the device or system in a manner that is out-of-phase with the emission of the short-duration clicks from the device or system. In some embodiments, the light pulses of the light-emitting diodes (LEDs) are emitted from the device or system in a manner that is in-phase and staggered in time with respect to the emission of the short-duration clicks from the device or system. In some embodiments, the light pulses of the light-emitting diodes (LEDs) are emitted from the device at a time consistently staggered with respect to the emission of the short-duration clicks from the device or system. In some embodiments, the light pulses are staggered by no more than 25 milliseconds with respect to the emission of the short-

duration clicks from the device or system. In some embodiments, the onset of the light pulses are staggered by no more than 25 milliseconds with respect to the emission of the onset of the short-duration clicks from the device or system.

[0371] In some embodiments, the portable system (or Combinatorial Neurostimulation System) is designed to be a prescription device intended for use under the direction of a clinician in the AD population. In some embodiments, the customized stimulation output is determined and verified by a clinician based on both patient-reported comfort information and the patient's quantitative electroencephalography (EEG) response to the stimulation. In some embodiments, the portable system (or Combinatorial Neurostimulation System) is then configured to the determined settings, and all subsequent use will be within this predefined operating range. In some embodiments, once a physician has prescribed a patient's use of the portable system, the patient uses the device at home for daily sessions lasting one hour. In some embodiments, a patient can adjust the brightness of the visual stimulation and the volume of the auditory stimulation within this predefined operating range via push buttons on the controller, and pause/resume a treatment session with assistance from a care partner as needed. In some embodiments, the system logs device usage and stimulation output settings for adherence monitoring; this information is uploaded to a "cloud" storage or a physical media storage device for remote monitoring.

[0372] In some embodiments,, the system is designed for ease of use for older adults: the controller user interface has a limited number of controls with no requirements for high dexterity manipulation, the device is accompanied by simple visual instructions in large print, and auditory (voice) prompts of a patient's progress during a treatment session are delivered through the headphones. In some embodiments, from a patient's perspective, the flashing light and auditory click stimulation result in the desired induced gamma brainwave activity without interruption of normal functioning. In some embodiments, the individual wearing the device remains oriented to the surrounding environment; s/he is readily able to converse and perform voluntary movements such as holding the hand of their care partner while remaining seated throughout the treatment session. In some embodiments, the flashing light and auditory click stimulation are administered to the user or patient while the user or patient is in a state of wakefulness. In some embodiments, the flashing light and auditory click stimulation are administered to the user or patient while the user or patient is attentive to the flashing light and auditory click stimulation.

v. Physical or Cognitive Assessment

[0373] In some embodiments, methods of using a device or system as disclosed herein comprise receiving an indication of a physiological, cognitive, neural, visual, or physical assessment of a

subject wearing a device or system as disclosed herein and emitting a stimulus in response to the indication. In some embodiments, a physiological, cognitive, neural, visual, or physical assessment is performed using a portable system as disclosed herein. In some embodiments, a physiological, cognitive, neural, visual, or physical assessment is performed using a portable system or single headset device as disclosed herein, wherein the system or single headset device comprises a processor and a feedback sensor, wherein the feedback sensor receives an indication of a physiological assessment, cognitive assessment, neural assessment, or physical assessment of a subject through said feedback sensor and transmits the a signal to the processor, wherein the processor instructs a stimulus-emitting component, to adjust at least one parameter associated with a auditory, visual, or haptic stimulus. In some embodiments, the adjustment of at least one parameter associated with said stimulus comprises an adjustment that induces gamma oscillations in a brain region of said subject. In some embodiments, the physical assessment of the subject involves ascertaining at least one of said subject's: compliance with proper use and positioning of said system, eye status, alert or sleep status, or environment and surroundings. In some embodiments, the neural assessment of said subject is received using brain wave sensors, an electroencephalography (EEG) device, an electrooculography (EOG) devices, or a magnetoencephalography (MEG) device. In some embodiments, the cognitive assessment of the subject is obtained through questions posed to said subject, activities and tasks performed by said subject in response to a prompt, or behaviors exhibited by said subject. In some embodiments, the processor further instructs the stimulus-emitting component to lengthen or shorten a duration of stimulation in response to the indication of the physiological, cognitive, neural, and/or physical assessment.

[0374] In some embodiments, the indication of the physical assessment of the subject comprises ascertaining at least one of the subject's: compliance with proper use and positioning of the system, eye status, alert or sleep status, or environment and surroundings.

[0375] In some embodiments, the indication of the cognitive assessment of the subject is obtained through questions posed to the subject, activities and tasks performed by the subject in response to a prompt, or behaviors exhibited by the subject.

[0376] In some embodiments, methods comprise instructing the device or system to lengthen or shorten a duration of stimulation in response to the indication of the physiological, cognitive, neural, visual, , or physical assessment. In some embodiments, the physical assessment of the subject is performed to determine hearing of the subject.

vi. Methods of Treating Diseases or Conditions

[0377] In some embodiments, methods of using a device or system as disclosed herein include using the device or system to treat, prevent, or mitigate cognitive dysfunction in a subject.

[0378] In some embodiments, the device or system is used to treat Alzheimer's disease or dementia in a subject in need thereof. In some embodiments, the dementia comprises, vascular dementia, Lewy body dementia, Pick's disease, fronto-temporal dementia (FTD), AIDS dementia, age-related cognitive impairments, and age-related memory impairments.

[0379] In some embodiments, the disease or condition comprises Parkinson's disease.

[0380] In some embodiments, the method of treatment comprises stimulating a subject with a stimulus generated by a device or system disclosed herein, thereby inducing gamma oscillations in brain region of the subject.

[0381] In some embodiments, the brain region comprises an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof.

[0382] In some embodiments, the induced gamma oscillations correspond to the frequency of the stimulus generated by a wireless audio or haptic device, or system used to administer the stimulus.

1. Additional Diseases and Conditions

[0383] In some embodiments, the systems, devices, and methods of the present disclosure can be useful for treating or benefiting a cognitive state or function of a brain of a subject including the following diseases and conditions.

[0384] In some embodiments, the disease or disorder can comprise a neurodegenerative disease associated with tauopathy, including but not limited to Alzheimer's disease, frontotemporal dementia, chronic traumatic encephalopathy (CTE), and corticobasilar degeneration.

[0385] Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by a decline in memory, orientation, and reasoning. AD can be characterized by the accumulation of amyloid plaques comprising the amyloid-3 (A3) peptide and neurofibrillary tangles (NFTs) made of the tau protein. Under normal conditions, the soluble A3 peptide is produced and secreted by neurons and subsequently cleared from the brain via cerebral spinal fluid (CSF) pathways. However, in subjects with AD, the A β peptide appears to aggregate into higher-order species to form soluble oligomers and insoluble plaques in a concentration-dependent manner. This aggregation can initiate many neurotoxic events including disrupted brain metabolism,

neuroinflammation, reduced functional connectivity, synaptic and neuronal loss, and/or formation of NFTs.

[0386] Frontotemporal dementia (FTD) is a group of disorders that result from damage to the frontal and temporal lobes of the brain. Depending on the location of the damage, the disorder causes changes in social behavior, personality, and/or loss of language skills. In some people, FTD can also lead to neuromuscular disorder, such as parkinsonism. Frontotemporal dementia occurs where abnormal proteins build up in the brain, leading to death of brain cells and atrophy of the frontal and temporal lobes of the brain. Frontotemporal dementia occurs in Alzheimer's disease, although it can be caused by other neurodegenerative diseases as well.

[0387] Chronic traumatic encephalopathy (CTE) is characterized by symptoms that can include memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, anxiety, suicidality, parkinsonism, and progressive dementia. CTE results from traumatic injury to the head triggers microglia, leading to tau proteins becoming phosphorylated at progressively higher rates and, accordingly, accumulation of hyperphosphorylated tau deposits. The buildup of phosphorylated tau proteins can lead to axonal transport defects, neuroinflammation, and synapse loss.

[0388] Corticobasal degeneration (CBD) is characterized by cell loss and deterioration of specific areas of the brain. In corticobasal degeneration, abnormal levels of tau accumulate in certain brain cells, eventually causing their deterioration. Symptoms often initially include experiencing motor abnormalities in one limb that progressively spreads to all limbs. Such motor abnormalities include, for example, progressive stiffening or tightening of muscles in the limb (progressive asymmetric rigidity) and the inability to perform purposeful or voluntary movements (apraxia). Trouble with speech and language, including aphasia, apraxia of speech, dysarthria, dysphagia. Symptoms can also be reflected in physical movements and tremors, such as experiencing action tremor, postural tremor, bradykinesia, akinesia, myoclonus, and ataxic gait. The severity and type of symptoms depend on the area of the brain affected by the disease, which is most commonly the cerebral cortex and basal ganglia.

a) Genetic Disorders: Inherited Ataxias

[0389] Hereditary ataxias are characterized by slowly progressive incoordination of gait and are often associated with poor coordination of hands, speech, and eye movements. Hereditary ataxias frequently cause atrophy of the cerebellum as a result of impaired circuitry and function of the cerebellar cortex, a result of neurodegeneration of cellular afferents and the Pukinje cells, which have long axonal projections that comprise the only sources of output from the cerebellar cortex to deep cerebellar nuclei.

b) Neuropsychiatric Disorders: Schizophrenia,

Depression, Chronic Stress

[0390] In other embodiments, the present disclosure provides system and methods for treating neuropsychiatric disorders associated with brain atrophy, which is mediated by microglial cells. For example, individuals with schizophrenia often show reduced postmortem cortical tissue. This phenomenon is caused by synaptic pruning, which reflects abnormalities in microglia-like cells and synaptic function. In other embodiments, the present disclosure provides methods and systems for alleviating symptoms of depression. Stress, impaired neurogenesis, and defects in synaptic plasticity are associated with depression. Chronic stress promotes microglial hyper-ramification and astroglial atrophy. Thus, in some embodiments, the system and methods disclosed can alleviate symptoms associated with chronic stress or depression by improving synaptic plasticity and stimulating neural networking, along with improving microglial-mediated clearance.

c) Brain Injury: Stroke and Related Cerebrovascular

Diseases

[0391] In some embodiments, the present disclosure provides systems, devices, and methods for alleviating symptoms associated with a stroke. For example, the stroke can be an ischemic stroke, which causes a neuroinflammatory response and activates microglia to help repair the brain. Ischemic stroke is associated with disappearance of synaptic activity. As a result, brain tissue within the penumbra during an ischemic stroke is structurally intact, but functionally silent. Failure to reperfuse this penumbral region or resupply glucose and oxygen in time can lead to atrophy of brain cells located in the penumbra. In contrast, activating synapses in this region can delay cell death and salvage brain tissue. By improving synaptic plasticity and stimulating neural networking, the present systems, devices, and methods can reduce brain atrophy and related symptoms associated with ischemic stroke. Other forms cerebrovascular diseases with similar symptoms— e.g., neuroimmune modulation, synaptic function—can also be treated by the present disclosure, including but not limited to: transient ischemic attack (TIA), hemorrhagic stroke, arteriovenous malformation, intracranial atherosclerosis (ICAD), and Moyamoya.

d) Demyelinating Diseases: Multiple Sclerosis and

Acute Disseminated Encephalomyelitis

[0392] In some embodiments, the present disclosure provides systems, devices, and methods for alleviating symptoms of demyelinating diseases associated with brain atrophy. For example, the demyelinating disease can comprise Multiple Sclerosis or Acute disseminated encephalomyelitis, both of which can cause neuroinflammation and cerebral atrophy. In multiple sclerosis (MS), brain or cerebral atrophy is common due to demyelination and destruction of nerve cells.

Widespread myelin damage occurs, causing damage to the myelin-rich white matter of the brain, occurs as a result of a number of attacks which occur over time. In acute disseminated encephalomyelitis, similar symptoms are seen, but the onset of widespread myelin damage is often due to a single episode or attack. By reducing neuroinflammation and stimulating neural networking, the present disclosure provides systems, devices, and methods for slowing brain atrophy associated with demyelinating diseases and related symptoms.

e) Sleep

[0393] In some embodiments, the systems, devices, and methods of the present disclosure are also directed towards improvement in sleep quality, including reduced sleep fragmentation and increased nighttime restful periods as assessed from actigraphy data, through non-invasive, convenient, and easily tolerated treatment, in mild to moderate AD subjects, with applications to wider populations of users. Moreover, the present solution, i.e., use of a portable system as disclosed herein, provides a method that can be easily administered in the home or other familiar setting by the patient or caregiver, thus avoiding transportation between home and clinical facility. In some cases, the present solution, i.e., use of a portable system as disclosed herein, can improve sleep quality and potentially prevent, mitigate, and/or treat dementia, in particular AD, along with other sleep-related benefits.

[0394] Sleep fragmentation is associated with increased expression of genes characteristic of aged microglia and the proportion of morphologically activated microglia, which are in turn correlated with, and can underlie, sleep-fragmentation associated cognitive deficits. Based on these and other clinical observations, reducing sleep fragmentation and/or improving sleep quality in MCI and AD patients can provide multiple benefits: better sleep can enhance patients' daytime performance, including cognitive function, and reduce behavioral pathologies and daytime sleepiness. Furthermore, improved sleep quality as a result of reduced sleep fragmentation can also positively modify disease progression.

[0395] In some embodiments, the present disclosure describes systems, devices, and methods for delivering gamma oscillation inducing waveform directed at producing a reduction in sleep fragmentation during night-time sleep of mild to moderate AD patients. In some embodiments, the present disclosure describes systems, devices, and methods for increasing the length of restful periods during sleep and/or reducing the frequency of awakenings during sleep.

[0396] In some embodiments, the present disclosure describes systems, devices, and methods for delivering a gamma oscillation inducing waveform directed at producing beneficial changes in actigraphy during night-time sleep of mild to moderate AD patients. In some embodiments, the present disclosure describes systems, devices, and methods for delivering gamma oscillation inducing waveform directed at producing beneficial changes in actigraphy during sleep periods in

mild to moderate AD patients. In some embodiments, the present disclosure describes systems, devices, and methods for producing changes in actigraphy during sleep in mild to moderate AD patients through the application of audio-visual gamma wave stimulation. In some embodiments, the present disclosure describes systems, devices, and methods for producing beneficial changes in sleep of mild to moderate AD patients through the application of audio-visual gamma wave stimulation.

[0397] In some embodiments, the present disclosure describes systems, devices, and methods for delivering gamma oscillation inducing waveform directed at producing beneficial changes in actigraphy during sleep periods in one or more of: subjects at risk of AD, subjects experiencing cognitive decline, subjects experiencing sleep disruption, subjects diagnosed with AD, subjects diagnosed with MCI, healthy subjects, subjects with sleep pathologies, and subjects with sleep disruptions. In some embodiments, beneficial changes in actigraphy includes reduction in sleep fragmentation. In some embodiments, beneficial changes in actigraphy includes one or more of: increases the frequency of restful periods during sleep periods and/or reduction in the frequency of sleep interruptions during sleep periods. In some embodiments, the present disclosure delivers gamma oscillation inducing waveform directed at producing a reduction in sleep fragmentation during night-time sleep of mild to moderate AD patients. In some embodiments, the present disclosure further describes technologies directed at increasing the length of restful periods during sleep and/or reducing the frequency of awakenings during sleep.

[0398] In some embodiments, systems, devices, and methods directed at producing beneficial changes in actigraphy are further directed at producing beneficial sleep-related health outcomes. In some embodiments, beneficial sleep-related health outcomes include one or more of: clearance of brain waste products, mitigation of various afflictions that negatively affect cognitive function, slowing or delay of AD progression, reduction of circadian rhythm disruptions, reduction of microglial aging and activation, reduction in cognitive impairment, reduction in depression symptoms, mitigation of appetite or eating disorders, reduction in agitation, reduction in apathy, reduction in psychosis symptoms (including delusions and hallucinations), reduction in aggression, reduction in behavioral and psychiatric symptoms of dementia, stabilizing and/or preventing the degradation of one or more measures of performance. In some embodiments, mitigated circadian rhythm disruptions include but are not limited to disruptions associated with: AD, MCI, ageing, eating disorders, irregular sleep wake rhythm disorder, depression, anxiety, stress.

[0399] In some embodiments, sleep, during sleep, or sleep periods can refer to nighttime periods of relative inactivity or periods of frequent rest. In some further embodiments, such periods of relative inactivity or frequent rest refer to those characterized patterns of actigraphy, including

but not limited to patterns of actigraphy identified using the methods described in embodiments of the present technological solution. FIGs. 34 and 35 provides an example of a pattern of actigraphy identified using the methods described herein. FIGs. 34 and 35 shows twenty-four (24) hours of activity levels (gray; 1501, **FIG. 37**) over two days for a single example patient, centered around 12 AM (indicated by the thick, gray arrows) along with a median filtered curve (labelled by thin arrows; 1507, **FIG. 37**). The horizontal axis shows time of day; the vertical axis is relative activity recorded on a wrist-worn actigraphic measuring device (arbitrary log scale). Calculated sleep periods (black horizontal lines; see 1508, **FIG. 37**) along with individual sample rest periods (yellow horizontal lines; see 1509, **FIG. 37**) are shown: with (a) showing an example pattern for frequent movements and short rest periods during sleep periods, and (b) showing an exemplary pattern of less frequent movements and longer rest periods during sleep periods. Similarly, **FIG. 33** provides example patterns of actigraphy (arbitrary units, see **FIG. 34**). **FIG. 33** provides actigraphy data for over several days (gray; e.g., 1501, **FIG. 37**), and a smooth curve is superposed. The cutoff line (black line) separates active vs rest periods (e.g., 1505, **FIG. 37**). The black squares represent initial estimation for the mid-night point (e.g., 1507, **FIG. 37**), of which a final assessment of the mid-night points will be determined through optimization algorithm e.g., 1508, **FIG. 37**).

f) Brain Atrophy

[0400] In some embodiments, systems, devices, and methods described herein can also be used to slow brain atrophy, and thus mediate symptoms associated with brain atrophy through a variety of mechanisms. For example, the present disclosure describes systems, devices, and methods for reducing neuroinflammation, improving synaptic plasticity and stimulating neural networking, and improving microglial-mediated clearance of cerebral insults, all of which can contribute to the progression of brain atrophy, by inducing synchronized gamma oscillations in at least one region of a brain in a subject. The at least one brain region, for example, can include a visual cortex, a somatosensory cortex, an insular cortex, and/or a hippocampus of the subject. The present disclosure also describes systems, devices, and methods for alleviating symptoms of diseases and disorders associated with brain atrophy through non-invasive stimulation of gamma oscillations.

[0401] Atrophy of brain tissue describes the loss of volume within neurons, extracellular space, or glia. Atrophy can occur at different rates in different areas or regions of the brain, and it can be reflected by changes in whole brain volume. For an adult, whole brain volume can be, for example, between around 950 ml and 1550 ml. For an adult female, average whole brain volume can be around 1130 ml. For an adult male, average brain volume can be around 1260 ml.

[0402] For a child of an age between around 4 years old and 16 years old, whole brain volume can be, for example, between 60 ml and 120 ml.

[0403] Brain volume can be measured using magnetic resonance imaging (MRI) or computerized tomography (CT) scans. Loss of brain volume can be measured by comparing brain volume over time. Various methods can be used to measure brain volume or changes in brain volume, which indicate brain atrophy. Most commonly, brain volume or brain volume loss can be measured using cross-sectional methods or longitudinal methods. Cross-sectional methods can use a single MRI scan to segment particular tissues or structures and calculate the volume of these tissue types and/or structures. Longitudinal methods can use at least two MRI scans of the same subject at different points in time to calculate brain volume changes or atrophy. Longitudinal methods can seek to match the two MRI scans using warping techniques and, from this process, directly extract small changes in brain volume.

[0404] Various tools and algorithms can be employed to determine brain volume through CT or MRI scans. Of the various toolkits available for determining brain volume and changes in brain volume based on the scanned images, examples include, but are not limited to, the following tools: Atropos, an opensource tissue segmentation algorithm; CIVET, a web-based image-processing tool for volumetric analysis with different human brain images; the Structural Image Evaluation using Normalization of Atrophy (SIENA and SIENAX), a software that applies a Brain Extraction Tool (BET) to determine cross-sectional volumes; MSmetrix, a fully-automatic tool that detects brain lesions and calculates lesion volume and measures whole-brain and gray matter atrophy; and Statistical Parametric Mapping (SPM), which for analysis of images in a MATLAB environment.

[0405] A subject with brain atrophy can experience this as a cause or result of a variety of conditions, disorders, or diseases, including but not limited to: Alzheimer's Disease (AD), dementia, Parkinson's disease, seizure, cerebral palsy, senile dementia, pick's disease, Huntington's disease, Krabbe disease, leukodystrophies, multiple sclerosis, epilepsy, anorexia nervosa, aphasia, learning disability, frontotemporal dementia, expressive aphasia, receptive aphasia, Lewy body dementia, chronic traumatic encephalopathy (CTE), and others.

[0406] The change in brain volume can be a reduction of around: 0.3 cm³ per month, 0.5 cm³ per month, 1 cm³ per month, 2 cm³ per month, 0.3 cm³ per year, 0.5 cm³ per year, 1 cm³ per year, 2 cm³ per year, 3 cm³ per year, 4 cm³ per year, 5 cm³ per year, 6 cm³ per year, 7 cm³ per year, 8 cm³ per year, 9 cm³ per year, 10 cm³ per year, 11 cm³ per year, 12 cm³ per year, 13 cm³ per year, 14 cm³ per year, or 15 cm³ per year, or 16 cm³ per year. The rate of brain atrophy can differ between individuals. Exemplary rates of brain atrophy can include, but are not limited to, rates around: between 0.1% and 0.5% per year, between 0.5% and 1.5% per year, between 1.0%

and 3.0% per year, or between 3.0% and 6.0% per year. The rate of brain atrophy can vary based on the cause of atrophy. For example, a healthy individual can experience an average brain atrophy rate of 0.1% and 0.4% per year. In contrast, for subjects with Multiple Sclerosis (MS), the average brain atrophy rate can be between 0.5% and 1.3% per year. The average rate of whole brain atrophy for a patient with Alzheimer's Disease can be, for example, between 1.0% and 4.0% per year. Aging can also cause brain atrophy rates to increase. For example, an individual in their mid-thirties can experience a rate of brain atrophy that is around 0.2% per year, and an individual at around age sixty can experience a rate of brain atrophy that is around 0.5% per year.

[0407] The systems, devices, and methods of the present disclosure are also directed to alleviating symptoms of brain atrophy. Symptoms can include a loss of neurons, memory loss, blurred vision, aphasia, impaired balance, paralysis, decreases in cortical volume, increases in CSF volume, loss of motor control, difficulty speaking, comprehension, reading comprehension, memory, decrease in gray and/or white matter, decrease in neuronal size, loss of neuronal cytoplasmic proteins, or any combination thereof. In some embodiments, the present disclosure describes systems, devices, and methods which act to slow the onset of symptoms of brain atrophy. The present disclosure provides systems, devices, and methods for treating any of the above-listed diseases and disorders by reducing any of the above-listed symptoms associated with brain atrophy. In some embodiments, brain atrophy is reduced or maintained in the corpus callosum. In some embodiments, the brain region comprises an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof. In some embodiments, a level of atrophy in a brain region of a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

vii. Methods of Inducing Gamma Oscillations During Daily Activities

[0408] Also described herein are systems, devices, and methods for providing a gamma oscillation inducing waveform to a subject, wherein the gamma oscillation inducing waveform is imperceptible to the subject. An imperceptible waveform can be integrated into various activities in the daily life of the subject, for instance, watching television, working on a computer, listening to music, playing video games, and other aspects of life.

[0409] When the gamma oscillation inducing waveform is imperceptible to the subject, the subject can enjoy various daily activities while benefiting from the therapeutic effects of the gamma-oscillation inducing waveform without feeling the intrusion of the gamma oscillation inducing waveform into the daily activities. An advantage of providing the gamma oscillation inducing waveform in an imperceptible manner can be that various daily activities (e.g., work or pleasure) that a subject takes part in will not be disrupted by the gamma oscillation inducing waveform.

[0410] Furthermore, if the daily activity is social in nature, for instance, watching television with family, playing video games with a friend, etc., providing the gamma-oscillation inducing waveform in an imperceptible manner can bring additional benefits. A family member, a husband or spouse, a friend, and other acquaintances important to the subject may not feel disrupted, annoyed, or bothered by the gamma oscillation inducing waveform when it is imperceptible to them.

B. Methods of Inducing Improvements in a Brain Region via Use of Portable Systems and Devices as Disclosed Herein

i. Cognition

[0411] The present technological solution achieves the induction of gamma wave oscillations in the brain through a variety of methods and systems, and includes aspects covering the monitoring and analysis of patient activity, motivation and feedback to users and/or third parties, and specific stimulation parameters targeted at improving cognition and cognitive functioning. Induction of gamma wave oscillations in the brain can be done using non-invasive sensory stimulation, which can include haptic or mechanical stimulation, peripheral nerve stimulation, visual stimulation, auditory stimulation, or a combination thereof. The disclosure further achieves improved brain wave coherence, measured through increased power in alpha and other frequency bands and other methods for assessing functional connectivity, which are associated with cognitive function, brain health, and general wellbeing.

[0412] In some embodiments, the present disclosure describes systems, devices, and methods for benefiting a cognitive state or function of a brain of a subject, by delivering a gamma oscillation inducing waveform to improve cognitive function and/or to evoke gamma wave oscillations in a subject. In some embodiments, the gamma oscillation inducing waveform achieves cognitive function improvement by inducing gamma oscillations in at least one brain region of the subject.

[0413] Systems, devices, and methods of the present disclosure can be directed to improving the cognitive capacity of a person. In some embodiments, the present disclosure can improve or maintain cognitive functioning of an individual. Any individual can use the systems, devices, and methods of the present disclosure. The individual can be neurotypical or neurodivergent. In some embodiments, the individual has a neurodegenerative disease. In some embodiments, the individual has a physiological disorder, a psychological disorder, a psychosomatic disorder, or a psychiatric disorder.

[0414] In some embodiments, stimulating a subject with the stimulus according to the methods disclosed herein comprises inducing one or more improvements in a brain region of the subject. In some embodiments, the one or more improvements comprises maintaining or improving cognitive function in said brain region of said subject. In some embodiments, said maintaining or improving cognitive function comprises maintaining or improving recognition, discrimination, spatial memory, working memory, attention, or a combination thereof. Systems, devices, and methods described herein can influence one or more of a cognitive process in order to cause a therapeutic improvement. For example, systems, devices, and methods described herein can cause an improvement in emotional control, perceptual reasoning, cognitive flexibility, goal-directed persistence, metacognition, organization, planning/prioritization, response inhibition, stress tolerance, sustained attention, task initiation, time management, working memory, or a combination thereof. Other cognitive processes that can benefit from the systems, devices, and methods described herein include sensory register, short-term memory formation, long-term memory formation, memory encoding, memory consolidation, molecular or cellular memory consolidation, memory recall, perception, attention, knowledge formation, problem solving, concept formation, pattern recognition, association, decision making, motor coordination, decision making, planning, language production, or language comprehension. Further mental processes that can benefit from the technology described herein can also comprise mental calculation, visual encoding and decoding, auditory coding and decoding, sensory encoding and decoding, visual processing, visual-motor planning and processing, visual-spatial planning and processing, auditory memory, visual memory, and task planning, sequencing, initiation, and completion.

[0415] The present disclosure is also directed towards improving cognitive skills. Cognitive skills can include one or more of sustained attention, selective attention, divided attention, long-term memory, working memory, logic and reasoning, auditory processing, visual processing, processing speed, cognitive control, cognitive inhibition, declarative memory, procedural memory, episodic memory, semantic memory, autobiographical memory.

ii. Additional Improvements

[0416] In some embodiments, the one or more improvements comprise the maintenance or reduction of a level of tau phosphorylation in a brain region of the subject. In some embodiments, a level of tau phosphorylation in a brain region of a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0417] In some embodiments, stimulating a subject with a portable system or device results in the maintenance or reduction of punctate localization of phosphorylated tau protein in a brain region of the subject. In some embodiments, punctate localization of phosphorylated tau protein in a brain region of a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0418] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in maintaining or improving cognitive function in the subject. In some embodiments, the maintaining or improving cognitive function comprises maintaining or improving recognition, discrimination, spatial memory, working memory, attention, or a combination thereof.

[0419] In some embodiments, a level of cognitive function in a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% improved as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0420] In some embodiments, a level of cognitive function in a subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% improved as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0421] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in maintaining or reducing an amount of amyloid- β ($A\beta$) peptide in a brain region of a subject.

[0422] In some embodiments, a level of amyloid- β ($A\beta$) peptide in a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% improved as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0423] In some embodiments, a level of amyloid- β ($A\beta$) peptide in a subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% improved as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0424] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in maintaining or reducing an amount of C-terminal

fragments (CTFs) and N-terminal fragments (NTFs) of amyloid precursor protein (APP) in a brain region of a subject.

[0425] In some embodiments, a level of C-terminal fragments (CTFs) and N-terminal fragments (NTFs) of amyloid precursor protein (APP) in a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0426] In some embodiments, a level of C-terminal fragments (CTFs) and N-terminal fragments (NTFs) of amyloid precursor protein (APP) in a subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0427] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in maintaining or reducing an amount of cleavage of APP into CTFs and NTFs by at least one of β -secretase (BACE1) and γ -secretase in a brain region of a subject.

[0428] In some embodiments, a level of cleavage of APP into CTFs and NTFs by at least one of β -secretase (BACE1) and γ -secretase in a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0429] In some embodiments, a level of cleavage of APP into CTFs and NTFs by at least one of β -secretase (BACE1) and γ -secretase in a subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% reduced as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0430] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in maintaining or reducing an amount of a number of endosomes in a brain region of a subject.

[0431] In some embodiments, a number of endosomes in a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% reduced as compared to a subject not stimulated by a closed view visual stimulation device as disclosed herein.

[0432] In some embodiments, a number of endosomes in a subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% reduced as compared to a subject stimulated by a portable system or device as disclosed herein.

[0433] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in clearance of A β peptide in a brain region of the subject.

[0434] In some embodiments, clearance of A β peptide in a brain region of a subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% increased as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0435] In some embodiments, clearance of A β peptide in a brain region of a subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% increased as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0436] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in increasing uptake of A β peptide by microglia in a brain region of the subject.

[0437] In some embodiments, increasing uptake of A β peptide by microglia in a brain region of the subject stimulated by a portable system or device as disclosed herein is about 1% to about 100% increased uptake as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0438] In some embodiments, increasing uptake of A β peptide by microglia in a brain region of the subject stimulated by a portable system or device as disclosed herein is at least 1% to at least 100% increased uptake as compared to a subject not stimulated by a portable system or device as disclosed herein.

[0439] In some embodiments, stimulating a subject with a portable system or device according to the methods disclosed herein results in inducing a change in microglial cells in a brain region of a subject, thereby improving the cognitive function of the subject, or preventing, reducing, or treating cognitive decline in the subject.

[0440] In some embodiments, also described herein are systems, devices, and methods for providing a gamma oscillation inducing waveform to a subject via stimulus emitting components, for benefiting a cognitive state or function of a brain of a subject. Gamma oscillation inducing waveforms delivered to the subject can produce gamma wave oscillations in various regions in the nervous system of the subject, and bring about therapeutic benefits to the subject as a result, thereby slowing progression of mild cognitive impairment or Alzheimer's disease in said subject.

[0441] By integrating the delivery of the gamma oscillation inducing waveform with a portable system as disclosed herein, or a neurostimulation device (e.g., a single headset device through a visual source, a haptic source, and/or an auditory source), the subject can experience therapeutic benefits of receiving the gamma oscillation inducing waveform in various daily activities.

Integrating the delivery of the gamma oscillation inducing waveform with a portable system or a neurostimulation device can bring therapeutic benefits to the subject with little intrusion into and/or disruption of the daily life of the subject.

[0442] In some cases, the gamma oscillation can lead to a therapeutic improvement in one or more cognitive functions. For example, the gamma oscillation inducing waveform can generate sensory-evoked potentials in at least one region of the nervous system and, as a result, bring about therapeutic improvements in one or more cognitive functions of the subject, for instance, improvements in neurotic behavior, anxious behavior, depressive behavior, addictive behavior, food-seeking behavior, or sleeping behavior.

[0443] In some embodiments, the present disclosure provides systems, devices, and methods for alleviating symptoms associated with a microglial-mediated disease or disorder associated with brain atrophy. For example, the microglial-mediated disease or disorder can comprise a neurodegenerative disease associated with tauopathy, including but not limited to chronic traumatic encephalopathy, frontotemporal dementia, and corticobasilar degeneration. The microglial-mediated disease or disorder can comprise a genetic disorder, such as an inherited ataxia associated with brain atrophy. The microglial-mediated disease or disorder can also comprise a neuropsychiatric disorder associated with brain atrophy, such as depression or schizophrenia; brain injury, such as stroke; or demyelinating diseases, such as Multiple Sclerosis and Acute disseminated encephalomyelitis.

C. Methods for Neural Stimulation with an NSS via Visual Stimulation

In some aspects, described herein are methods of neural stimulation via visual stimulation. In some embodiments, a method of visual neurostimulation comprises a method of using a portable system or single headset device as disclosed herein. In some embodiments, a method of visual neurostimulation comprises a method of using a portable system as disclosed herein, wherein the portable system comprises an NSS. Illustrative embodiments are described as follows.

[0444] In **FIG. 8** is a flow diagram of a method of performing visual brain stimulation in accordance with an embodiment. The method 800 can be performed by one or more systems, component, modules or elements depicted in **FIGS. 1-7B**, including, for example, a neural stimulation system (NSS). In brief overview, the NSS can identify a visual signal to provide at block 805. At block 810, the NSS can generate and transmit the identified visual signal. At 815 the NSS can receive or determine feedback associated with neural activity, physiological activity, environmental parameters, or device parameters. At 820 the NSS can manage, control, or adjust the visual signal based on the feedback.

i. NSS Operating With A Frame

[0445] The NSS 105 can operate in conjunction with the frame 400 including a light source 305 as depicted in **FIG. 4A**. The NSS 105 can operate in conjunction with the frame 400 including a

light source 30 and a feedback sensor 605 as depicted in **FIG. 6A**. The NSS 105 can operate in conjunction with the frame 400 including at least one shutter 430 as depicted in **FIG. 4B**. The NSS 105 can operate in conjunction with the frame 400 including at least one shutter 430 and a feedback sensor 605.

[0446] In operation, a user of the frame 400 can wear the frame 400 on their head such that eye wires 415 encircle or substantially encircle their eyes. In some cases, the user can provide an indication to the NSS 105 that the glass frames 400 have been worn and that the user is ready to undergo brainwave entrainment. The indication can include an instruction, command, selection, input, or other indication via an input/output interface, such as a keyboard 726, pointing device 727, or other I/O devices 730a-n. The indication can be a motion-based indication, visual indication, or voice-based indication. For example, the user can provide a voice command that indicates that the user is ready to undergo brainwave entrainment.

[0447] In some cases, the feedback sensor 605 can determine that the user is ready to undergo brainwave entrainment. The feedback sensor 605 can detect that the glass frames 400 have been placed on a user's head. The NSS 105 can receive motion data, acceleration data, gyroscope data, temperature data, or capacitive touch data to determine that the frames 400 have been placed on the user's head. The received data, such as motion data, can indicate that the frames 400 were picked up and placed on the user's head. The temperature data can measure the temperature of or proximate to the frames 400, which can indicate that the frames are on the user's head. In some cases, the feedback sensor 605 can perform eye tracking to determine a level of attention a user is paying to the light source 305 or feedback sensor 605. The NSS 105 can detect that the user is ready responsive to determining that the user is paying a high level of attention to the light source 305 or feedback sensor 605. For example, staring at, gazing or looking in the direction of the light source 305 or feedback sensor 605 can provide an indication that the user is ready to undergo brainwave entrainment.

[0448] Thus, the NSS 105 can detect or determine that the frames 400 have been worn and that the user is in a ready state, or the NSS 105 can receive an indication or confirmation from the user that the user has worn the frames 400 and the user is ready to undergo brainwave entrainment. Upon determining that the user is ready, the NSS 105 can initialize the brainwave entrainment process. In some embodiments, the NSS 105 can access a profile data structure 145. For example, a profile manager 125 can query the profile data structure 145 to determine one or more parameter for the external visual stimulation used for the brain entrainment process. Parameters can include, for example, a type of visual stimulation, an intensity of the visual stimulation, frequency of the visual stimulation, duration of the visual stimulation, or wavelength of the visual stimulation. The profile manager 125 can query the profile data structure 145 to

obtain historical brain entrainment information, such as prior visual stimulation sessions. The profile manager 125 can perform a lookup in the profile data structure 145. The profile manager 125 can perform a look-up with a username, user identifier, location information, fingerprint, biometric identifier, retina scan, voice recognition and authentication, or other identifying technique.

[0449] The NSS 105 can determine a type of external visual stimulation based on the hardware 400. The NSS 105 can determine the type of external visual stimulation based on the type of light source 305 available. For example, if the light source 305 includes a monochromatic LED that generates light waves in the red spectrum, the NSS 105 can determine that the type of visual stimulation includes pulses of light transmitted by the light source. However, if the frames 400 do not include an active light source 305, but, instead, include one or more shutters 430, the NSS 105 can determine that the light source is sunlight or ambient light that is to be modulated as it enters the user's eye via a plane formed by the eye wire 415.

[0450] In some embodiments, the NSS 105 can determine the type of external visual stimulation based on historical brainwave entrainment sessions. For example, the profile data structure 145 can be pre-configured with information about the type of visual signaling component 150.

[0451] The NSS 105 can determine, via the profile manager 125, a modulation frequency for the pulse train or the ambient light. For example, NSS 105 can determine, from the profile data structure 145, that the modulation frequency for the external visual stimulation should be set to 40 Hz. Depending on the type of visual stimulation, the profile data structure 145 can further indicate a pulse length, intensity, wavelength of the light wave forming the light pulse, or duration of the pulse train.

[0452] In some cases, the NSS 105 can determine or adjust one or more parameter of the external visual stimulation. For example, the NSS 105 (e.g., via feedback component 160 or feedback sensor 605) can determine a level or amount of ambient light. The NSS 105 (e.g., via light adjustment module 115 or side effects management module 130) can establish, initialize, set, or adjust the intensity or wavelength of the light pulse. For example, the NSS 105 can determine that there is a low level of ambient light. Due to the low level of ambient light, the user's pupils may be dilated. The NSS 105 can determine, based on detecting a low level of ambient light, that the user's pupils are likely dilated. In response to determining that the user's pupils are likely dilated, the NSS 105 can set a low level of intensity for the pulse train. The NSS 105 can further use a light wave having a longer wavelength (e.g., red), which may reduce strain on the eyes.

[0453] In some embodiments, the NSS 105 can monitor (e.g., via feedback monitor 135 and feedback component 160) the level of ambient light throughout the brainwave entrainment process to automatically and periodically adjust the intensity or color of light pulses. For

example, if the user began the brainwave entrainment process when there was a high level of ambient light, the NSS 105 can initially set a higher intensity level for the light pulses and use a color that includes light waves having lower wavelengths (e.g., blue). However, in some embodiments in which the ambient light level decreases throughout the brainwave entrainment process, the NSS 105 can automatically detect the decrease in ambient light and, in response to the detection, adjust or lower the intensity while increasing the wavelength of the light wave. The NSS 105 can adjust the light pulses to provide a high contrast ratio to facilitate brainwave entrainment.

[0454] In some embodiments, the NSS 105 (e.g., via feedback monitor 135 and feedback component 160) can monitor or measure physiological conditions to set or adjust a parameter of the light wave. For example, the NSS 105 can monitor or measure a level of pupil dilation to adjust or set a parameter of the light wave. In some embodiments, the NSS 105 can monitor or measure heart rate, pulse rate, blood pressure, body temperature, perspiration, or brain activity to set or adjust a parameter of the light wave.

[0455] In some embodiments, the NSS 105 can be preconfigured to initially transmit light pulses having a lowest setting for light wave intensity (e.g., low amplitude of the light wave or high wavelength of the light wave) and gradually increase the intensity (e.g., increase the amplitude of the light wave or decrease the wavelength of the light wave) while monitoring feedback until an optimal light intensity is reached. An optimal light intensity can refer to a highest intensity without adverse physiological side effects, such as blindness, seizures, heart attack, migraines, or other discomfort. The NSS 105 (e.g., via side effects management module 130) can monitor the physiological symptoms to identify the adverse side effects of the external visual stimulation, and adjust (e.g., via light adjustment module 115) the external visual stimulation accordingly to reduce or eliminate the adverse side effects.

[0456] In some embodiments, the NSS 105 (e.g., via light adjustment module 115) can adjust a parameter of the light wave or light pulse based on a level of attention. For example, during the brainwave entrainment process, the user may get bored, lose focus, fall asleep, or otherwise not pay attention to the light pulses. Not paying attention to the light pulses may reduce the efficacy of the brainwave entrainment process, resulting in neurons oscillating at a frequency different from the desired modulation frequency of the light pulses.

[0457] NSS 105 can detect the level of attention the user is paying to the light pulses using the feedback monitor 135 and one or more feedback component 160. The NSS 105 can perform eye tracking to determine the level of attention the user is providing to the light pulses based on the gaze direction of the retina or pupil. The NSS 105 can measure eye movement to determine the level of attention the user is paying to the light pulses. The NSS 105 can provide a survey or

prompt asking for user feedback that indicates the level of attention the user is paying to the light pulses. Responsive to determining that the user is not paying a satisfactory amount of attention to the light pulses (e.g., a level of eye movement that is greater than a threshold or a gaze direction that is outside the direct visual field of the light source 305), the light adjustment module 115 can change a parameter of the light source to gain the user's attention. For example, the light adjustment module 115 can increase the intensity of the light pulse, adjust the color of the light pulse, or change the duration of the light pulse. The light adjustment module 115 can randomly vary one or more parameters of the light pulse. The light adjustment module 115 can initiate an attention seeking light sequence configured to regain the user's attention. For example, the light sequence can include a change in color or intensity of the light pulses in a predetermined, random, or pseudo-random pattern. The attention seeking light sequence can enable or disable different light sources if the visual signaling component 150 includes multiple light sources. Thus, the light adjustment module 115 can interact with the feedback monitor 135 to determine a level of attention the user is providing to the light pulses, and adjust the light pulses to regain the user's attention if the level of attention falls below a threshold.

[0458] In some embodiments, the light adjustment module 115 can change or adjust one or more parameter of the light pulse or light wave at predetermined time intervals (e.g., every 5 minutes, 10 minutes, 15 minutes, or 20 minutes) to regain or maintain the user's attention level.

[0459] In some embodiments, the NSS 105 (e.g., via unwanted frequency filtering module 120) can filter, block, attenuate, or remove unwanted visual external stimulation. Unwanted visual external stimulation can include, for example, unwanted modulation frequencies, unwanted intensities, or unwanted wavelengths of light waves. The NSS 105 can deem a modulation frequency to be unwanted if the modulation frequency of a pulse train is different or substantially different (e.g., 1%, 2%, 5%, 10%, 15%, 20%, 25%, or more than 25%) from a desired frequency.

[0460] For example, the desired modulation frequency for brainwave entrainment can be 40 Hz. However, a modulation frequency of 20 Hz or 80 Hz can hinder brainwave entrainment. Thus, the NSS 105 can filter out the light pulses or light waves corresponding to the 20 Hz or 80 Hz modulation frequency.

[0461] In some embodiments, the NSS 105 can detect, via feedback component 160, that there are light pulses from an ambient light source that corresponds to an unwanted modulation frequency of 20 Hz. The NSS 105 can further determine the wavelength of the light waves of the light pulses corresponding to the unwanted modulation frequency. The NSS 105 can instruct the filtering component 155 to filter out the wavelength corresponding to the unwanted modulation frequency. For example, the wavelength corresponding to the unwanted modulation frequency can correspond to the color blue. The filtering component 155 can include an optical filter that

can selectively transmit light in a particular range of wavelengths or colors, while blocking one or more other ranges of wavelengths or colors. The optical filter can modify the magnitude or phase of the incoming light wave for a range of wavelengths. For example, the optical filter can be configured to block, reflect or attenuate the blue light wave corresponding to the unwanted modulation frequency. The light adjustment module 115 can change the wavelength of the light wave generated by the light generation module 110 and light source 305 such that the desired modulation frequency is not blocked or attenuated by the unwanted frequency filtering module 120.

ii. NSS Operating with a Virtual Reality Headset

[0462] The NSS 105 can operate in conjunction with the virtual reality headset 401 including a light source 305 as depicted in **FIG. 4C**. The NSS 105 can operate in conjunction with the virtual reality headset 401 including a light source 305 and a feedback sensor 605 as depicted in **FIG. 4C**. In some embodiments, the NSS 105 can determine that the visual signaling component 150 hardware includes a virtual reality headset 401. Responsive to determining that the visual signaling component 150 includes a virtual reality headset 401, the NSS 105 can determine that the light source 305 includes a display screen of a smartphone or other mobile computing device.

[0463] The virtual reality headset 401 can provide an immersive, non-disruptive visual stimulation experience. The virtual reality headset 401 can provide an augmented reality experience. The feedback sensors 605 can capture pictures or video of the physical, real world to provide the augmented reality experience. The unwanted frequency filtering module 120 can filter out unwanted modulation frequencies prior to projecting, displaying or providing the augmented reality images via the display screen 305.

[0464] In operation, a user of the frame 401 can wear the frame 401 on their head such that the virtual reality headset eye sockets 465 cover the user's eyes. The virtual reality headset eye sockets 465 can encircle or substantially encircle their eyes. The user can secure the virtual reality headset 401 to the user's headset using one or more straps 455 or 460, a skull cap, or other fastening mechanism. In some cases, the user can provide an indication to the NSS 105 that the virtual reality headset 401 has been placed and secured to the user's head and that the user is ready to undergo brainwave entrainment. The indication can include an instruction, command, selection, input, or other indication via an input/output interface, such as a keyboard 726, pointing device 727, or other I/O devices 730a-n. The indication can be a motion-based indication, visual indication, or voice-based indication. For example, the user can provide a voice command that indicates that the user is ready to undergo brainwave entrainment.

[0465] In some cases, the feedback sensor 605 can determine that the user is ready to undergo brainwave entrainment. The feedback sensor 605 can detect that the virtual reality headset 401 has been placed on a user's head. The NSS 105 can receive motion data, acceleration data, gyroscope data, temperature data, or capacitive touch data to determine that the virtual reality headset 401 has been placed on the user's head. The received data, such as motion data, can indicate that the virtual reality headset 401 was picked up and placed on the user's head. The temperature data can measure the temperature of or proximate to the virtual reality headset 401, which can indicate that the virtual reality headset 401 is on the user's head. In some cases, the feedback sensor 605 can perform eye tracking to determine a level of attention a user is paying to the light source 305 or feedback sensor 605. The NSS 105 can detect that the user is ready responsive to determining that the user is paying a high level of attention to the light source 305 or feedback sensor 605. For example, staring at, gazing or looking in the direction of the light source 305 or feedback sensor 605 can provide an indication that the user is ready to undergo brainwave entrainment.

[0466] In some embodiments, a sensor 605 on the straps 455, straps 460 or eye socket 605 can detect that the virtual reality headset 401 is secured, placed, or positioned on the user's head. The sensor 605 can be a touch sensor that senses or detects the touch of the user's head.

[0467] Thus, the NSS 105 can detect or determine that the virtual reality headset 401 has been worn and that the user is in a ready state, or the NSS 105 can receive an indication or confirmation from the user that the user has worn the virtual reality headset 401 and the user is ready to undergo brainwave entrainment. Upon determining that the user is ready, the NSS 105 can initialize the brainwave entrainment process. In some embodiments, the NSS 105 can access a profile data structure 145. For example, a profile manager 125 can query the profile data structure 145 to determine one or more parameter for the external visual stimulation used for the brain entrainment process. Parameters can include, for example, a type of visual stimulation, an intensity of the visual stimulation, frequency of the visual stimulation, duration of the visual stimulation, or wavelength of the visual stimulation. The profile manager 125 can query the profile data structure 145 to obtain historical brain entrainment information, such as prior visual stimulation sessions. The profile manager 125 can perform a lookup in the profile data structure 145. The profile manager 125 can perform a look-up with a username, user identifier, location information, fingerprint, biometric identifier, retina scan, voice recognition and authentication, or other identifying technique.

[0468] The NSS 105 can determine a type of external visual stimulation based on the hardware 401. The NSS 105 can determine the type of external visual stimulation based on the type of light source 305 available. For example, if the light source 305 includes a smartphone or display

device, the visual stimulation can include turning on and off the display screen of the display device. The visual stimulation can include displaying a pattern on the display device 305, such as a checkered pattern, that can alternate in accordance with the desired frequency modulation. The visual stimulation can include light pulses generated by a light source 305 such as an LED that is placed within the virtual reality headset 401 enclosure.

[0469] In cases where the virtual reality headset 401 provides an augmented reality experience, the visual stimulation can include overlaying content on the display device and modulating the overlaid content at the desired modulation frequency. For example, the virtual reality headset 401 can include a camera 605 that captures the real, physical world. While displaying the captured image of the real, physical world, the NSS 105 can also display content that is modulated at the desired modulation frequency. The NSS 105 can overlay the content modulated at the desired modulation frequency. The NSS 105 can otherwise modify, manipulate, modulation, or adjust a portion of the display screen or a portion of the augmented reality to generate or provide the desired modulation frequency.

[0470] For example, the NSS 105 can modulate one or more pixels based on the desired modulation frequency. The NSS 105 can turn pixels on and off based on the modulation frequency. The NSS 105 can turn of pixels on any portion of the display device. The NSS 105 can turn on and off pixels in a pattern. The NSS 105 can turn on and off pixels in the direct visual field or peripheral visual field. The NSS 105 can track or detect a gaze direction of the eye and turn on and off pixels in the gaze direction so the light pulses (or modulation) are in the direct vision field. Thus, modulating the overlaid content or otherwise manipulated the augmented reality display or other image provided via a display device in the virtual reality headset 401 can generate light pulses or light flashes having a modulation frequency configured to facilitate brainwave entrainment.

[0471] The NSS 105 can determine, via the profile manager 125, a modulation frequency for the pulse train or the ambient light. For example, NSS 105 can determine, from the profile data structure 145, that the modulation frequency for the external visual stimulation should be set to 40 Hz. Depending on the type of visual stimulation, the profile data structure 145 can further indicate a number of pixels to modulate, intensity of pixels to modulate, pulse length, intensity, wavelength of the light wave forming the light pulse, or duration of the pulse train.

[0472] In some cases, the NSS 105 can determine or adjust one or more parameter of the external visual stimulation. For example, the NSS 105 (e.g., via feedback component 160 or feedback sensor 605) can determine a level or amount of light in captured image used to provide the augmented reality experience. The NSS 105 (e.g., via light adjustment module 115 or side effects management module 130) can establish, initialize, set, or adjust the intensity or wavelength of the

light pulse based on the light level in the image data corresponding to the augmented reality experience. For example, the NSS 105 can determine that there is a low level of light in the augmented reality display because it may be dark outside. Due to the low level of light in the augmented reality display, the user's pupils may be dilated. The NSS 105 can determine, based on detecting a low level of light, that the user's pupils are likely dilated. In response to determining that the user's pupils are likely dilated, the NSS 105 can set a low level of intensity for the light pulses or light source providing the modulation frequency. The NSS 105 can further use a light wave having a longer wavelength (e.g., red), which may reduce strain on the eyes.

[0473] In some embodiments, the NSS 105 can monitor (e.g., via feedback monitor 135 and feedback component 160) the level of light throughout the brainwave entrainment process to automatically and periodically adjust the intensity or color of light pulses. For example, if the user began the brainwave entrainment process when there was a high level of ambient light, the NSS 105 can initially set a higher intensity level for the light pulses and use a color that includes light waves having lower wavelengths (e.g., blue). However, as the light level decreases throughout the brainwave entrainment process, the NSS 105 can automatically detect the decrease in light and, in response to the detection, adjust or lower the intensity while increasing the wavelength of the light wave. The NSS 105 can adjust the light pulses to provide a high contrast ratio to facilitate brainwave entrainment.

[0474] In some embodiments, the NSS 105 (e.g., via feedback monitor 135 and feedback component 160) can monitor or measure physiological conditions to set or adjust a parameter of the light pulses while the user is wearing the virtual reality headset 401. For example, the NSS 105 can monitor or measure a level of pupil dilation to adjust or set a parameter of the light wave. In some embodiments, the NSS 105 can monitor or measure, via one or more feedback sensor of the virtual reality headset 401 or other feedback sensor, a heart rate, pulse rate, blood pressure, body temperature, perspiration, or brain activity to set or adjust a parameter of the light wave.

[0475] In some embodiments, the NSS 105 can be preconfigured to initially transmit, via display device 305, light pulses having a lowest setting for light wave intensity (e.g., low amplitude of the light wave or high wavelength of the light wave) and gradually increase the intensity (e.g., increase the amplitude of the light wave or decrease the wavelength of the light wave) while monitoring feedback until an optimal light intensity is reached. An optimal light intensity can refer to a highest intensity without adverse physiological side effects, such as blindness, seizures, heart attack, migraines, or other discomfort. The NSS 105 (e.g., via side effects management module 130) can monitor the physiological symptoms to identify the adverse side effects of the external visual stimulation, and adjust (e.g., via light adjustment module 115) the external visual stimulation accordingly to reduce or eliminate the adverse side effects.

[0476] In some embodiments, the NSS 105 (e.g., via light adjustment module 115) can adjust a parameter of the light wave or light pulse based on a level of attention. For example, during the brainwave entrainment process, the user may get bored, lose focus, fall asleep, or otherwise not pay attention to the light pulses generated via the display screen 305 of the virtual reality headset 401. Not paying attention to the light pulses may reduce the efficacy of the brainwave entrainment process, resulting in neurons oscillating at a frequency different from the desired modulation frequency of the light pulses.

[0477] NSS 105 can detect the level of attention the user is paying or providing to the light pulses using the feedback monitor 135 and one or more feedback component 160 (e.g., including feedback sensors 605). The NSS 105 can perform eye tracking to determine the level of attention the user is providing to the light pulses based on the gaze direction of the retina or pupil. The NSS 105 can measure eye movement to determine the level of attention the user is paying to the light pulses. The NSS 105 can provide a survey or prompt asking for user feedback that indicates the level of attention the user is paying to the light pulses. Responsive to determining that the user is not paying a satisfactory amount of attention to the light pulses (e.g., a level of eye movement that is greater than a threshold or a gaze direction that is outside the direct visual field of the light source 305), the light adjustment module 115 can change a parameter of the light source 305 or display device 305 to gain the user's attention. For example, the light adjustment module 115 can increase the intensity of the light pulse, adjust the color of the light pulse, or change the duration of the light pulse. The light adjustment module 115 can randomly vary one or more parameters of the light pulse. The light adjustment module 115 can initiate an attention seeking light sequence configured to regain the user's attention. For example, the light sequence can include a change in color or intensity of the light pulses in a predetermined, random, or pseudo-random pattern. The attention seeking light sequence can enable or disable different light sources if the visual signaling component 150 includes multiple light sources. Thus, the light adjustment module 115 can interact with the feedback monitor 135 to determine a level of attention the user is providing to the light pulses, and adjust the light pulses to regain the user's attention if the level of attention falls below a threshold.

[0478] In some embodiments, the light adjustment module 115 can change or adjust one or more parameter of the light pulse or light wave at predetermined time intervals (e.g., every 5 minutes, 10 minutes, 15 minutes, or 20 minutes) to regain or maintain the user's attention level.

[0479] In some embodiments, the NSS 105 (e.g., via unwanted frequency filtering module 120) can filter, block, attenuate, or remove unwanted visual external stimulation. Unwanted visual external stimulation can include, for example, unwanted modulation frequencies, unwanted intensities, or unwanted wavelengths of light waves. The NSS 105 can deem a modulation

frequency to be unwanted if the modulation frequency of a pulse train is different or substantially different (e.g., 1%, 2%, 5%, 10%, 15%, 20%, 25%, or more than 25%) from a desired frequency.

[0480] For example, the desired modulation frequency for brainwave entrainment can be 40 Hz. However, a modulation frequency of 20 Hz or 80 Hz can hinder brainwave entrainment. Thus, the NSS 105 can filter out the light pulses or light waves corresponding to the 20 Hz or 80 Hz modulation frequency. For example, the virtual reality headset 401 can detect unwanted modulation frequencies in the physical, real world and eliminate, attenuate, filter out or otherwise remove the unwanted frequencies providing to generating the or providing the augmented reality experience. The NSS 105 can include an optical filter configured to perform digital signal processing or digital image processing to detect the unwanted modulation frequency in the real world captured by the feedback sensor 605. The NSS 105 can detect other content, image or motion having an unwanted parameter (e.g., color, brightness, contrast ratio, modulation frequency), and eliminate same from the augmented reality experience projected to the user via the display screen 305. The NSS 105 can apply a color filter to adjust the color or remove a color of the augmented reality display. The NSS 105 can adjust, modify, or manipulate the brightness, contrast ratio, sharpness, tint, hue, or other parameter of the image or video displayed via the display device 305.

[0481] In some embodiments, the NSS 105 can detect, via feedback component 160, that there is captured image or video content from the real, physical world that corresponds to an unwanted modulation frequency of 20 Hz. The NSS 105 can further determine the wavelength of the light waves of the light pulses corresponding to the unwanted modulation frequency. The NSS 105 can instruct the filtering component 155 to filter out the wavelength corresponding to the unwanted modulation frequency. For example, the wavelength corresponding to the unwanted modulation frequency can correspond to the color blue. The filtering component 155 can include a digital optical filter that can digitally remove content or light in a particular range of wavelengths or colors, while allowing one or more other ranges of wavelengths or colors. The digital optical filter can modify the magnitude or phase of the image for a range of wavelengths. For example, the digital optical filter can be configured to attenuate, erase, replace or otherwise alter the blue light wave corresponding to the unwanted modulation frequency. The light adjustment module 115 can change the wavelength of the light wave generated by the light generation module 110 and display device 305 such that the desired modulation frequency is not blocked or attenuated by the unwanted frequency filtering module 120.

iii. NSS Operating With a Tablet

[0482] The NSS 105 can operate in conjunction with the tablet 500 as depicted in FIGs. 5A-5D. In some embodiments, the NSS 105 can determine that the visual signaling component 150 hardware includes a tablet device 500 or other display screen that is not affixed or secured to a user's head. The tablet 500 can include a display screen that has one or more component or function of the display screen 305 or light source 305 depicted in conjunction with FIGs. 4A and 4C. The light source 305 in a tablet can be the display screen. The tablet 500 can include one or more feedback sensor that includes one or more component or function of the feedback sensors depicted in conjunction with FIGs. 4B, 4C and 6A.

[0483] The tablet 500 can communicate with the NSS 105 via a network, such as a wireless network or a cellular network. The NSS 105 can, in some embodiments, execute the NSS 105 or a component thereof. For example, the tablet 500 can launch, open or switch to an application or resource configured to provide at least one functionality of the NSS 105. The tablet 500 can execute the application as a background process or a foreground process. For example, the graphical user interface for the application can be in the background while the application causes the display screen 305 of the tablet to overlay content or light that changes or modulates at a desired frequency for brain entrainment (e.g., 40 Hz).

[0484] The tablet 500 can include one or more feedback sensors 605. In some embodiments, the tablet can use the one or more feedback sensors 605 to detect that a user is holding the tablet 500. The tablet can use the one or more feedback sensors 605 to determine a distance between the light source 305 and the user. The tablet can use the one or more feedback sensors 605 to determine a distance between the light source 305 and the user's head. The tablet can use the one or more feedback sensors 605 to determine a distance between the light source 305 and the user's eyes.

[0485] In some embodiments, the tablet 500 can use a feedback sensor 605 that includes a receiver to determine the distance. The tablet can transmit a signal and measure the amount of time it takes for the transmitted signal to leave the tablet 500, bounce on the object (e.g., user's head) and be received by the feedback sensor 605. The tablet 500 or NSS 105 can determine the distance based on the measured amount of time and the speed of the transmitted signal (e.g., speed of light).

[0486] In some embodiments, the tablet 500 can include two feedback sensors 605 to determine a distance. The two feedback sensors 605 can include a first feedback sensor 605 that is the transmitter and a second feedback sensor that is the receiver.

[0487] In some embodiments, the tablet 500 can include two or more feedback sensors 605 that include two or more cameras. The two or more cameras can measure the angles and the position

of the object (e.g., the user's head) on each camera, and use the measured angles and position to determine or compute the distance between the tablet 500 and the object.

[0488] In some embodiments, the tablet 500 (or application thereof) can determine the distance between the tablet and the user's head by receiving user input. For example, user input can include an approximate size of the user's head. The tablet 500 can then determine the distance from the user's head based on the inputted approximate size.

[0489] The tablet 500, application, or NSS 105 can use the measured or determined distance to adjust the light pulses or flashes of light emitted by the light source 305 of the tablet 500. The tablet 500, application, or NSS 105 can use the distance to adjust one or more parameter of the light pulses, flashes of light or other content emitted via the light source 305 of the tablet 500. For example, the tablet 500 can adjust the intensity of the light pulses emitted by light source 305 based on the distance. The tablet 500 can adjust the intensity based on the distance in order to maintain a consistent or similar intensity at the eye irrespective of the distance between the light source 305 and the eye. The tablet can increase the intensity proportional to the square of the distance.

[0490] The tablet 500 can manipulate one or more pixels on the display screen 305 to generate the light pulses or modulation frequency for brainwave entrainment. The tablet 500 can overlay light sources, light pulses or other patterns to generate the modulation frequency for brainwave entrainment. Similar to the virtual reality headset 401, the tablet can filter out or modify unwanted frequencies, wavelengths or intensity.

[0491] Similar to the frames 400, the tablet 500 can adjust a parameter of the light pulses or flashes of light generated by the light source 305 based on ambient light, environmental parameters, or feedback.

[0492] In some embodiments, the tablet 500 can execute an application that is configured to generate the light pulses or modulation frequency for brainwave entrainment. The application can execute in the background of the tablet such that all content displayed on a display screen of the tablet are displayed as light pulses at the desired frequency. The tablet can be configured to detect a gaze direction of the user. In some embodiments, the tablet may detect the gaze direction by capturing an image of the user's eye via the camera of the tablet. The tablet 500 can be configured to generate light pulses at particular locations of the display screen based on the gaze direction of the user. In embodiments where direct vision field is to be employed, the light pulses can be displayed at locations of the display screen that correspond to the user's gaze. In embodiments where peripheral vision field is to be employed, the light pulses can be displayed at locations of the displays screen that are outside the portion of the display screen corresponding to the user's gaze.

D. Methods for Neural Stimulation with an NSS via Auditory Stimulation

[0493] In some aspects, described herein are methods of neural stimulation via auditory stimulation. In some embodiments, a method of auditory neurostimulation comprises a method of using a portable system or single headset device as disclosed herein. In some embodiments, a method of auditory neurostimulation comprises a method of using a portable system as disclosed herein, wherein the portable system comprises an NSS. Illustrative embodiments are described as follows.

[0494] **FIG. 9** is a block diagram depicting a system for neural stimulation via auditory stimulation in accordance with an embodiment. The system 900 can include a neural stimulation system (“NSS”) 905. The NSS 905 can be referred to as an auditory NSS 905 or NSS 905. In brief overview, the auditory neural stimulation system (“NSS”) 905 can include, access, interface with, or otherwise communicate with one or more of an audio generation module 910, audio adjustment module 915, unwanted frequency filtering module 920, profile manager 925, side effects management module 930, feedback monitor 935, data repository 940, audio signaling component 950, filtering component 955, or feedback component 960. The audio generation module 910, audio adjustment module 915, unwanted frequency filtering module 920, profile manager 925, side effects management module 930, feedback monitor 935, audio signaling component 950, filtering component 955, or feedback component 960 can each include at least one processing unit or other logic device such as programmable logic array engine, or module configured to communicate with the database repository 950. The audio generation module 910, audio adjustment module 915, unwanted frequency filtering module 920, profile manager 925, side effects management module 930, feedback monitor 935, audio signaling component 950, filtering component 955, or feedback component 960 can be separate components, a single component, or part of the NSS 905. The system 100 and its components, such as the NSS 905, can include hardware elements, such as one or more processors, logic devices, or circuits. The system 100 and its components, such as the NSS 905, can include one or more hardware or interface component depicted in system 700 in FIGs. 7A and 7B. For example, a component of system 100 can include or execute on one or more processors 721, access storage 728 or memory 722, and communicate via network interface 718.

[0495] Still referring to **FIG. 9**, and in further detail, the NSS 905 can include at least one audio generation module 910. The audio generation module 910 can be designed and constructed to interface with an audio signaling component 950 to provide instructions or otherwise cause or facilitate the generation of an audio signal, such as an audio burst, audio pulse, audio chirp, audio sweep, or other acoustic wave having one or more predetermined parameters. The audio

generation module 910 can include hardware or software to receive and process instructions or data packets from one or more module or component of the NSS 905. The audio generation module 910 can generate instructions to cause the audio signaling component 950 to generate an audio signal. The audio generation module 910 can control or enable the audio signaling component 950 to generate the audio signal having one or more predetermined parameters.

[0496] The audio generation module 910 can be communicatively coupled to the audio signaling component 950. The audio generation module 910 can communicate with the audio signaling component 950 via a circuit, electrical wire, data port, network port, power wire, ground, electrical contacts or pins. The audio generation module 910 can wirelessly communicate with the audio signaling component 950 using one or more wireless protocols such as BlueTooth, BlueTooth Low Energy, Zigbee, Z-Wave, IEEE 802, WIFI, 3G, 4G, LTE, near field communications (“NFC”), or other short, medium or long range communication protocols, etc. The audio generation module 910 can include or access network interface 718 to communicate wirelessly or over a wire with the audio signaling component 950.

[0497] The audio generation module 910 can interface, control, or otherwise manage various types of audio signaling components 950 in order to cause the audio signaling component 950 to generate, block, control, or otherwise provide the audio signal having one or more predetermined parameters. The audio generation module 910 can include a driver configured to drive an audio source of the audio signaling component 950. For example, the audio source can include a speaker, and the audio generation module 910 (or the audio signaling component) can include a transducer that converts electrical energy to sound waves or acoustic waves. The audio generation module 910 can include a computing chip, microchip, circuit, microcontroller, operational amplifiers, transistors, resistors, or diodes configured to provide electricity or power having certain voltage and current characteristics to drive the speaker to generate an audio signal with desired acoustic characteristics.

[0498] In some embodiments, the audio generation module 910 can instruct the audio signaling component 950 to provide an audio signal. For example, the audio signal can include an acoustic wave 1000 as depicted in **FIG. 10A**. The audio signal can include multiple acoustic waves. The audio signal can generate one or more acoustic waves. The acoustic wave 1000 can include or be formed of a mechanical wave of pressure and displacement that travels through media such as gases, liquids, and solids. The acoustic wave can travel through a medium to cause vibration, sound, ultrasound or infrasound. The acoustic wave can propagate through air, water or solids as longitudinal waves. The acoustic wave can propagate through solids as a transverse wave.

[0499] The acoustic wave can generate sound due to the oscillation in pressure, stress, particle displacement, or particle velocity propagated in a medium with internal forces (e.g., elastic or

viscous), or the superposition of such propagated oscillation. Sound can refer to the auditory sensation evoked by this oscillation. For example, sound can refer to the reception of acoustic waves and their perception by the brain.

[0500] The audio signaling component 950 or audio source thereof can generate the acoustic waves by vibrating a diaphragm of the audio source. For example, the audio source can include a diaphragm such as a transducer configured to inter-convert mechanical vibrations to sounds. The diaphragm can include a thin membrane or sheet of various materials, suspended at its edges. The varying pressure of sound waves imparts mechanical vibrations to the diaphragm which can then create acoustic waves or sound.

[0501] The acoustic wave 1000 illustrated in **FIG. 10A** includes a wavelength 1010. The wavelength 1010 can refer to a distance between successive crests 1020 of the wave. The wavelength 1010 can be related to the frequency of the acoustic wave and the speed of the acoustic wave. For example, the wavelength can be determined as the quotient of the speed of the acoustic wave divided by the frequency of the acoustic wave. The speed of the acoustic wave can be the product of the frequency and the wavelength. The frequency of the acoustic wave can be the quotient of the speed of the acoustic wave divided by the wavelength of the acoustic wave. Thus, the frequency and the wavelength of the acoustic wave can be inversely proportional. The speed of sound can vary based on the medium through which the acoustic wave propagates. For example, the speed of sound in air can be 343 meters per second.

[0502] A crest 1020 can refer to the top of the wave or point on the wave with the maximum value. The displacement of the medium is at a maximum at the crest 1020 of the wave. The trough 1015 is the opposite of the crest 1020. The trough 1015 is the minimum or lowest point on the wave corresponding to the minimum amount of displacement.

[0503] The acoustic wave 1000 can include an amplitude 1005. The amplitude 1005 can refer to a maximum extent of a vibration or oscillation of the acoustic wave 1000 measured from a position of equilibrium. The acoustic wave 1000 can be a longitudinal wave if it oscillates or vibrates in the same direction of travel 1025. In some cases, the acoustic wave 1000 can be a transverse wave that vibrates at right angles to the direction of its propagation.

[0504] The audio generation module 910 can instruct the audio signaling component 950 to generate acoustic waves or sound waves having one or more predetermined amplitude or wavelength. Wavelengths of the acoustic wave that are audible to the human ear range from approximately 17 meters to 17 millimeters (or 20 Hz to 20 kHz). The audio generation module 910 can further specify one or more properties of an acoustic wave within or outside the audible spectrum. For example, the frequency of the acoustic wave can range from 0 to 50 kHz. In some

embodiments, the frequency of the acoustic wave can range from 8 to 12 kHz. In some embodiments, the frequency of the acoustic wave can be 10 kHz.

[0505] The NSS 905 can modulate, modify, change or otherwise alter properties of the acoustic wave 1000. For example, the NSS 905 can modulate the amplitude or wavelength of the acoustic wave. As depicted in **FIG. 10B** and **FIG. 10C**, the NSS 905 can adjust, manipulate, or otherwise modify the amplitude 1005 of the acoustic wave 1000. For example, the NSS 905 can lower the amplitude 1005 to cause the sound to be quieter, as depicted in **FIG. 10B**, or increase the amplitude 1005 to cause the sound to be louder, as depicted in **FIG. 10C**.

[0506] In some cases, the NSS 905 can adjust, manipulate or otherwise modify the wavelength 1010 of the acoustic wave. As depicted in **FIG. 10D** and **FIG. 10E**, the NSS 905 can adjust, manipulate, or otherwise modify the wavelength 1010 of the acoustic wave 1000. For example, the NSS 905 can increase the wavelength 1010 to cause the sound to have a lower pitch, as depicted in **FIG. 10D**, or reduce the wavelength 1010 to cause the sound to have a higher pitch, as depicted in **FIG. 10E**.

[0507] The NSS 905 can modulate the acoustic wave. Modulating the acoustic wave can include modulating one or more properties of the acoustic wave. Modulating the acoustic wave can include filtering the acoustic wave, such as filtering out unwanted frequencies or attenuating the acoustic wave to lower the amplitude. Modulating the acoustic wave can include adding one or more additional acoustic waves to the original acoustic wave. Modulating the acoustic wave can include combining the acoustic wave such that there is constructive or destructive interference where the resultant, combined acoustic wave corresponds to the modulated acoustic wave.

[0508] The NSS 905 can modulate or change one or more properties of the acoustic wave based on a time interval. The NSS 905 can change the one or more properties of the acoustic at the end of the time interval. For example, the NSS 905 can change a property of the acoustic wave every 30 seconds, 1 minute, 2 minutes, 3 minutes, 5 minutes, 7 minutes, 10 minutes, or 15 minutes. The NSS 905 can change a modulation frequency of the acoustic wave, where the modulation frequency refers to the repeated modulations or inverse of the pulse rate interval of the acoustic pulses. The modulation frequency can be a predetermined or desired frequency. The modulation frequency can correspond to a desired stimulation frequency of neural oscillations. The modulation frequency can be set to facilitate or cause brainwave entrainment. The NSS 905 can set the modulation frequency to a frequency in the range of 0.1 Hz to 10,000 Hz. For example, the NSS 905 can set the modulation frequency to .1 Hz, 1 Hz, 5 Hz, 10 Hz, 20 Hz, 25 Hz, 30 Hz, 31 Hz, 32 Hz, 33 Hz, 34 Hz, 35 Hz, 36 Hz, 37 Hz, 38 Hz, 39 Hz, 40 Hz, 41 Hz, 42 Hz, 43 Hz, 44 Hz, 45 Hz, 46 Hz, 47 Hz, 48 Hz, 49 Hz, 50 Hz, 60 Hz, 70 Hz, 80 Hz, 90 Hz, 100 Hz, 150 Hz,

200 Hz, 250 Hz, 300 Hz, 400 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4,000 Hz, 5000 Hz, 6,000 Hz, 7,000 Hz, 8,000 Hz, 9,000 Hz, or 10,000 Hz.

[0509] The audio generation module 910 can determine to provide audio signals that include bursts of acoustic waves, audio pulses, or modulations to acoustic waves. The audio generation module 910 can instruct or otherwise cause the audio signaling component 950 to generate acoustic bursts or pulses. An acoustic pulse can refer to a burst of acoustic waves or a modulation to a property of an acoustic wave that is perceived by the brain as a change in sound. For example, an audio source that is intermittently turned on and off can create audio bursts or changes in sound. The audio source can be turned on and off based on a predetermined or fixed pulse rate interval, such as every 0.025 seconds, to provide a pulse repetition frequency of 40 Hz. The audio source can be turned on and off to provide a pulse repetition frequency in the range of 0.1 Hz to 10 kHz or more.

[0510] For example, FIGs. 10F-10I illustrates bursts of acoustic waves or bursts of modulations that can be applied to acoustic waves. The bursts of acoustic waves can include, for example, audio tones, beeps, or clicks. The modulations can refer to changes in the amplitude of the acoustic wave, changes in frequency or wavelength of the acoustic wave, overlaying another acoustic wave over the original acoustic wave, or otherwise modifying or changing the acoustic wave.

[0511] For example, **FIG. 10F** illustrates acoustic bursts 1035a-c (or modulation pulses 1035a-c) in accordance with an embodiment. The acoustic bursts 1035a-c can be illustrated via a graph where the y-axis represents a parameter of the acoustic wave (e.g., frequency, wavelength, or amplitude) of the acoustic wave. The x-axis can represent time (e.g., seconds, milliseconds, or microseconds).

[0512] The audio signal can include a modulated acoustic wave that is modulated between different frequencies, wavelengths, or amplitudes. For example, the NSS 905 can modulate an acoustic wave between a frequency in the audio spectrum, such as M_a , and a frequency outside the audio spectrum, such as M_o . The NSS 905 can modulate the acoustic wave between two or more frequencies, between an on state and an off state, or between a high power state and a low power state.

[0513] The acoustic bursts 1035a-c can have an acoustic wave parameter with value M_a that is different from the value M_o of the acoustic wave parameter. The modulation M_a can refer to a frequency or wavelength, or amplitude. The pulses 1035a-c can be generated with a pulse rate interval (PRI) 1040.

[0514] For example, the acoustic wave parameter can be the frequency of the acoustic wave. The first value M_o can be a low frequency or carrier frequency of the acoustic wave, such as 10 kHz.

The second value, M_a , can be different from the first frequency M_o . The second frequency M_a can be lower or higher than the first frequency M_o . For example, the second frequency M_a can be 11 kHz. The difference between the first frequency and the second frequency can be determined or set based on a level of sensitivity of the human ear. The difference between the first frequency and the second frequency can be determined or set based on profile information 945 for the subject. The difference between the first frequency M_o and the second frequency M_a can be determined such that the modulation or change in the acoustic wave facilitate brainwave entrainment.

[0515] In some cases, the parameter of the acoustic wave used to generate the acoustic burst 1035a can be constant at M_a , thereby generating a square wave as illustrated in **FIG. 10F**. In some embodiments, each of the three pulses 1035a-c can include acoustic waves having a same frequency M_a .

[0516] The width of each of the acoustic bursts or pulses (e.g., the duration of the burst of the acoustic wave with the parameter M_a) can correspond to a pulse width 1030a. The pulse width 1030a can refer to the length or duration of the burst. The pulse width 1030a can be measured in units of time or distance. In some embodiments, the pulses 1035a-c can include acoustic waves having different frequencies from one another. In some embodiments, the pulses 1035a-c can have different pulse widths 1030a from one another, as illustrated in **FIG. 10G**. For example, a first pulse 1035d of **FIG. 10G** can have a pulse width 1030a, while a second pulse 1035e has a second pulse width 1030b that is greater than the first pulse width 1030a. A third pulse 1035f can have a third pulse width 1030c that is less than the second pulse width 1030b. The third pulse width 1030c can also be less than the first pulse width 1030a. While the pulse widths 1030a-c of the pulses 1035d-f of the pulse train can vary, the audio generation module 910 can maintain a constant pulse rate interval 1040 for the pulse train.

[0517] The pulses 1035a-c can form a pulse train having a pulse rate interval 1040. The pulse rate interval 1040 can be quantified using units of time. The pulse rate interval 1040 can be based on a frequency of the pulses of the pulse train 201. The frequency of the pulses of the pulse train 201 can be referred to as a modulation frequency. For example, the audio generation module 910 can provide a pulse train 201 with a predetermined frequency, such as 40 Hz. To do so, the audio generation module 910 can determine the pulse rate interval 1040 by taking the multiplicative inverse (or reciprocal) of the frequency (e.g., 1 divided by the predetermined frequency for the pulse train). For example, the audio generation module 910 can take the multiplicative inverse of 40 Hz by dividing 1 by 40 Hz to determine the pulse rate interval 1040 as 0.025 seconds. The pulse rate interval 1040 can remain constant throughout the pulse train. In some embodiments, the pulse rate interval 1040 can vary throughout the pulse train or from one pulse train to a

subsequent pulse train. In some embodiments, the number of pulses transmitted during a second can be fixed, while the pulse rate interval 1040 varies.

[0518] In some embodiments, the audio generation module 910 can generate an audio burst or audio pulse having an acoustic wave that varies in frequency, amplitude, or wavelength. For example, the audio generation module 910 can generate up-chirp pulses where the frequency, amplitude or wavelength of the acoustic wave of the audio pulse increases from the beginning of the pulse to the end of the pulse as illustrated in **FIG. 10H**. For example, the frequency, amplitude or wavelength of the acoustic wave at the beginning of pulse 1035g can be Ma. The frequency, amplitude or wavelength of the acoustic wave of the pulse 1035g can increase from Ma to Mb in the middle of the pulse 1035g, and then to a maximum of Mc at the end of the pulse 1035g. Thus, the frequency, amplitude or wavelength of the acoustic wave used to generate the pulse 1035g can range from Ma to Mc. The frequency, amplitude or wavelength can increase linearly, exponentially, or based on some other rate or curve. One or more of the frequency, amplitude or wavelength of the acoustic wave can change from the beginning of the pulse to the end of the pulse.

[0519] The audio generation module 910 can generate down-chirp pulses, as illustrated in **FIG. 10I**, where the frequency, amplitude or wavelength of the acoustic wave of the acoustic pulse decreases from the beginning of the pulse to the end of the pulse. For example, the frequency, amplitude or wavelength of an acoustic wave at the beginning of pulse 1035j can be Mc. The frequency, amplitude or wavelength of the acoustic wave of the pulse 1035j can decrease from Mc to Mb in the middle of the pulse 1035j, and then to a minimum of Ma at the end of the pulse 1035j. Thus, the frequency, amplitude or wavelength of the acoustic wave used to generate the pulse 1035j can range from Mc to Ma. The frequency, amplitude or wavelength can decrease linearly, exponentially, or based on some other rate or curve. One or more of the frequency, amplitude or wavelength of the acoustic wave can change from the beginning of the pulse to the end of the pulse.

[0520] In some embodiments, the audio generation module 910 can instruct or cause the audio signaling component 950 to generate audio pulses to stimulate specific or predetermined portions of the brain or a specific cortex. The frequency, wavelength, modulation frequency, amplitude and other aspects of the audio pulse, tone or music based stimuli can dictate which cortex or cortices are recruited to process the stimuli. The audio signaling component 950 can stimulate discrete portions of the cortex by modulating the presentation of the stimuli to target specific or general regions of interest. The modulation parameters or amplitude of the audio stimuli can dictate which region of the cortex is stimulated. For example, different regions of the cortex are recruited to process different frequencies of sound, called their characteristic frequencies.

Further, ear laterality of stimulation can have an effect on cortex response since some subjects can be treated by stimulating one ear as opposed to both ears.

[0521] An audio signaling component 950 can be designed and constructed to generate the audio pulses responsive to instructions from the audio generation module 910. The instructions can include, for example, parameters of the audio pulse such as a frequency, wavelength or of the acoustic wave, duration of the pulse, frequency of the pulse train, pulse rate interval, or duration of the pulse train (e.g., a number of pulses in the pulse train or the length of time to transmit a pulse train having a predetermined frequency). The audio pulse can be perceived, observed, or otherwise identified by the brain via cochlear means such as ears. The audio pulses can be transmitted to the ear via an audio source speaker in close proximity to the ear, such as headphones, earbuds, bone conduction transducers, or cochlear implants. The audio pulses can be transmitted to the ear via an audio source or speaker not in close proximity to the ear, such as a surround sound speaker system, bookshelf speakers, or other speaker not directly or indirectly in contact with the ear.

[0522] **FIG. 11A** illustrates audio signals using binaural beats or binaural pulses, in accordance with an embodiment. In brief summary, binaural beats refers to providing a different tone to each ear of the subject. When the brain perceives the two different tones, the brain mixes the two tones together to create a pulse. The two different tones can be selected such that the sum of the tones creates a pulse train having a desired pulse rate interval 1040.

[0523] The audio signaling component 950 can include a first audio source that provides an audio signal to the first ear of a subject, and a second audio source that provides a second audio signal to the second ear of a subject. The first audio source and the second audio source can be different. The first ear can only perceive the first audio signal from the first audio source, and the second ear can only receive the second audio signal from the second audio source. Audio sources can include, for example, headphones, earbuds, or bone conduction transducers. The audio sources can include stereo audio sources.

[0524] The audio generation component 910 can select a first tone for the first ear and a different second tone for the second ear. A tone can be characterized by its duration, pitch, intensity (or loudness), or timbre (or quality). In some cases, the first tone and the second tone can be different if they have different frequencies. In some cases, the first tone and the second tone can be different if they have different phase offsets. The first tone and the second tone can each be pure tones. A pure tone can be a tone having a sinusoidal waveform with a single frequency.

[0525] As illustrated in **FIG. 11A**, the first tone or offset wave 1105 is slightly different from the second tone 1110 or carrier wave 1110. The first tone 1105 has a higher frequency than the second tone 1110. The first tone 1105 can be generated by a first earbud that is inserted into one

of the subject's ears, and the second tone 1110 can be generated by a second earbud that is inserted into the other of the subject's ears. When the auditory cortex of the brain perceives the first tone 1105 and the second tone 1110, the brain can sum the two tones. The brain can sum the acoustic waveforms corresponding to the two tones. The brain can sum the two waveforms as illustrated by waveform sum 1115. Due to the first and second tones having a different parameter (such as a different frequency or phase offset), portions of the waves can add and subtract from another to result in waveform 1115 having one or more pulses 1130 (or beats 1130). The pulses 1130 can be separated by portions 1125 that are at equilibrium. The pulses 1130 perceived by the brain by mixing these two different waveforms together can induce brainwave entrainment.

[0526] In some embodiments, the NSS 905 can generate binaural beats using a pitch panning technique. For example, the audio generation module 910 or audio adjustment module 915 can include or use a filter to modulate the pitch of a sound file or single tone up and down, and at the same time pan the modulation between stereo sides, such that one side will have a slightly higher pitch while the other side has a pitch that is slightly lower. The stereo sides can refer to the first audio source that generates and provides the audio signal to the first ear of the subject, and the second audio source that generates and provides the audio signal to the second ear of the subject. A sound file can refer to a file format configured to store a representation of, or information about, an acoustic wave. Example sound file formats can include .mp3, .wav, .aac, .m4a, .smf, etc.

[0527] The NSS 905 can use this pitch panning technique to generate a type of spatial positioning that, when listened to through stereo headphones, is perceived by the brain in a manner similar to binaural beats. The NSS 905 can, therefore, use this pitch panning technique to generate pulses or beats using a single tone or a single sound file.

[0528] In some cases, the NSS 905 can generate monaural beats or monaural pulses. Monaural beats or pulses are similar to binaural beats in that they are also generated by combining two tones to form a beat. The NSS 905 or component of system 100 can form monaural beats by combining the two tones using a digital or analog technique before the sound reaches the ears, as opposed to the brain combining the waveforms as in binaural beats. For example, the NSS 905 (or audio generation component 910) can identify and select two different waveforms that, when combined, produce beats or pulses having a desired pulse rate interval. The NSS 905 can identify a first digital representation of a first acoustic waveform, and identify a second digital representation of a second acoustic waveform have a different parameter than the first acoustic waveform. The NSS 905 can combine the first and second digital waveforms to generate a third digital waveform different from the first digital waveform and the second digital waveform. The NSS 905 can then transmit the third digital waveform in a digital form to the audio signaling

component 950. The NSS 905 can translate the digital waveform to an analog format and transmit the analog format to the audio signaling component 950. The audio signaling component 950 can then, via an audio source, generate the sound to be perceived by one or both ears. The same sound can be perceived by both ears. The sound can include the pulses or beats spaced at the desired pulse rate interval 1040.

[0529] FIG. 11B illustrates acoustic pulses having isochronic tones, in accordance with an embodiment. Isochronic tones are evenly spaced tone pulses. Isochronic tones can be created without having to combine two different tones. The NSS 905 or other component of system 100 can create the isochronic tone by turning a tone on and off. The NSS 905 can generate the isochronic tones or pulses by instructing the audio signaling component to turn on and off. The NSS 905 can modify a digital representation of an acoustic wave to remove or set digital values of the acoustic wave such that sound is generated during the pulses 1135 and no sound is generated during the null portions 1140.

[0530] By turning on and off the acoustic wave, the NSS 905 can establish acoustic pulses 1135 that are spaced apart by a pulse rate interval 1040 that corresponds to a desired stimulation frequency, such as 40 Hz. The isochronic pulses spaced part at the desired PRI 1040 can induce brainwave entrainment.

[0531] FIG. 11C illustrates audio pulses generated by the NSS 905 using a sound track, in accordance with an embodiment. A sound track can include or refer to a complex acoustical wave that includes multiple different frequencies, amplitudes, or tones. For example, a sound track can include a voice track, a musical instrument track, a musical track having both voice and musical instruments, nature sounds, or white noise.

[0532] The NSS 905 can modulate the sound track to induce brainwave entrainment by rhythmically adjusting a component in the sound. For example, the NSS 905 can modulate the volume by increasing and decreasing the amplitude of the acoustic wave or sound track to create the rhythmic stimulus corresponding to the stimulation frequency for inducing brainwave entrainment. Thus, the NSS 905 can embed, into a sound track acoustic pulses having a pulse rate interval corresponding to the desired stimulation frequency to induce brainwave entrainment. The NSS 905 can manipulate the sound track to generate a new, modified sound track having acoustic pulses with a pulse rate interval corresponding to the desired stimulation frequency to induce brainwave entrainment.

[0533] As illustrated in **FIG. 11C**, pulses 1135 are generated by modulating the volume from a first level V_a to a second level V_b . During portions 1140 of the acoustic wave 345, the NSS 905 can set or keep the volume at V_a . The volume V_a can refer to an amplitude of the wave, or a maximum amplitude or crest of the wave 345 during the portion 1140. The NSS 905 can then

adjust, change, or increase the volume to Vb during portion 1135. The NSS 905 can increase the volume by a predetermined amount, such as a percentage, a number of decibels, a subject-specified amount, or other amount. The NSS 905 can set or maintain the volume at Vb for a duration corresponding to a desired pulse length for the pulse 1135.

[0534] In some embodiments, the NSS 905 can include an attenuator to attenuate the volume from level Vb to level Va. In some embodiments, the NSS 905 can instruct an attenuator (e.g., an attenuator of audio signaling component 950) to attenuate the volume from level Vb to level Va. In some embodiments, the NSS 905 can include an amplifier to amplify or increase the volume from Va to Vb. In some embodiments, the NSS 905 can instruct an amplifier (e.g., an amplifier of the audio signaling component 950) to amplify or increase the volume from Va to Vb.

[0535] Referring back to **FIG. 9**, the NSS 905 can include, access, interface with, or otherwise communicate with at least one audio adjustment module 915. The audio adjustment module 915 can be designed and constructed to adjust a parameter associated with the audio signal, such as a frequency, amplitude, wavelength, pattern or other parameter of the audio signal. The audio adjustment module 915 can automatically vary a parameter of the audio signal based on profile information or feedback. The audio adjustment module 915 can receive the feedback information from the feedback monitor 935. The audio adjustment module 915 can receive instructions or information from a side effects management module 930. The audio adjustment module 915 can receive profile information from profile manager 925.

[0536] The NSS 905 can include, access, interface with, or otherwise communicate with at least one unwanted frequency filtering module 920. The unwanted frequency filtering module 920 can be designed and constructed to block, mitigate, reduce, or otherwise filter out frequencies of audio signals that are undesired to prevent or reduce an amount of such audio signals from being perceived by the brain. The unwanted frequency filtering module 920 can interface, instruct, control, or otherwise communicate with a filtering component 955 to cause the filtering component 955 to block, attenuate, or otherwise reduce the effect of the unwanted frequency on the neural oscillations.

[0537] The unwanted frequency filtering module 920 can include an active noise control component (e.g., active noise cancellation component 1215 depicted in **FIG. 12B**). Active noise control can be referred to or include active noise cancellation or active noise reduction. Active noise control can reduce an unwanted sound by adding a second sound having a parameter specifically selected to cancel or attenuate the first sound. In some cases, the active noise control component can emit a sound wave with the same amplitude but with an inverted phase (or antiphase) to the original unwanted sound. The two waves can combine to form a new wave, and effectively cancel each other out by destructive interference.

[0538] The active noise control component can include analog circuits or digital signal processing. The active noise control component can include adaptive techniques to analyze waveforms of the background aural or nonaural noise. Responsive to the background noise, the active noise control component can generate an audio signal that can either phase shift or invert the polarity of the original signal. This inverted signal can be amplified by a transducer or speaker to create a sound wave directly proportional to the amplitude of the original waveform, creating destructive interference. This can reduce the volume of the perceivable noise.

[0539] In some embodiments, a noise-cancellation speaker can be co-located with a sound source speaker. In some embodiments, a noise cancellation speaker can be co-located with a sound source that is to be attenuated.

[0540] The unwanted frequency filtering module 920 can filter out unwanted frequencies that can adversely impact auditory brainwave entrainment. For example, an active noise control component can identify that audio signals include acoustic bursts having the desired pulse rate interval, as well as acoustic bursts having an unwanted pulse rate interval. The active noise control component can identify the waveforms corresponding to the acoustic bursts having the unwanted pulse rate interval, and generate an inverted phase waveform to cancel out or attenuate the unwanted acoustic bursts.

[0541] The NSS 905 can include, access, interface with, or otherwise communicate with at least one profile manager 925. The profile manager 925 can be designed or constructed to store, update, retrieve or otherwise manage information associated with one or more subjects associated with the auditory brain entrainment. Profile information can include, for example, historical treatment information, historical brain entrainment information, dosing information, parameters of acoustic waves, feedback, physiological information, environmental information, or other data associated with the systems and methods of brain entrainment.

[0542] The NSS 905 can include, access, interface with, or otherwise communicate with at least one side effects management module 930. The side effects management module 930 can be designed and constructed to provide information to the audio adjustment module 915 or the audio generation module 910 to change one or more parameter of the audio signal in order to reduce a side effect. Side effects can include, for example, nausea, migraines, fatigue, seizures, ear strain, deafness, ringing, or tinnitus.

[0543] The side effects management module 930 can automatically instruct a component of the NSS 905 to alter or change a parameter of the audio signal. The side effects management module 930 can be configured with predetermined thresholds to reduce side effects. For example, the side effects management module 930 can be configured with a maximum duration of a pulse train, maximum amplitude of acoustic waves, maximum volume, maximum duty cycle of a pulse

train (e.g., the pulse width multiplied by the frequency of the pulse train), maximum number of treatments for brainwave entrainment in a time period (e.g., 1 hour, 2 hours, 12 hours, or 24 hours).

[0544] The side effects management module 930 can cause a change in the parameter of the audio signal in response to feedback information. The side effect management module 930 can receive feedback from the feedback monitor 935. The side effects management module 930 can determine to adjust a parameter of the audio signal based on the feedback. The side effects management module 930 can compare the feedback with a threshold to determine to adjust the parameter of the audio signal.

[0545] The side effects management module 930 can be configured with or include a policy engine that applies a policy or a rule to the current audio signal and feedback to determine an adjustment to the audio signal. For example, if feedback indicates that a patient receiving audio signals has a heart rate or pulse rate above a threshold, the side effects management module 930 can turn off the pulse train until the pulse rate stabilizes to a value below the threshold, or below a second threshold that is lower than the threshold.

[0546] The NSS 905 can include, access, interface with, or otherwise communicate with at least one feedback monitor 935. The feedback monitor can be designed and constructed to receive feedback information from a feedback component 960. Feedback component 960 can include, for example, a feedback sensor 1405 such as a temperature sensor, heart or pulse rate monitor, physiological sensor, ambient noise sensor, microphone, ambient temperature sensor, blood pressure monitor, brain wave sensor, EEG probe, electrooculography (“EOG”) probes configured measure the corneo-retinal standing potential that exists between the front and the back of the human eye, accelerometer, gyroscope, motion detector, proximity sensor, camera, microphone, or photo detector.

[0547] **FIG. 15** is a flow diagram of a method of performing auditory brain stimulation in accordance with an embodiment. The method 800 can be performed by one or more system, component, module or element depicted in FIGS. 7A, 7B, and 9-14, including, for example, a neural stimulation system (NSS). In brief overview, the NSS can identify an audio signal to provide at block 1505. At block 1510, the NSS can generate and transmit the identified audio signal. At 1515 the NSS can receive or determine feedback associated with neural activity, physiological activity, environmental parameters, or device parameters. At 1520 the NSS can manage, control, or adjust the audio signal based on the feedback.

i. NSS Operating With Headphones

[0548] The NSS 905 can operate in conjunction with the speakers 1205 as depicted in **FIG. 12A**. The NSS 905 can operate in conjunction with earphones or in-ear phones including the speaker 1205 and a feedback sensor 1405.

[0549] In operation, a subject using the headphones can wear the headphones on their head such that speakers or placed at or in the ear canals. In some cases, the subject can provide an indication to the NSS 905 that the headphones have been worn and that the subject is ready to undergo brainwave entrainment. The indication can include an instruction, command, selection, input, or other indication via an input/output interface, such as a keyboard 726, pointing device 727, or other I/O devices 730a-n. The indication can be a motion-based indication, visual indication, or voice-based indication. For example, the subject can provide a voice command that indicates that the subject is ready to undergo brainwave entrainment.

[0550] In some cases, the feedback sensor 1405 can determine that the subject is ready to undergo brainwave entrainment. The feedback sensor 1405 can detect that the headphones have been placed on a subject's head. The NSS 905 can receive motion data, acceleration data, gyroscope data, temperature data, or capacitive touch data to determine that the headphones have been placed on the subject's head. The received data, such as motion data, can indicate that the headphones were picked up and placed on the subject's head. The temperature data can measure the temperature of or proximate to the headphones, which can indicate that the headphones are on the subject's head. The NSS 905 can detect that the subject is ready responsive to determining that the subject is paying a high level of attention to the headphones or feedback sensor 1405.

[0551] Thus, the NSS 905 can detect or determine that the headphones have been worn and that the subject is in a ready state, or the NSS 905 can receive an indication or confirmation from the subject that the subject has worn the headphones and the subject is ready to undergo brainwave entrainment. Upon determining that the subject is ready, the NSS 905 can initialize the brainwave entrainment process. In some embodiments, the NSS 905 can access a profile data structure 945. For example, a profile manager 925 can query the profile data structure 945 to determine one or more parameter for the external auditory stimulation used for the brain entrainment process. Parameters can include, for example, a type of audio stimulation technique, an intensity or volume of the audio stimulation, frequency of the audio stimulation, duration of the audio stimulation, or wavelength of the audio stimulation. The profile manager 925 can query the profile data structure 945 to obtain historical brain entrainment information, such as prior auditory stimulation sessions. The profile manager 925 can perform a lookup in the profile data structure 945. The profile manager 925 can perform a look-up with a username, user identifier, location information, fingerprint, biometric identifier, retina scan, voice recognition and authentication, or other identifying technique.

[0552] The NSS 905 can determine a type of external auditory stimulation based on the components connected to the headphones. The NSS 905 can determine the type of external auditory stimulation based on the type of speakers 1205 available. For example, if the headphones are connected to an audio player, the NSS 905 can be determined to embed acoustic pulses. If the headphones are not connected to an audio player, but only the microphone, the NSS 905 can determine to inject a pure tone or modify ambient noise.

[0553] In some embodiments, the NSS 905 can determine the type of external auditory stimulation based on historical brainwave entrainment sessions. For example, the profile data structure 945 can be pre-configured with information about the type of audio signaling component 950.

[0554] The NSS 905 can determine, via the profile manager 925, a modulation frequency for the pulse train or the audio signal. For example, NSS 905 can determine, from the profile data structure 945, that the modulation frequency for the external auditory stimulation should be set to 40 Hz. Depending on the type of auditory stimulation, the profile data structure 945 can further indicate a pulse length, intensity, wavelength of the acoustic wave forming the audio signal, or duration of the pulse train.

[0555] In some cases, the NSS 905 can determine or adjust one or more parameter of the external auditory stimulation. For example, the NSS 905 (e.g., via feedback component 960 or feedback sensor 1405) can determine an amplitude of the acoustic wave or volume level for the sound. The NSS 905 (e.g., via audio adjustment module 915 or side effects management module 930) can establish, initialize, set, or adjust the amplitude or wavelength of the acoustic waves or acoustic pulses. For example, the NSS 905 can determine that there is a low level of ambient noise. Due to the low level of ambient noise, subject's hearing may not be impaired or distracted. The NSS 905 can determine, based on detecting a low level of ambient noise, that it may not be necessary to increase the volume, or that it may be possible to reduce the volume to maintain the efficacy of brainwave entrainment.

[0556] In some embodiments, the NSS 905 can monitor (e.g., via feedback monitor 935 and feedback component 960) the level of ambient noise throughout the brainwave entrainment process to automatically and periodically adjust the amplitude of the acoustic pulses. For example, if the subject began the brainwave entrainment process when there was a high level of ambient noise, the NSS 905 can initially set a higher amplitude for the acoustic pulses and use a tone that includes frequencies that are easier to perceive, such as 10 kHz. However, in some embodiments in which the ambient noise level decreases throughout the brainwave entrainment process, the NSS 905 can automatically detect the decrease in ambient noise and, in response to the detection, adjust or lower the volume while decreasing the frequency of the acoustic wave.

The NSS 905 can adjust the acoustic pulses to provide a high contrast ratio with respect to ambient noise to facilitate brainwave entrainment.

[0557] In some embodiments, the NSS 905 (e.g., via feedback monitor 935 and feedback component 960) can monitor or measure physiological conditions to set or adjust a parameter of the acoustic wave. In some embodiments, the NSS 905 can monitor or measure heart rate, pulse rate, blood pressure, body temperature, perspiration, or brain activity to set or adjust a parameter of the acoustic wave.

[0558] In some embodiments, the NSS 905 can be preconfigured to initially transmit acoustic pulses having a lowest setting for the acoustic wave intensity (e.g., low amplitude or high wavelength) and gradually increase the intensity (e.g., increase the amplitude of the or decrease the wavelength) while monitoring feedback until an optimal audio intensity is reached. An optimal audio intensity can refer to a highest intensity without adverse physiological side effects, such as deafness, seizures, heart attack, migraines, or other discomfort. The NSS 905 (e.g., via side effects management module 930) can monitor the physiological symptoms to identify the adverse side effects of the external auditory stimulation, and adjust (e.g., via audio adjustment module 915) the external auditory stimulation accordingly to reduce or eliminate the adverse side effects.

[0559] In some embodiments, the NSS 905 (e.g., via audio adjustment module 915) can adjust a parameter of the audio wave or acoustic pulse based on a level of attention. For example, during the brainwave entrainment process, the subject can get bored, lose focus, fall asleep, or otherwise not pay attention to the acoustic pulses. Not paying attention to the acoustic pulses can reduce the efficacy of the brainwave entrainment process, resulting in neurons oscillating at a frequency different from the desired modulation frequency of the acoustic pulses.

[0560] NSS 905 can detect the level of attention the subject is paying to the acoustic pulses using the feedback monitor 935 and one or more feedback component 960. Responsive to determining that the subject is not paying a satisfactory amount of attention to the acoustic pulses, the audio adjustment module 915 can change a parameter of the audio signal to gain the subject's attention. For example, the audio adjustment module 915 can increase the amplitude of the acoustic pulse, adjust the tone of the acoustic pulse, or change the duration of the acoustic pulse. The audio adjustment module 915 can randomly vary one or more parameters of the acoustic pulse. The audio adjustment module 915 can initiate an attention seeking acoustic sequence configured to regain the subject's attention. For example, the audio sequence can include a change in frequency, tone, amplitude, or insert words or music in a predetermined, random, or pseudo-random pattern. The attention seeking audio sequence can enable or disable different acoustic sources if the audio signaling component 950 includes multiple audio sources or speakers. Thus,

the audio adjustment module 915 can interact with the feedback monitor 935 to determine a level of attention the subject is providing to the acoustic pulses, and adjust the acoustic pulses to regain the subject's attention if the level of attention falls below a threshold.

[0561] In some embodiments, the audio adjustment module 915 can change or adjust one or more parameter of the acoustic pulse or acoustic wave at predetermined time intervals (e.g., every 5 minutes, 10 minutes, 15 minutes, or 20 minutes) to regain or maintain the subject's attention level.

[0562] In some embodiments, the NSS 905 (e.g., via unwanted frequency filtering module 920) can filter, block, attenuate, or remove unwanted auditory external stimulation. Unwanted auditory external stimulation can include, for example, unwanted modulation frequencies, unwanted intensities, or unwanted wavelengths of sound waves. The NSS 905 can deem a modulation frequency to be unwanted if the modulation frequency of a pulse train is different or substantially different (e.g., 1%, 2%, 5%, 10%, 15%, 20%, 25%, or more than 25%) from a desired frequency.

[0563] For example, the desired modulation frequency for brainwave entrainment can be 40 Hz. However, a modulation frequency of 20 Hz or 80 Hz can reduce the beneficial effects to cognitive functioning of the brain, a cognitive state of the brain, the immune system, or inflammation that can result from brainwave entrainment at other frequencies, such as 40 Hz. Thus, the NSS 905 can filter out the acoustic pulses corresponding to the 20 Hz or 80 Hz modulation frequency.

[0564] In some embodiments, the NSS 905 can detect, via feedback component 960, that there are acoustic pulses from an ambient noise source that corresponds to an unwanted modulation frequency of 20 Hz. The NSS 905 can further determine the wavelength of the acoustic waves of the acoustic pulses corresponding to the unwanted modulation frequency. The NSS 905 can instruct the filtering component 955 to filter out the wavelength corresponding to the unwanted modulation frequency.

E. Methods for Neural Stimulation with NSS via Peripheral Nerve Stimulation

[0565] In some aspects, described herein are methods of neural stimulation via peripheral nerve stimulation. In some embodiments, a method of peripheral nerve stimulation comprises a method of using a portable system or single headset device as disclosed herein. In some embodiments, a method of peripheral nerve stimulation neurostimulation comprises a method of using a portable system as disclosed herein, wherein the portable system comprises an NSS. Illustrative embodiments are described as follows.

[0566] In some embodiments, systems and methods of the present disclosure can provide peripheral nerve stimulation to cause or induce neural oscillations. For example, haptic stimulation on the skin around sensory nerves forming part of or connected to the peripheral nervous system can cause or induce electrical activity in the sensory nerves, causing a transmission to the brain via the central nervous system, which can be perceived by the brain or can cause or induce electrical and neural activity in the brain, including activity resulting in neural oscillations. Similarly, electric currents on or through the skin around sensory nerves forming part of or connected to the peripheral nervous system can cause or induce electrical activity in the sensory nerves, causing a transmission to the brain via the central nervous system, which can be perceived by the brain or can cause or induce electrical and neural activity in the brain, including activity resulting in neural oscillations. The brain, responsive to receiving the peripheral nerve stimulations, can adjust, manage, or control the frequency of neural oscillations. The electric currents can result in depolarization of neural cells, such as due to electric current stimuli such as time-varying pulses. The electric current pulse can directly cause depolarization. Secondary effects in other regions of the brain can be gated or controlled by the brain in response to the depolarization. The peripheral nerve stimulations generated at a predetermined frequency can trigger neural activity in the brain to cause or induce neural oscillations. The frequency of neural oscillations can be based on or correspond to the frequency of the peripheral nerve stimulations, or a modulation frequency associated with the peripheral nerve stimulations. Thus, systems and methods of the present disclosure can cause or induce neural oscillations using peripheral nerve stimulations such as electric current pulses modulated at a predetermined frequency to synchronize electrical activity among groups of neurons based on the frequency of the peripheral nerve stimulations. Brain entrainment associated with neural oscillations can be observed based on the aggregate frequency of oscillations produced by the synchronous electrical activity in ensembles of cortical neurons. The frequency of the modulation of the electric currents, or pulses thereof, can cause or adjust this synchronous electrical activity in the ensembles of cortical neurons to oscillate at a frequency corresponding to the frequency of the peripheral nerve stimulation pulses.

[0567] **FIG. 16A** is a block diagram depicting a system to perform peripheral nerve stimulation to cause or induce neural oscillations, such as to cause brain entrainment, in accordance with an embodiment. The system 1600 can include a peripheral nerve stimulation system 1605. In brief overview, the peripheral nerve stimulation system (or peripheral nerve stimulation neural stimulation system) (“NSS”) 1605 can include, access, interface with, or otherwise communicate with one or more of a nerve stimulus generation module 1610, nerve stimulus adjustment module 1615, profile manager 1625, side effects management module 1630, feedback monitor 1635, data

repository 1640, nerve stimulus generator component 1650, shielding component 1655, feedback component 1660, or nerve stimulus amplification component 1665. The nerve stimulus generation module 1610, nerve stimulus adjustment module 1615, profile manager 1625, side effects management module 1630, feedback monitor 1635, nerve stimulus generator component 1650, shielding component 1655, feedback component 1660, or nerve stimulus amplification component 1665 can each include at least one processing unit or other logic device such as programmable logic array engine, or module configured to communicate with the database repository 1650. The nerve stimulus generation module 1610, nerve stimulus adjustment module 1615, profile manager 1625, side effects management module 1630, feedback monitor 1635, nerve stimulus generator component 1650, shielding component 1655, feedback component 1660, or nerve stimulus amplification component 1665 can be separate components, a single component, or part of the NSS 1605. The system 1600 and its components, such as the NSS 1605, can include hardware elements, such as one or more processors, logic devices, or circuits. The system 1600 and its components, such as the NSS 1605, can include one or more hardware or interface component depicted in system 700 in FIGS. 7A and 7B. For example, a component of system 1600 can include or execute on one or more processors 721, access storage 728 or memory 722, and communicate via network interface 718.

F. Methods for Neural Stimulation with an NSS Via Multiple Modes of Stimulation

[0568] In some embodiments, a portable system or single headset comprising an NSS is configured to deliver multiple types of stimulation, e.g., visual and auditory, or visual, auditory, and haptic stimulation, or any combination thereof. **FIG. 16B** is a block diagram depicting a system for neural stimulation via multiple modes of stimulation in accordance with an embodiment. The portable system or single headset device 1600 can include a neural stimulation orchestration system (“NSOS”) 1605. The NSOS 1605 can provide multiple modes of stimulation. For example, the NSOS 1605 can provide a first mode of stimulation that includes visual stimulation, and a second mode of stimulation that includes auditory stimulation. For each mode of stimulation, the NSOS 1605 can provide a type of signal. For example, for the visual mode of stimulation, the NSOS 1605 can provide the following types of signals: light pulses, image patterns, flicker of ambient light, or augmented reality. NSOS 1605 can orchestrate, manage, control, or otherwise facilitate providing multiple modes of stimulation and types of stimulation.

[0569] In brief overview, the NSOS 1605 can include, access, interface with, or otherwise communicate with one or more of a stimuli orchestration component 1610, a subject assessment module 1650, a data repository 1615, one or more signaling components 1630a-n, one or more filtering components 1635a-n, one or more feedback components 1640a-n, and one or more

neural stimulation systems (“NSS”) 1645a-n. The data repository 1615 can include or store a profile data structure 1620 and a policy data structure 1625. The stimuli orchestration component 1610 and subject assessment module 1650 can include at least one processing unit or other logic device such as programmable logic array engine, or module configured to communicate with the database repository 1615. The stimuli orchestration component 1610 and subject assessment module 1650 can be a single component, include separate components, or be part of the NSOS 1605. The system 1600 and its components, such as the NSOS 1605, can include hardware elements, such as one or more processors, logic devices, or circuits. The system 1600 and its components, such as the NSOS 1605, can include one or more hardware or interface component depicted in system 700 in FIGs. 7A and 7B. For example, a component of system 1600 can include or execute on one or more processors 721, access storage 728 or memory 722, and communicate via network interface 718. The system 1600 can include one or more component or functionality depicted in FIGs. 1-15, including, for example, system 100, system 900, visual NSS 105, or auditory NSS 905. For example, at least one of the signaling components 1630a-n can include one or more component or functionality of visual signaling component 150 or audio signaling component 950. At least one of the filtering components 1635a-n can include one or more component or functionality of filtering component 155 or filtering component 955. At least one of the feedback components 1640a-n can include one or more component or functionality of feedback component 160 or feedback component 960. At least one of the NSS 1645a-n can include one or more component or functionality of visual NSS 105 or auditory NSS 905.

[0570] Still referring to **FIG. 16B**, and in further detail, the NSOS 1605 can include at least stimuli orchestration component 1610. The stimuli orchestration component 1610 can be designed and constructed to perform neural stimulation using multiple modalities of stimulation. The stimuli orchestration component 1610 or NSOS 1605 can interface with at least one of the signaling components 1630a-n, at least one of the filtering components 1635a-n or at least one of the feedback components 1640a-n. One or more of the signaling components 1630a-n can be a same type of signaling component or a different type of signaling component. The type of signaling component can correspond to a mode of stimulation. For example, multiple types of signaling components 1630a-n can correspond to visual signaling components or auditory signaling components. In some cases, at least one of the signaling components 1630a-n includes a visual signaling component 150 such as a light source, LED, laser, tablet computing device, or virtual reality headset. At least one of the signaling components includes an audio signaling component 950, such as headphones, speakers, cochlear implants, or air jets.

[0571] One or more of the filtering components 1635a-n can be a same type of filtering component or a different type of filtering component. One or more of the feedback components

1640a-n can be a same type of feedback component or a different type of feedback component. For example, the feedback components 1640a-n can include an electrode, dry electrode, gel electrode, saline soaked electrode, adhesive-based electrodes, a temperature sensor, heart or pulse rate monitor, physiological sensor, ambient light sensor, ambient temperature sensor, sleep status via actigraphy, blood pressure monitor, respiratory rate monitor, brain wave sensor, EEG probe, EOG probes configured measure the corneo-retinal standing potential that exists between the front and the back of the human eye, accelerometer, gyroscope, motion detector, proximity sensor, camera, microphone, or photo detector.

[0572] The stimuli orchestration component 1610 can include or be configured with an interface to communicate with different types of signaling components 1630a-n, filtering components 1635a-n or feedback components 1640a-n. The NSOS 1605 or stimuli orchestration component 1610 can interface with system intermediary to one of the signaling components 1630a-n, filtering components 1635a-n, or feedback components 1640a-n. For example, the stimuli orchestration component 1610 can interface with the visual NSS 105 depicted in **FIG. 1** or auditory NSS 905 depicted in **FIG. 9**. Thus, in some embodiments, the stimuli orchestration component 1610 or NSOS 1605 can indirectly interface with at least one of the signaling components 1630a-n, filtering components 1635a-n, or feedback components 1640a-n.

[0573] The stimuli orchestration component 1610 (e.g., via the interface) can ping each of the signaling components 1630a-n, filtering components 1635a-n, and feedback components 1640a-n to determine information about the components. The information can include a type of the component (e.g., visual, auditory, attenuator, optical filter, temperature sensor, or light sensor), configuration of the component (e.g., frequency range, amplitude range), or status information (e.g., standby, ready, online, enabled, error, fault, offline, disabled, warning, service needed, availability, or battery level).

[0574] The stimuli orchestration component 1610 can instruct or cause at least one of the signaling components 1630a-n to generate, transmit or otherwise provide a signal that can be perceived, received or observed by the brain and affect a frequency of neural oscillations in at least one region or portion of a subject's brain. The signal can be perceived via various means, including, for example, optical nerves or cochlear cells.

[0575] The stimuli orchestration component 1610 can access the data repository 1615 to retrieve profile information 1620 and a policy 1625. The profile information 1620 can include profile information 145 or profile information 945. The policy 1625 can include a multi-modal stimulation policy. The policy 1625 can indicate a multi-modal stimulation program. The stimuli orchestration component 1610 can apply the policy 1625 to profile information to determine a type of stimulation (e.g., visual or auditory) and determine a value for a parameter for each type

of stimulation (e.g., amplitude, frequency, wavelength, color, etc.). The stimuli orchestration component 1610 can apply the policy 1625 to the profile information 1620 and feedback information received from one or more feedback components 1640a-n to determine or adjust the type of stimulation (e.g., visual or auditory) and determine or adjust the value parameter for each type of stimulation (e.g., amplitude, frequency, wavelength, color, etc.). The stimuli orchestration component 1610 can apply the policy 1625 to profile information to determine a type of filter to be applied by at least one of the filtering components 1635a-n (e.g., audio filter or visual filter) and determine a value for a parameter for the type of filter (e.g., frequency, wavelength, color, sound attenuation, etc.). The stimuli orchestration component 1610 can apply the policy 1625 to profile information and feedback information received from one or more feedback components 1640a-n to determine or adjust the type of filter to be applied by at least one of the filtering components 1635a-n (e.g., audio filter or visual filter) and determine or adjust the value for the parameter for filter (e.g., frequency, wavelength, color, sound attenuation, etc.).

[0576] The NSOS 1605 can obtain the profile information 1620 via a subject assessment module 1650. The subject assessment module 1650 can be designed and constructed to determine, for one or more subjects, information that can facilitate neural stimulation via one or more modes of stimulation. The subject assessment module 1650 can receive, obtain, detect, determine or otherwise identify the information via feedback components 1640a-n, surveys, queries, questionnaires, prompts, remote profile information accessible via a network, diagnostic tests, or historical treatments.

[0577] The subject assessment module 1650 can receive the information prior to initiating neural stimulation, during neural stimulation, or after neural stimulation. For example, the subject assessment module 1650 can provide a prompt with a request for information prior to initiating the neural stimulation session. The subject assessment module 1650 can provide a prompt with a request for information during the neural stimulation session. The subject assessment module 1650 can receive feedback from feedback component 1640a-n (e.g., an EEG probe) during the neural stimulation session. The subject assessment module 1650 can provide a prompt with a request for information subsequent to termination of the neural stimulation session. The subject assessment module 1650 can receive feedback from feedback component 1640a-n subsequent to termination of the neural stimulation session.

[0578] The subject assessment module 1650 can use the information to determine an effectiveness of a modality of stimulation (e.g., visual stimulation or auditory stimulation) or a type of signal (e.g., light pulse from a laser or LED source, ambient light flicker, or image pattern displayed by a tablet computing device). For example, the subject assessment module 1650 can determine that the desired neural stimulation resulted from a first mode of stimulation or first

type of signal, while the desired neural stimulation did not occur or took longer to occur with the second mode of stimulation or second type of signal. The subject assessment module 1650 can determine that the desired neural stimulation was less pronounced from the second mode of stimulation or second type of signal relative to the first mode of stimulation or first type of signal based on feedback information from a feedback component 1640a-n.

[0579] The subject assessment module 1650 can determine the level of effectiveness of each mode or type of stimulation independently, or based on a combination of modes or types of stimulation. A combination of modes of stimulation can refer to transmitting signals from different modes of stimulation at the same or substantially similar time. A combination of modes of stimulation can refer to transmitting signals from different modes of stimulation in an overlapping manner. A combination of modes of stimulation can refer to transmitting signals from different modes of stimulation in a non-overlapping manner, but within a time interval from one another (e.g., transmit a signal pulse train from a second mode of stimulation within 0.5 seconds, 1 second, 1.5 seconds, 2 seconds, 2.5 seconds, 3 seconds, 5 seconds, 7 seconds, 10 seconds, 12 seconds, 15 seconds, 20 seconds, 30 seconds, 45 seconds, 60 seconds, 1 minute, 2 minutes 3 minutes 5 minutes, 10 minutes, or other time interval where the effect on the frequency of neural oscillation by a first mode can overlap with the second mode).

[0580] The subject assessment module 1650 can aggregate or compile the information and update the profile data structure 1620 stored in data repository 1615. In some cases, the subject assessment module 1650 can update or generate a policy 1625 based on the received information. The policy 1625 or profile information 1620 can indicate which modes or types of stimulation are more likely to have a desired effect on neural stimulation, while reducing side effects.

[0581] The stimuli orchestration component 1610 can instruct or cause multiple signaling components 1630a-n to generate, transmit or otherwise provide different types of stimulation or signals pursuant to the policy 1625, profile information 1620 or feedback information detected by feedback components 1640a-n. The stimuli orchestration component 1610 can cause multiple signaling components 1630a-n to generate, transmit or otherwise provide different types of stimulation or signals simultaneously or at substantially the same time. For example, a first signaling component 1630a can transmit a first type of stimulation at the same time as a second signaling component 1630b transmits a second type of stimulation. The first signaling component 1630a can transmit or provide a first set of signals, pulses or stimulation at the same time the second signaling component 1630b transmits or provides a second set of signals, pulses or stimulation. For example, a first pulse from a first signaling component 1630a can begin at the same time or substantially the same time (e.g., 1%, 2%, 3%, 4%, 5%, 6%, 7%, 10%, 15%, 20%) as a second pulse from a second signaling component 1630b. First and second pulses can end at

the same time or substantially same time. In another example, a first pulse train can be transmitted by the first signaling component 1630a at the same or substantially similar time as a second pulse train transmitted by the second signaling component 1630b.

[0582] The stimuli orchestration component 1610 can cause multiple signaling components 1630a-n to generate, transmit or otherwise provide different types of stimulation or signals in an overlapping manner. The different pulses or pulse trains may overlap one another, but may not be necessary being or end at a same time. For example, at least one pulse in the first set of pulses from the first signaling component 1630a can at least partially overlap, in time, with at least one pulse from the second set of pulses from the second signaling component 1630b. For example, the pulses can straddle one another. In some cases, a first pulse train transmitted or provided by the first signaling component 1630a can at least partially overlap with a second pulse train transmitted or provided by the second signaling component 1630b. The first pulse train can straddle the second pulse train.

[0583] The stimuli orchestration component 1610 can cause multiple signaling components 1630a-n to generate, transmit or otherwise provide different types of stimulation or signals such that they are received, perceived or otherwise observed by one or more regions or portions of the brain at the same time, simultaneously or at substantially the same time. The brain can receive different modes of stimulation or types of signals at different times. The duration of time between transmission of the signal by a signaling component 1630a-n and reception or perception of the signal by the brain can vary based on the type of signal (e.g., visual, auditory), parameter of the signal (e.g., velocity or speed of the wave, amplitude, frequency, wavelength), or distance between the signaling component 1630a-n and the nerves or cells of the subject configured to receive the signal (e.g., eyes or ears). The stimuli orchestration component 1610 can offset or delay the transmission of signals such that the brain perceives the different signals at the desired time. The stimuli orchestration component 1610 can offset or delay the transmission of a first signal transmitted by a first signaling component 1630a relative to transmission of a second signal transmitted by a second signaling component 1630b. The stimuli orchestration component 1610 can determine an amount of an offset for each type of signal or each signaling component 1630a-n relative to a reference clock or reference signal. The stimuli orchestration component 1610 can be preconfigured or calibrated with an offset for each signaling component 1630a-n.

[0584] The stimuli orchestration component 1610 can determine to enable or disable the offset based on the policy 1625. For example, the policy 1625 can indicate to transmit multiple signals at the same time, in which case the stimuli orchestration component 1610 can disable or not use an offset. In another example, the policy 1625 can indicate to transmit multiple signals such that

they are perceived by the brain at the same time, in which case the stimuli orchestration component 1610 can enable or use the offset.

[0585] In some embodiments, the stimuli orchestration component 1610 can stagger signals transmitted by different signaling components 1630a-n. For example, the stimuli orchestration component 1610 can stagger the signals such that the pulses from different signaling components 1630a-n are non-overlapping. The stimuli orchestration component 1610 can stagger pulse trains from different signaling components 1630a-n such that they are non-overlapping. The stimuli orchestration component 1610 can set parameters for each mode of stimulation or signaling component 1630a-n such that the signals they are non-overlapping.

[0586] Thus, the stimuli orchestration component 1610 can set parameters for signals transmitted by one or more signaling components 1630a-n such that the signals are transmitted in a synchronously or asynchronously, or perceived by the brain synchronously or asynchronously. The stimuli orchestration component 1610 can apply the policy 1625 to available signaling components 1630a-n to determine the parameters to set for each signaling component 1630a-n for the synchronous or asynchronous transmission. The stimuli orchestration component 1610 can adjust parameters such as a time delay, phase offset, frequency, pulse rate interval, or amplitude to synchronize the signals.

[0587] In some embodiments, the NSOS 1605 can adjust or change the mode of stimulation, or a type of signal based on feedback received from a feedback component 1640a-n. The stimuli orchestration component 1610 can adjust the mode of stimulation or type of signal based on feedback on the subject, feedback on the environment, or a combination of feedback on the subject and the environment. Feedback on the subject can include, for example, physiological information, temperature, attention level, level of fatigue, activity (e.g., sitting, laying down, walking, biking, or driving), vision ability, hearing ability, side effects (e.g., pain, migraine, ringing in ear, or blindness), or frequency of neural oscillation at a region or portion of the brain (e.g., EEG probes). Feedback information on the environment can include, for example, ambient temperature, ambient light, ambient sound, battery information, or power source.

[0588] The stimuli orchestration component 1610 can determine to maintain or change an aspect of the stimulation treatment based on the feedback. For example, the stimuli orchestration component 1610 can determine that the neurons are not oscillating at the desired frequency in response to the first mode of stimulation. Responsive to determining that the neurons are not oscillating at the desired frequency, the stimuli orchestration component 1610 can disable the first mode of stimulation and enable a second mode of stimulation. The stimuli orchestration component 1610 can again determine (e.g., via feedback component 1640a) that the neurons are not oscillating at the desired frequency in response to the second mode of stimulation.

Responsive to determining that the neurons are still not oscillating at the desired frequency, the stimuli orchestration component 1610 can increase an amplitude of the signal corresponding to the second mode of stimulation. The stimuli orchestration component 1610 can determine that the neurons are oscillating at the desired frequency in response to increasing the amplitude of a signal corresponding to the second mode of stimulation.

[0589] The stimuli orchestration component 1610 can monitor the frequency of neural oscillations at a region or portion of the brain. The stimuli orchestration component 1610 can determine that neurons in a first region of the brain are oscillating at the desired frequency, whereas neurons in a second region of the brain are not oscillating at the desired frequency. The stimuli orchestration component 1610 can perform a lookup in the profile data structure 1620 to determine a mode of stimulation or type of signal that maps to the second region of the brain. The stimuli orchestration component 1610 can compare the results of the lookup with the currently enabled mode of stimulation to determine that a third mode of stimulation is more likely to cause the neurons in the second region of the brain to oscillate at the desired frequency. Responsive to the determination, the stimuli orchestration component 1610 can identify a signaling component 1630a-n configured to generate and transmit signals corresponding to the selected third mode of stimulation, and instruct or cause the identified signaling component 1630a-n to transmit the signals.

[0590] In some embodiments, the stimuli orchestration component 1610 can determine, based on feedback information, that a mode of stimulation is likely to affect the frequency of neural oscillation, or unlikely to affect the frequency of neural oscillation. The stimuli orchestration component 1610 can select a mode of stimulation from a plurality of modes of stimulation that is most likely to affect the frequency of neural stimulation or result in a desired frequency of neural oscillation. If the stimuli orchestration component 1610 determines, based on the feedback information, that a mode of stimulation is unlikely to affect the frequency of neural oscillation, the stimuli orchestration component 1610 can disable the mode of stimulation for a predetermined duration or until the feedback information indicates that the mode of stimulation would be effective.

[0591] The stimuli orchestration component 1610 can select one or more modes of stimulation to conserve resources or minimize resource utilization. For example, the stimuli orchestration component 1610 can select one or more modes of stimulation to reduce or minimize power consumption if the power source is a battery or if the battery level is low. In another example, the stimuli orchestration component 1610 can select one or more modes of stimulation to reduce heat generation if the ambient temperature is above a threshold or the temperature of the subject is above a threshold. In another example, the stimuli orchestration component 1610 can select one

or more modes of stimulation to increase the level of attention if the stimuli orchestration component 1610 determines that the subject is not focusing on the stimulation (e.g., based on eye tracking or an undesired frequency of neural oscillations).

i. Neural Stimulation with an NSS via Visual Stimulation and Auditory Stimulation

[0592] FIG. 17A is a block diagram depicting an embodiment of a system for neural stimulation via visual stimulation and auditory stimulation. The system 1700 can include the NSOS 1605. The NSOS 1605 can interface with the visual NSS 105 and the auditory NSS 905. The visual NSS 105 can interface or communicate with the visual signaling component 150, filtering component 155, and feedback component 160. The auditory NSS 905 can interface or communicate with the audio signaling component 950, filtering component 955, and feedback component 960.

[0593] To provide neural stimulation via visual stimulation and auditory stimulation, the NSOS 1605 can identify the types of available components for the neural stimulation session. The NSOS 1605 can identify the types of visual signals the visual signaling component 150 is configured to generate. The NSOS 1605 can also identify the type of audio signals the audio signaling component 950 is configured to generate. The NSOS 1605 can be configured about the types of visual signals and audio signals the components 150 and 950 are configured to generate. The NSOS 1605 can ping the components 150 and 950 for information about the components 150 and 950. The NSOS 1605 can query the components, send an SNMP request, broadcast a query, or otherwise determine information about the available visual signaling component 150 and audio signaling component 950.

[0594] For example, the NSOS 1605 can determine that the following components are available for neural stimulation: the visual signaling component 150 includes the virtual reality headset 401 depicted in FIG. 4C; the audio signaling component 950 includes the speaker 1205 depicted in FIG. 12B; the feedback component 160 includes an ambient light sensor 605, an eye tracker 605 and an EEG probe depicted in FIG. 4C; the feedback component 960 includes a microphone 1210 and feedback sensor 1225 depicted in FIG. 12B; and the filtering component 955 includes a noise cancellation component 1215. The NSOS 1605 can further determine an absence of filtering component 155 communicatively coupled to the visual NSS 105. The NSOS 1605 can determine the presence (available or online) or absence (offline) of components via visual NSS 105 or auditory NSS 905. The NSOS 1605 can further obtain identifiers for each of the available or online components.

[0595] The NSOS 1605 can perform a lookup in the profile data structure 1620 using an identifier of the subject to identify one more types of visual signals and audio signals to provide to the subject. The NSOS 1605 can perform a lookup in the profile data structure 1620 using identifiers for the subject and each of the online components to identify one more types of visual signals and audio signals to provide to the subject. The NSOS 1605 can perform a lookup up in the policy data structure 1625 using an identifier of the subject to obtain a policy for the subject. The NSOS 1605 can perform a lookup in the policy data structure 1625 using identifiers for the subject and each of the online components to identify a policy for the types of visual signals and audio signals to provide to the subject.

[0596] FIG. 17B is a diagram depicting waveforms used for neural stimulation via visual stimulation and auditory stimulation in accordance with an embodiment. **FIG. 17B** illustrates example sequences or a set of sequences 1701 that the stimuli orchestration component 1610 can generate or cause to be generated by one or more visual signaling components 150 or audio signal components 950. The stimuli orchestration component 1610 can retrieve the sequences from a data structure stored in data repository 1615 of NSOS 1605, or a data repository corresponding to NSS 105 or NSS 905. The sequences can be stored in a table format, such as Table 1 below. In some embodiments, the NSOS 1605 can select predetermined sequences to generate a set of sequences for a treatment session or time period, such as the set of sequences in Table 1. In some embodiments, the NSOS 1605 can obtain a predetermined or preconfigured set of sequences. In some embodiments, the NSOS 1605 can construct or generate the set of sequences or each sequence based on information obtained from the subject assessment module 1650. In some embodiments, the NSOS 1605 can remove or delete sequences from the set of sequences based on feedback, such as adverse side effects. The NSOS 1605, via subject assessment module 1650, can include sequences that are more likely to stimulate neurons in a predetermined region of the brain to oscillate at a desired frequency.

[0597] The NSOS 1605 can determine, based on the profile information, policy, and available components, to use the following sequences illustrated in example Table 1 provide neural stimulation using both visual signals and auditory signals.

[0598] Table 1. Audio and Video Stimulation Sequences

Sequence Identifier	Mode	Signal Type	Signal Parameter	Stimulation Frequency	Timing Schedule
1755	visual	light pulses from a laser light source	Color: red; Intensity: low; PW: 230a	40 Hz	{t0:t8)

1760	visual	checkerboard pattern image from a tablet display screen light source	color: black/white; intensity: high; PW:230a	40 Hz	{t1:t4}
1765	visual	modulated ambient light by a frame with actuated shutters	PW: 230c/230a;	40 Hz	{t2:t6}
1770	audio	music from headphones or speakers connected to an audio player	amplitude variation from M_a to M_c ; PW: 1030a	40 Hz	{t3:t5}
1775	audio	acoustic or audio bursts provided by headphones or speakers	PW: 1030a; frequency variation from M_c to M_o ;	39.8 Hz	{t4:t7}
1780	audio	air pressure generated by a cochlear air jet	PW: 1030a; pressure varies from M_c to M_a	40 Hz	{t6:t8}

[0599] As illustrated in Table 1, each waveform sequence can include one or more characteristics, such as a sequence identifier, a mode, a signal type, one or more signal parameters, a modulation or stimulation frequency, and a timing schedule. As illustrated in **FIG. 17B** and Table 1, the sequence identifiers are 1755, 1760, 1765, 1765, 1770, 1775, and 1760.

[0600] The stimuli orchestration component 1610 can receive the characteristics of each sequence. The stimuli orchestration component 1610 can transmit, configure, load, instruct or otherwise provide the sequence characteristics to a signaling component 1630a-n. In some embodiments, the stimuli orchestration component 1610 can provide the sequence characteristics to the visual NSS 105 or the auditory NSS 905, while in some cases the stimuli orchestration component 1610 can directly provide the sequence characteristics to the visual signaling component 150 or audio signaling component 950.

[0601] The NSOS 1605 can determine, from the Table 1 data structure, that the mode of stimulation for sequences 1755, 1760 and 1765 is visual by parsing the table and identifying the mode. The NSOS 1605, responsive to determine the mode is visual, can provide the information

or characteristics associated with sequences 1755, 1760 and 1765 to the visual NSS 105. The NSS 105 (e.g., via the light generation module 110) can parse the sequence characteristics and then instruct the visual signaling component 150 to generate and transmit the corresponding visual signals. In some embodiments, the NSOS 1605 can directly instruct the visual signaling component 150 to generate and transmit visual signals corresponding to sequences 1755, 1760 and 1765.

[0602] The NSOS 1605 can determine, from the Table 1 data structure, that the mode of stimulation for sequences 1770, 1775 and 1780 is audio by parsing the table and identifying the mode. The NSOS 1605, responsive to determine the mode is audio, can provide the information or characteristics associated with sequences 1770, 1775 and 1780 to the auditory NSS 905. The NSS 905 (e.g., via the light generation module 110) can parse the sequence characteristics and then instruct the audio signaling component 950 to generate and transmit the corresponding audio signals. In some embodiments, the NSOS 1605 can directly instruct the visual signaling component 150 to generate and transmit visual signals corresponding to sequences 1770, 1775 and 1780.

[0603] For example, the first sequence 1755 can include a visual signal. The signal type can include light pulses 235 generated by a light source 305 that includes a laser. The light pulses can include light waves having a wavelength corresponding to the color red in the visible spectrum. The intensity of the light can be set to low. An intensity level of low can correspond to a low contrast ratio (e.g., relative to the level of ambient light) or a low absolute intensity. The pulse width for the light burst can correspond to pulsewidth 230a depicted in **FIG. 2C**. The stimulation frequency can be 40 Hz, or correspond to a pulse rate interval (“PRI”) of 0.025 seconds. The first sequence 1655 can run from t0 to t8. The first sequence 1655 can run for the duration of the session or treatment. The first sequence 1655 can run while one or more other sequences are other running. The time intervals can refer to absolute times, time periods, number of cycles, or other event. The time interval from t0 to t8 can be, for example, 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 7 minutes, 10 minutes, 12 minutes, 15 minutes, 20 minutes or more or less. The time interval can be cut short or terminated by the subject or responsive to feedback information. The time intervals can be adjusted based on profile information or by the subject via an input device.

[0604] The second sequence 1760 can be another visual signal that begins at t1 and ends at t4. The second sequence 1760 can include a signal type of a checkerboard image pattern that is provided by a display screen of a tablet. The signal parameters can include the colors black and white such that the checkerboard alternates black and white squares. The intensity can be high, which can correspond to a high contrast ratio relative to ambient light; or there can be a high

contrast between the objects in the checkerboard pattern. The pulse width for the checkerboard pattern can be the same as the pulse width 230a as in sequence 1755. Sequence 1760 can begin and end at a different time than sequence 1755. For example, sequence 1760 can begin at t₁, which can be offset from t₀ by 5 seconds, 10 seconds, 15 seconds, 20 seconds, 20 seconds, 30 seconds, 1 minute, 2 minutes, 3 minutes, or more or less. The visual signaling component 150 can initiate the second sequence 1760 at t₁, and terminate the second sequence at t₄. Thus, the second sequence 1760 can overlap with the first sequence 1755.

[0605] While pulse trains or sequences 1755 and 1760 can overlap with one another, the pulses 235 of the second sequence 1760 may not overlap with the pulses 235 of the first sequence 1755. For example, the pulses 235 of the second sequence 1760 can be offset from the pulses 235 of the first sequence 1755 such that they are non-overlapping.

[0606] The third sequence 1765 can include a visual signal. The signal type can include ambient light that is modulated by actuated shutters configured on frames (e.g., frames 400 depicted in **FIG. 4B**). The pulse width can vary from 230c to 230a in the third sequence 1765. The stimulation frequency can still be 40 Hz, such that the PRI is the same as the PRI in sequence 1760 and 1755. The pulses 235 of the third sequence 1765 can at least partially overlap with the pulses 235 of sequence 1755, but may not overlap with the pulses 235 of the sequence 1760. Further, the pulse 235 can refer to block ambient light or allowing ambient light to be perceived by the eyes. In some embodiments, pulse 235 can correspond to blocking ambient light, in which case the laser light pulses 1755 may appear to have a higher contrast ratio. In some cases, the pulses 235 of sequence 1765 can correspond to allowing ambient light to enter the eyes, in which case the contrast ratio for pulses 235 of sequence 1755 may be lower, which may mitigate adverse side effects.

[0607] The fourth sequence 1770 can include an auditory stimulation mode. The fourth sequence 1770 can include upchirp pulses 1035. The audio pulses can be provided via headphones or speakers 1205 of **FIG. 12B**. For example, the pulses 1035 can correspond to modulating music played by an audio player 1220 as depicted in **FIG. 12B**. The modulation can range from Ma to Mc. The modulation can refer to modulating the amplitude of the music. The amplitude can refer to the volume. Thus, the NSOS 1605 can instruct the audio signaling component 950 to increase the volume from a volume level Ma to a volume level Mc during a duration PW 1030a, and then return the volume to a baseline level or muted level in between pulses 1035. The PRI 240 can be .025, or correspond to a 40 Hz stimulation frequency. The NSOS 1605 can instruct the fourth sequence 1770 to begin at t₃, which overlaps with visual stimulation sequences 1755, 1760 and 1765.

[0608] The fifth sequence 1775 can include another audio stimulation mode. The fifth sequence 1775 can include acoustic bursts. The acoustic bursts can be provided by the headphones or speakers 1205 of **FIG. 12B**. The sequence 1775 can include pulses 1035. The pulses 1035 can vary from one pulse to another pulse in the sequence. The fifth waveform 1775 can be configured to re-focus the subject to increase the subject's attention level to the neural stimulation. The fifth sequence 1775 can increase the subject's attention level by varying parameters of the signal from one pulse to the other pulse. The fifth sequence 1775 can vary the frequency from one pulse to the other pulse. For example, the first pulse 1035 in sequence 1775 can have a higher frequency than the previous sequences. The second pulse can be an upchirp pulse having a frequency that increases from a low frequency to a high frequency. The third pulse can be a sharper upchirp pulse that has frequency that increases from an even lower frequency to the same high frequency. The fifth pulse can have a low stable frequency. The sixth pulse can be a downchirp pulse going from a high frequency to the lowest frequency. The seventh pulse can be a high frequency pulse with a small pulsewidth. The fifth sequence 1775 can begin at t4 and end at t7. The fifth sequence can overlap with sequence 1755; and partially overlap with sequence 1765 and 1770. The fifth sequence may not overlap with sequence 1760. The stimulation frequency can be 39.8 Hz.

[0609] The sixth sequence 1780 can include an audio stimulation mode. The signal type can include pressure or air provided by an air jet. The sixth sequence can begin at t6 and end at t8. The sixth sequence 1780 can overlap with sequence 1755, and partially overlap with sequences 1765 and 1775. The sixth sequence 1780 can end the neural stimulation session along with the first sequence 1755. The air jet can provide pulses 1035 with pressure ranging from a high pressure M_c to a low pressure M_a . The pulse width can be 1030a, and the stimulation frequency can be 40 Hz.

[0610] The NSOS 1605 can adjust, change, or otherwise modify sequences or pulses based on feedback. In some embodiments, the NSOS 1605 can determine, based on the profile information, policy, and available components, to provide neural stimulation using both visual signals and auditory signals. The NSOS 1605 can determine to synchronize the transmit time of the first visual pulse train and the first audio pulse train. The NSOS 1605 can transmit the first visual pulse train and the first audio pulse train for a first duration (e.g., 1 minute, 2 minutes, or 3 minutes). At the end of the first duration, the NSOS 1605 can ping an EEG probe to determine a frequency of neural oscillation in a region of the brain. If the frequency of oscillation is not at the desired frequency of oscillation, the NSOS 1605 can select a sequence out of order or change the timing schedule of a sequence.

[0611] For example, the NSOS 1605 can ping a feedback sensor at t1. The NSOS 1605 can determine, at t1, that neurons of the primary visual cortex are oscillating at the desired frequency. Thus, the NSOS 1605 can determine to forego transmitting sequences 1760 and 1765 because neurons of the primary visual cortex are already oscillating at the desired frequency. The NSOS 1605 can determine to disable sequences 1760 and 1765. The NSOS 1605, responsive to the feedback information, can disable the sequences 1760 and 1765. The NSOS 1605, responsive to the feedback information, can modify a flag in the data structure corresponding to Table 1 to indicate that the sequences 1760 and 1765 are disabled.

[0612] The NSOS 1605 can receive feedback information at t2. At t2, the NSOS 1605 can determine that the frequency of neural oscillation in the primary visual cortex is different from the desired frequency. Responsive to determining the difference, the NSOS 1605 can enable or re-enable sequence 1765 in order to stimulate the neurons in the primary visual cortex such that the neurons can oscillate at the desired frequency.

[0613] Similarly, the NSOS 1605 can enable or disable audio stimulation sequences 1770, 1775 and 1780 based on feedback related to the auditory cortex. In some cases, the NSOS 1605 can determine to disable all audio stimulation sequences if the visual sequence 1755 is successfully affecting the frequency of neural oscillations in the brain at each time period t1, t2, t3, t4, t5, t6, t7, and t8. In some cases, the NSOS 1605 can determine that the subject is not paying attention at t4, and go from only enabling visual sequence 1755 directly to enabling audio sequence 1755 to re-focus the user using a different stimulation mode.

[0614] FIG. 18 is a flow diagram of a method for neural stimulation via visual stimulation and auditory stimulation in accordance with an embodiment. The method 180 can be performed by one or more system, component, module or element depicted in FIGS. 1-17B, including, for example, a neural stimulation orchestration component or neural stimulations system. In brief overview, the NSOS can identify multiple modes of signals to provide at block 1805. At block 1810, the NSOS can generate and transmit the identified signals corresponding to the multiple modes. At 1815 the NSOS can receive or determine feedback associated with neural activity, physiological activity, environmental parameters, or device parameters. At 1820 the NSOS can manage, control, or adjust the one or more signals based on the feedback.

[0615] While this specification contains many specific implementation details, these should not be construed as limitations on the scope of any inventions or of what can be claimed, but rather as descriptions of features specific to particular embodiments of particular aspects. Certain features described in this specification in the context of separate embodiments can also be implemented in combination in a single embodiment. Conversely, various features described in the context of a single embodiment can also be implemented in multiple embodiments separately

or in any suitable subcombination. Moreover, although features can be described above as acting in certain combinations and even initially claimed as such, one or more features from a claimed combination can in some cases be excised from the combination, and the claimed combination can be directed to a subcombination or variation of a subcombination.

[0616] Similarly, while operations are depicted in the drawings in a particular order, this should not be understood as requiring that such operations be performed in the particular order shown or in sequential order, or that all illustrated operations be performed, to achieve desirable results. In certain circumstances, multitasking and parallel processing can be advantageous. Moreover, the separation of various system components in the embodiments described above should not be understood as requiring such separation in all embodiments, and it should be understood that the described program components and systems can generally be integrated in a single software product or packaged into multiple software products.

[0617] References to “or” can be construed as inclusive so that any terms described using “or” can indicate any of a single, more than one, and all of the described terms. References to at least one of a conjunctive list of terms can be construed as an inclusive OR to indicate any of a single, more than one, and all of the described terms. For example, a reference to “at least one of ‘A’ and ‘B’” can include only ‘A’, only ‘B’, as well as both ‘A’ and ‘B’.

[0618] Thus, particular exemplary embodiments of the subject matter have been described. In some cases, the actions recited in the claims can be performed in a different order and still achieve desirable results. In addition, the processes depicted in the accompanying figures do not necessarily require the particular order shown, or sequential order, to achieve desirable results.

[0619] The present technology, including the systems, methods, devices, components, modules, elements or functionality described or illustrated in, or in association with, the figures can treat, prevent, protect against or otherwise affect brain atrophy and disorders, conditions and diseases associated with brain atrophy.

G. Methods of Neural Stimulation with an NSS via Sleep-Related Monitoring

Modules

[0620] In some embodiments, a portable system or single headset comprising an NSS is configured with a sleep-related monitoring module, wherein the NSS comprises the sleep-related monitoring module.

[0621] **FIG. 33** provides a neural stimulation system comprising a stimulus delivery system coupled to an analysis and monitoring system. In some embodiments, the present technological solution comprises a stimulus delivery system which includes one or more of: one or more Audio Stimulus Module (110), one or more Visual Stimulus Module (120). These modules can be in

addition to tactile or other stimulus modules (not shown). These modules provide the delivery of audio or visual stimulus at specific parameter values. In some embodiments the values of these parameters are responsive to one or more of: one or more Audio Monitoring Module (111), one or more Visual Monitoring Module (121).

[0622] In some embodiments, the present technological solution includes one or more of: one or more Feedback Module (150) collecting, storing, or processing feedback from users or third parties; one or more Profile Module (161) storing and processing profile or demographic information related to one or more users or third parties, or of populations of users or third parties; one or more History Module (162) storing or processing history and logs related to one or more users or third parties, or of populations of users or third parties; one or more Monitoring Module (163), collecting, storing, logging, and/or analysing aspects of one or more users or third parties, including but not limited to: aspects of the environment, state, behavior, input, responses, diagnosis, disease progression, compliance, engagement, mood, adherence. In some embodiments the present technological solution includes one or more Brain Wave Monitoring Module (190) measuring and analysing brain wave activity in one or more users, including but not limited to detecting and characterizing gamma wave power and gamma entrainment.

[0623] In some embodiments, the present technological solution includes one or more of: one or more Actigraphy Monitoring Module (130), one or more Sleep Analysis Module (140). In some embodiments, one or more Sleep Analysis Module is responsive, at least in part, to information communicated from one or more Actigraphy Monitoring Module. In some embodiments, a Sleep Analysis Module performs sleep analysis based at least in part on actigraphy information collected at least in part by an Actigraphy Monitoring Module. In some embodiments, Sleep Analysis Module performs one or more analysis steps described in FIG 37.

[0624] In some embodiments, one or more of an Audio Stimulus Module, a Visual Stimulus Module, and/or a Stimulus Delivery System (170) managing or incorporating one or more stimulus modules, can be responsive to one or more of: one or more Analysis and Monitoring System (130) and/or monitoring modules, including but not limited to: one or more Feedback Module (150), one or more Profile Module (161), one or more History Module (162), one or more Monitoring Module (163), one or more Sleep Analysis Module (140), one or more Actigraphy Monitoring Module (130), one or more Brain Wave Monitoring Module (190), and/or one or more Stimulus Delivery System (170) managing or incorporating one or more analysis and monitoring module.

III. Combination Therapies

[0625] In one aspect, the present disclosure provides combination therapies comprising the administration of one or more additional therapeutic regimens in conjunction with methods described herein. In some embodiments, the additional therapeutic regimens are directed to the treatment or prevention of the disease or disorder targeted by methods of the present technology.

[0626] In some embodiments, the additional therapeutic regimens comprise administration of one or more pharmacological agents that are used to treat or prevent disorders targeted by methods of the present technology. In some embodiments, methods of the present technology facilitate the use of lower doses of pharmacological agents to treat or prevent targeted disorders.

[0627] In some embodiments, the additional therapeutic regimens comprise non-pharmacological therapies that are used to treat or prevent disorders targeted by methods of the present technology such as, but not limited to, cognitive or physical therapeutic regimens.

[0628] In some embodiments, a pharmacological agent is administered in conjunction with therapeutic methods described herein. In some embodiments, the pharmacological agent is directed to inducing a relaxed state in a subject administered methods of the present technology. In some embodiments, the pharmacological agent is directed to inducing a heightened state of awareness in a subject administered methods of the present technology. In some embodiments, the pharmacological agent is directed to modulating neuronal and/or synaptic activity. In some embodiments, the agent promotes neuronal and/or synaptic activity. In some embodiments, the agent targets a cholinergic receptor. In some embodiments, the agent is a cholinergic receptor agonist. In some embodiments, the agent is acetylcholine or an acetylcholine derivative. In some embodiments, the agent is an acetylcholinesterase inhibitor.

[0629] In some embodiments, the agent inhibits neuronal and/or synaptic activity. In some embodiments, the agent is a cholinergic receptor antagonist. In some embodiments, the agent is an acetylcholine inhibitor or an acetylcholine derivative inhibitor. In some embodiments, the agent is acetylcholinesterase or an acetylcholinesterase derivative.

DEFINITIONS

[0630] As used herein, a “headband” is defined to mean any element of sufficient size and shape that adjoins an earphone that is situated on, positioned on, or secured to one ear of a user, around any portion or region of the user's head or neck (e.g., above-the-head, behind-the-head or behind-the-neck), to an earphone that is positioned on the opposite ear of the user. The headband can be a detachable headband. The detachable headband can have, for example, two first connecting elements in proximity to slits of the bodies of the headphones or earphones. The first and second connecting elements can have any suitable corresponding shapes that collectively create a mechanical connection fit between the elements, and which function to orient the headband and

earphones in a desired configuration with respect to each other. In particular, for example, it is suitable for all “female” connecting members to be situated on, or housed within, the first connecting elements of the headband and for all “female” connecting members to be situated on, or housed within, the second connecting members of the earphones. Alternatively, it is suitable for all “female” connecting members to be situated on, or housed within, the first connecting elements of the headphones and for all “male” connecting members to be situated on, or housed within, the second connecting members of the headband. Moreover, the first and second connecting elements can collectively form a snap-fit, a friction-fit, or a clamping, clasping or wrapping mechanism.

[0631] “Earphones” or “headphones” are used interchangeably, as discussed more fully below, are defined herein to mean any pair of earphones that can be placed on or near the ears of a user and which function to reproduce the sound of a digital or non-digital device (e.g., such as, for example, a portable music player (PMP) such as an iPOD™ digital storage device, a portable digital assistant (PDA), a digital camera, a telephone, a portable DVD player, an all-in-one device combining more than one functionality, or the like), either by wired communication or by wireless communication. The earphones can be any suitable size. As a nonlimiting example, the earphones can be any earphone that is designed to be worn in, on, or over the ear of a user. The earphones, in this regard, can be in the form of an ear clip, an ear bud, or any other form that can be securely positioned on or in the ear of a user, e.g., without the presence of structural components that extend or project substantially away from the ear. Portions of the earphones can partially cover, cover, or project into the ear canal of a user. Irrespective of the specific electronic hardware within the earphones for reproducing audio, the earphones preferably are positionable by a user to maximize comfort. The earphones, in this regard, can also be constructed of any suitable material(s), such as, for example, metal (e.g., a malleable metal, such as malleable stainless steel), plastic, fibrous, polymers, rubber, foam, fabric, or the like. The earphones can be wireless transmitter/receiver devices, so that the earphones can wirelessly communicate with each other and/or with other wireless devices (such as, Bluetooth™-enabled devices). In another embodiment, the earphones share a wired electric source, but collectively communicate wirelessly with other wireless devices.

[0632] “Ear buds” are defined to mean any earphones that can be substantially secured, secured, held, positioned, or inserted within (or at least partially within) either the concha or ear canal of the ear of a user.

EXAMPLES

Example 1. Human Clinical Study of Safety, Efficacy, and Results of Treatment

METHODS AND STUDY DESIGN

[0633] Examples demonstrating the use of systems promoting synchronized gamma oscillations in at least one brain region of a subject are described herein below.

[0634] A clinical study was performed to assess the safety, tolerability, and efficacy of long-term, daily use of gamma sensory stimulation therapy on cognition, functional ability, and biomarkers in a mild-to-moderate AD population via a prospective clinical study. The clinical study was a multi-center, randomized controlled trial evaluating daily gamma sensory stimulation received at home for a 6-month treatment period. Subjects included in the study were adults 50 years and older with a clinical diagnosis of mild to moderate AD (MMSE: 14-26, inclusive), a reliable care partner, and successful tolerance and entrainment screening via EEG. Key exclusion criteria included profound hearing or visual impairment, use of memantine, major psychiatric illness, clinically relevant history of seizure, or contraindication to imaging studies.

[0635] Study Participants and Design. A total of 135 patients were assessed for eligibility to participate in the study. Patients were first given a screening EEG, and then split into groups. One group was a sham control group that was not given treatment; the other was a group that was subjected to 1 hour of therapy, which involved subjecting the subject to audio and visual stimulation at a frequency of 40 Hz per day. Of those assessed for eligibility, 76 were randomized between the active treatment and sham control. Forty-seven of the randomized patients were allocated to the active group and 29 were allocated to the sham group. Of the active group, two patients withdrew prior to therapy and three had no post-baseline efficacy and were not included in the modified intent to treat (mITT) population. In sham group, one patient received active treatment and was not in the sham population. Completers included 33 patients in the active group and 28 in the sham group, with 10 early discontinuations in the active group. Seven of those discontinuations were due to consent withdraw and 23 were attributed to adverse events, whereas in the sham group, only six withdrew consent and one discontinued as a result of adverse events.

[0636] The study employed various clinical outcome assessment scales to assess cognitive decline or dysfunction. These included the Neuropsychiatric Inventory (NPI), Clinical Dementia Rating-Sum of Boxes (CDR-sb), the Clinical Dementia Rating-Global Score (CDR global), the Mini-Mental State Exam (MMSE), the Alzheimer's Disease Assessment Scale – Cognitive Subscale-14 (ADAS-Cog14), and a variation of the Alzheimer's Disease Composite Score (ADCOMS) as optimized for patients with mild or moderate Alzheimer's Disease. NPI examines 12 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities. The NPI can

be used to screen for multiple types of dementia, and it involves giving the caregiver of a subject the questions and then, based on the answers, rating the frequency of the symptoms, their severity, and the distress the symptoms cause on a three, four, and five-point scale, respectively.

[0637] CDR global is calculated based on testing performed for six different cognitive and behavioral domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care. To test these areas, an informant is given a set of questions about a subject's memory problem, judgment and problem-solving ability of the subject, community affairs of the subject, home life and hobbies of the subject, and personal questions related to the subject. The subject is given another set of questions that includes memory-related questions, orientation-related questions, and questions about judgment and problem-solving ability. The CDR global score is calculated based on the results of those questions, and it is measured using a scale of 0 to 3, with 0 representing no dementia, 0.5 indicating very mild dementia, 1 indicating mild dementia, 2 indicating moderate dementia/cognitive impairment, and 3 indicating severe dementia/cognitive impairment. CDR-sb is a clinical outcome assessment that looks at functional impact of cognitive impairment: memory, executive function, instrumental and basic activities of daily living and assesses them based on interviews with an informant and the patient. The CDR-sb score is based on assessment of items including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-sb is scored from 0 to 18, with higher scores representing greater severity of cognitive and functional impairment.

[0638] The MMSE looks at 11 items to assess memory, language, praxis and executive function based on a cognitive assessment of the patient. Items assessed include registration, recall, constructional praxis, attention and concentration, language, orientation time, and orientation place. The MMSE is scaled from 0 to 30, with higher scores representing lower severity of cognitive dysfunction. The ADAS-Cog14 assesses memory, language, praxis and executive function. The score is based on a cognitive assessment of the patient and assesses fourteen items: spoken language, maze, comprehension spoken language, remembering word recognition test instructions, ideational praxis, commands, naming, word finding difficulty, constructional praxis, orientation, digit cancellation, word recognition, word recall, and delayed recall. A score is based on points allocated to each item, and the maximum total score is 90, with higher numbers indicating greater severity of cognitive dysfunction. The Alzheimer's Disease Composite Score (ADCOMS) considers items from all of the above-discussed scores: items from Alzheimer's Disease Assessment Scale-cognitive subscale items, MMSE items, and all of the CDR-sb items. ADCOMS combines portions of the ADAS-cog, Clinical Dementia Rating (CDR) scale, and MMSE that have been shown to change the most over time in people who do not have functional

impairment yet. MADCOMS, which was used in the present example, optimizes the scale instead by combining items more significant for mild and moderate dementia.

[0639] The study design involved primary efficacy endpoints of MADCOMS, ADAS-cog14, and CDR-sb. Unlike ADCOMS, MADCOMS is optimized for patients with moderate or mild Alzheimer's Disease. These were optimized for AD-specific decline. A separate optimization was done for moderate and mild AD. Secondary efficacy endpoints consisted of ADCS-ADL, ADCOMS (adjusted), MMSE, CDR-global score and the Neuropsychiatric Inventory (NPI). Of the secondary endpoints, ADCS-ADL was measured monthly and MMSE was measured at the last time point.

[0640] The efficacy endpoints were analyzed by applying a linear model of analysis and/or a separate means model of analysis. The linear model of analysis involved employing a linear fit model to determine a value at T0 based on the difference from baseline in conditions at the end of the study. The separate means analysis employed estimates of mean values at each assess timepoint, which was either a monthly timepoint or at three and six months after treatment began, depending on the score that was being analyzed. In evaluating MADCOMS composite score, for example, the separate means analysis was applied using mean values that were estimated at three and six months. The linear model was applied by using the estimates of treatment difference at the end of the study and connecting a straight line to 0. Similar models were used for the other efficacy endpoints. **FIGS. 20, 21, 22, 23, and 24** show the various linear and separate means models generated for these endpoints.

[0641] To assess biomarkers, researchers used MRI, volumetric analyses, EEG, Amyloid positron emission tomography (PET), actigraphy, and plasma biomarkers. The study employed structural MRIs, taken before any treatment began and at the end of the sixth months and assessed these for volume-base morphology. Volumetric changes for the hippocampus, lateral ventricles, whole cortex (cerebral cortical gray matter) and whole brain (cerebrum and cerebellum) were determined, and the rate of atrophy was compared for active and sham groups using a linear model, as demonstrated in **FIG. 25**. To analyze for safety and tolerability, researchers looked for adverse events and presence of amyloid related imaging abnormalities (ARIA) on MRI. Therapy adherence was also analyzed. Blinding effectiveness for subjects, care partners, and assessors were prospectively analyzed by assessing baseline and follow up ascertainment of whether the care partner, assessor, or patient thought the patient was on active or sham treatment.

ANALYSIS

[0642] For the MADCOMS composite scores, both means of analysis demonstrated 35% slowing in decline rate, indicating that the active group progressed less than the placebo arm over

the six-month study. When a linear and means analysis were both employed, the sham group was slightly favored, but non-significantly. When these two separate means analyses were applied to the ADAS-cog14 data, both slightly favored the sham group, although not in a statistically significant manner. When CDR-sb results were analyzed, the mean-estimate model found a 28% slowing rate, whereas the linear extraction showed a 26% slowing rate, but the comparisons were not statistically significant.

[0643] Of the secondary endpoints, ADCS-ADL was measured monthly and MMSE was measured at the last time point. When analyzing ADCS-ADL values, the first analysis model employed used estimates for each month and showed 84% slowing over the 6-month time period. The linear fit model was again employed, and the same 84% slowing was found. When analyzing MMSE values, an 83% slowing was identified.

RESULTS

[0644] FIG. 19 and FIG. 26 summarize the efficacy findings of the study. Following informed consent and screening, a total of 76 subjects were randomized between the active treatment and sham control. The safety population for the study included 74 subjects who

received at least one treatment, and the modified intent to treat (mITT) population included a total of 70 subjects, 53 of whom completed the 6-month study, which form the basis for analysis of outcome measures.

[0645] Demographic and baseline characteristics

[0646] In terms of demographic and baseline characteristics of the mITT population, following randomization, the populations were balanced across gender, baseline MMSE, ApoE4 status, activities of daily living (ADL), and PET amyloid standardized uptake value ratio (SUVR) status; imbalances between the two groups were observed in age, ADAS-Cog11, and CDR-sb scores at baseline. Statistical models included covariates for age and MMSE at baseline.

[0647] Safety and tolerability

[0648] Gamma oscillation inducing waveform stimulus was safe and well-tolerated in the mild and moderate AD subjects. The active group had a lower rate of treatment emergent adverse events (TEAE) than the sham group (67% vs 79%).

[0649] Treatment related AEs (TRAEs) deemed definitely, probably, and possibly related to the therapy were elevated in the active group versus the sham group (41% vs 32%). One treatment related SAE was noted in the active group for a patient hospitalized for wandering while their care partner was located; this subject discontinued the study subsequently. Of the randomized subjects, withdraw rates were similar between both groups (active 28%, sham 29%) including withdraw rates due to an adverse event (active 7%, sham 7%). TEAEs that occurred more often

in the active group are tinnitus, delusions, broken bone. TEAEs that occurred more often in the sham group are upper respiratory infection, confusion, anxiety and dizziness.

[0650] Clinical assessments

[0651] Over the treatment period of 6-months, subjects were evaluated in-clinic and via phone visits for cognitive, functional, and biomarker changes on multiple measures.

[0652] The primary efficacy endpoints demonstrated effects favoring the active group on the MADCOMS (35% slowing; n.s.) and CDR-sb (27%; n.s.) and favoring the Sham group on the ADAS-cog14 (-15% slowing; n.s.). MADCOMS initially leaned in favor of active group, but the results were not statistically different. ADAS-cog14 was slightly in favor of the sham group but not statistically different. CDR-sb was also in favor of the active group, but the difference was not significant, as shown by the p-values that ranged between 0.39 and 0.7920.

[0653] Selected secondary endpoints demonstrated significant effects favoring the treatment (active) group. The active group had significant benefit on functional ability as measured by the ADCS-ADL ($p=0.0009$), which represented an 84% slowing of decline and a treatment difference of 7.59 points over the six-month duration of the trial (**FIG. 26**). The active group demonstrated significant benefit on the MMSE (ANCOVA $p=0.013$), which represented an 83% slowing in the rate of decline versus the Sham group and a treatment difference of 2.42 points.

[0654] Biomarker changes - MRI

[0655] Structural MR imaging was analyzed for volume-base morphometry using an automated image processing pipeline (Biospective, Montreal, Canada). Volumetric changes of the hippocampus, lateral ventricles, whole cortex (cerebral cortical gray matter) and whole brain (cerebrum and cerebellum, no cerebrospinal fluid (CSF)) for each subject were determined; no manual corrections were performed. No significant benefit on hippocampal volume was determined. Statistically-significant benefit favoring the active group ($p=0.0154$) on whole brain volume (WBV) was established, representing a 61% slowing compared to the Sham group progression. The treatment value for the active group was 9.34 cm³.

CONCLUSIONS

[0656] Gamma sensory stimulation was safe and well tolerated. Two of three primary efficacy outcomes (MADCOMS, CDR-sb) favored the active group but did not reach significance. Selected secondary endpoints demonstrated that active treatment with gamma sensory stimulation therapy led to significant benefits in the ability to perform activities of daily living via the ADCS-ADL and cognition via the MMSE, representing important treatment and management objectives for AD patients. Quantitative MR analysis demonstrated slowing of brain atrophy as measured by whole brain volume in the active group. The combined clinical and biomarker findings suggest beneficial effects of gamma sensory stimulation for AD subjects can

be facilitated via differentiated pathways. These surprising results indicates that the gamma sensory stimulation can be used to treat a range of diseases and disorders that cause or are caused by brain atrophy.

Example 2. Human Clinical Study to Determine Efficacy of NS Treatment for Sleep Abnormalities

METHODS

[0657] *Study Participants and Design.* Patients included in the present interim analysis were clinically diagnosed having mild to moderate AD and were under the care of their care neurologist. Inclusion criteria were age of 55 years or older, MMSE score 14-26 and participation of a caregiver, whereas exclusion criteria included profound hearing or visual impairment, seizure disorder, use of memantine, or implantable, non-MR compatible devices. Patients on therapy with an acetylcholine esterase inhibitor could enroll, but their dosing were maintained the same during the trial. Patients were randomized to receive either 40 Hz simultaneous auditory and visual sensory stimulation by a NS (treatment group; n=14) or placebo treatment (sham group; n=8).

[0658] *Neuromodulation System (NS).* In the present study, the system used for the neuromodulation provided gamma oscillation inducing waveform provided visual and audio stimulation to invoke gamma oscillations in a brain region, thereby improving sleep. Use of such a system is referred to herein as NS therapy or NS treatment. The system logs device usage and stimulation output settings for adherence monitoring. This information is uploaded to a secure cloud server for physician remote monitoring. The present experiment utilized a NS that included a handheld controller, an eye-set for visual stimulation, and headphones for auditory stimulation that work together to deliver precisely timed gamma oscillation inducing waveform stimulus to induce steady-state gamma brainwave activity. The visual stimulation generated by the NS consisted of precisely timed flashes of visible light from light emitting diodes, and the auditory stimulation consisted of short-duration clicks. The stimuli occurred at a pulse repetition frequency of 40 Hz. The on-off periods of the visual stimulation were perceivable by the patient but not disruptive; an individual remained aware of their surroundings and could converse with a care partner during use of the system. The customized stimulation output was determined and verified by a physician based on both patient-reported comfort information and on the patient's quantitative electroencephalography (EEG) response to the stimulation. The NS was then configured to the determined settings, and all subsequent use would be within this predefined operating range.

[0659] *Monitoring Sleep Fragmentation with Actigraphy and Signal Processing.* Effects of the NS therapy on sleep fragmentation were determined by continuous monitoring activity of AD patients with a wrist worn actigraphy watch (ActiGraph GT9X), and data was collected daily over a 6-month period. Collected data consisted of raw accelerometer readings in three orthogonal directions recorded at a 30Hz sampling frequency.

[0660] *Preprocessing the Data.* Accelerometer data from three orthogonal dimensions are filtered with a Butterworth bandpass (0.3-3.5Hz) filter. The magnitude of the bandpass filtered 3-d accelerometer vector was then down-sampled by a factor of 4. This process is done for all data collected from all patients over the six months period. Two representations of the data were made: (i) a binary representation and (ii) a smooth representation. For the binary representation, all data was pooled together and a histogram in the log scale was obtained. The resulting histogram had a bimodal distribution, one peak corresponding to higher changes in acceleration and hence high activity periods, and the second peak corresponding to lower changes in acceleration and hence rest periods. Taking the location of the minimum between the two peaks as a threshold, acceleration magnitudes higher than the threshold were represented by 1's and acceleration magnitudes smaller than the threshold were represented by 0's. For the smooth representation, a median filter with length of six hours was applied to the down-sampled data to get a smooth estimate of the activity levels.

[0661] *Extracting Nighttime (Sleep Segment).* Individual 24-h data segments were extracted from 12:00 pm midday on a given day to the next day 12:00 pm midday. The data was labeled with the binary representation for an initial estimate of the active - 1's and rest - 0's periods during the given 24-hour window. This window consisted of three segments: daytime (segment prior to sleep), nighttime (sleep segment) and daytime (segment after sleep). We proposed that the nighttime segment would consist of more 0's than 1's and daytime segments would consist of more 1's than 0's. Therefore, an ideal nighttime model was defined which was built with a function that takes a value 0 within continuous period of duration "L" centered at a time "T" with a value 1 outside this region. Given an initial estimate of L and T, the difference between the ideal nighttime model and the binary representation of movement was computed using a quadratic cost function. In this cost function each mismatch, occurring when the binary value is 1 during nighttime or 0 during daytime, contributes 1, and each match, occurring when the binary value is 0 during nighttime and 1 during daytime, contributes 0. The initial estimate for T was taken to be the time point corresponding to the minimum of the smooth representation mentioned above. Initial estimate for L is set to eight hours. Cost function was minimized using unconstrained nonlinear optimization. This led to the best model estimate for L, the nighttime length, and T, the nighttime mid-point, and allowed us to locate the borders for the three

segments (daytime, nighttime, daytime) from the 24-hour window. We then extracted the nighttime segment to evaluate the micro-changes within.

[0662] *Identification of Rest and Active Durations During Nighttime and Relating Them to Sleep.*

Within the nighttime segments, periods with all 0's is attributable to lack of movement and periods with all 1's is attributable to movement. However, mapping these periods directly to sleep fragmentation faces the problem that the durations of these periods can range from milliseconds to hours in actigraphy data, whereas analysis of sleep is carried out by classifying non-overlapping epochs of 30 second duration into awake and asleep. To link our actigraphy analysis to the analysis time-scales used in sleep studies, all segments of length N were taken and replaced the values in those segments by the median value over a window of 3N duration centered on the segment. While N=30 s was chosen, it was found that the results were not sensitive to this exact choice. After repeating this process for all short segments, consecutive time points in the nighttime segments corresponding to 0's were identified as rest durations and those corresponding to 1's were identified as active durations.

[0663] *Determining the Distributions of Rest and Active Durations.* Rest duration across all participants were pooled and the quantity $t \equiv \int p(w)dw$, where $p(w)$ is the probability density function of rest durations between w and $w+dw$, was examined. $P(t)$ represents the fraction of rest durations that are greater than length t and is referred to as the cumulative distribution function. Similarly, the cumulative distribution of the active durations was also calculated, and distributions of both rest and active durations are displayed in **FIG. 39**.

[0664] *Assessment of Functional Ability.* Activities of daily living were also assessed at baseline and regular monthly intervals during the 24-week treatment period in the same study population of actigraphy recordings using the clinically established ADCS-ADL scale (Galasko, D., D. Bennett, M. Sano, C. Ernesto, R. Thomas, M. Grundman and S. Ferris (1997). "An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study." *Alzheimer Dis Assoc Disord* 11 Suppl 2: S33-39. The ADCS-ADL assesses the competence of AD patients in basic and instrumental activities of daily living. The assessments were by a caregiver in questionnaire format or administered by a healthcare professional as a structured interview with the caregiver. The six basic ADL items cover everyday activities, such as eating, personal grooming or dressing, also providing information on level of competence. The 16 instrumental ADL items ask the level of patient's engagement with basic instruments, such as a phone or kitchen appliances. ADCS-ADL has been a critical instrument to standardize assessment in AD clinical trials and is used widely as a functional outcome measures in disease modifying trials.

[0665] Assessment of Cognitive Function. Subject cognitive function was assessed by the Mini-Mental State Exam (MMSE), which is a widely used instrument of cognitive function in AD patients, it tests patients' orientation, attention, memory, language, and visual-spatial skills.

[0666] Statistics. All statistical comparisons were done using Kolmogorov-Smirnov test.

RESULTS

[0667] This interim analysis reports results on 22 mild-to-moderate AD subjects who successfully completed the 6-month study. Demographic and clinical characteristics of all patients during the initial assessment are shown in Table 3.

[0668] Table 3: Demographic and Clinical Characteristics of all Patients During the Initial Assessment

Characteristic	Treatment Group (N=14)	Sham Group (N=8)
Demographics		
Age in years, mean $\pm$ sd	66.5 $\pm$ 8.0	73.5 $\pm$ 6.6
Gender, no (%)		
Female	10 (71)	5 (63)
Male	4 (29)	3 (37)
Race and Ethnicity, no (%)		
White	14 (100)	8 (100)
Hispanic or Latino	1 (7)	0 (0)
APOE- ϵ 4 Allele Status, no (%)		
0 copies	5 (36)	3 (37.5)
1 copy	8 (57)	4 (50)
2 copies	1 (7)	1 (12.5)
Cognitive Assessment		
MMSE score [†] , mean $\pm$ sd	19.9 $\pm$ 2.8	18.5 $\pm$ 2.7
Functional Assessment		
ADCS-ADL scores, mean $\pm$ sd	61.7 $\pm$ 9.2	65.0 $\pm$ 10.4

[†]Mini-Mental State Examination (MMSE) scores range between 0-30, higher scores indicating better cognitive performance.

[‡]Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scores range between 0-78, higher scores indicating better functioning.

[0669] Data on Safety & Adherence

[0670] *Sleep Evaluated by Continuous Actigraphy Recordings.* Outcomes from the NS treatment on sleep were revealed from continually recorded actigraphy data and constructing a nighttime

sleep model, which allowed to assess the durations of rest and active periods during sleep. Results from this analysis of a single patient are shown in **FIG. 38**. **FIG. 38** demonstrate nighttime active and rest periods; the level of continuous activity is determined and indicated by the black tracing. Furthermore, intervals were identified as sleep for each night (represented by horizontal light gray bars), and the longest movement periods are indicated by the dark gray bars. All rest and active durations identified by actigraphy data processing were pulled and analyzed from each participant as described in Methods section, and the results were compared to published data of rest and active periods obtained by polysomnography-based sleep analysis. As evidenced by straight-line fits on a log-linear scale, the rest durations follow an exponential distribution, $e^{(-t/\tau)}$ with $\tau=10.15$ min. In contrast, active durations follow power law distribution (straight-line fit on a log-log scale), $t^{(-\alpha)}$ with $\alpha=1.67$ (**FIG. 39**). As demonstrated by **FIG. 39**, the cumulative distributions for pooled, nighttime, rest (gray) and active (black) durations show exponential and power law distributions, respectively. The X axis of **FIG. 39** shows the nighttime durations. The Y axes show the cumulative distributions obtained from 14736 hours of data from 23 patients and the solid lines show the best straight-line fits. Such exponential and power law behaviors have been observed in sleep studies of healthy subjects (Lo, C. C., N. A. L.A., S. Havlin, P. C. Ivanov, T. Penzel, J. H. Peter and H. E. Stanley (2002). "Dynamics of Sleep-Wake Transitions During Sleep." *Europhys. Lett.* 57(5): 625-631; Lo, C. C., T. Chou, T. Penzel, T. E. Scammell, R. E. Strecker, H.-E. Stanley and P. C. Ivanov (2004). "Common scale-invariant patterns of sleep-wake transitions across mammalian species." *PNAS* 101(50): 17545-17548; Lo, C. C., R. P. Bartsch and P. C. Ivanov (2013). "Asymmetry and Basic Pathways in Sleep-Stage Transitions." *Europhys Lett* 102(1): 10008.). These authors analyzed nighttime sleep and awake states as obtained from polysomnographic recordings of healthy subjects and found that cumulative distribution of sleep state durations is characterized by an exponential distribution whereas those of awake state durations were characterized with a power law distribution. Thus, the exponential decay constant as $\tau=10.9$ min for light sleep, $\tau=12.3$ min for deep sleep, $\tau=9.9$ min for REM sleep durations and the power law exponent as $\alpha=1.1$ for awake durations were reported (Lo, Bartsch et al. 2013). It was found that the nighttime rest and active durations, estimated from actigraphy recordings of Alzheimer's disease patients show the same behavior as polysomnographic recordings of healthy subjects. Similarities in the form of the distributions between the results of the experiments described herein and previous work suggest that nighttime rest and active durations as assessed by actigraphy are analogous to sleep and awake states as assessed by polysomnography and that the effect of therapy on sleep can be indirectly assessed through its effect on active and rest durations.

[0671] *Effects of NS Treatment on Sleep Quality Determined by Continuous Actigraphy*

Recordings. Effects of NS treatment on sleep were determined by comparing the distribution of the length of nighttime uninterrupted rest durations in the first and the second 12-week periods of the study (**FIG. 40**). Only subjects who wore the actigraphy device for at least six weeks during both the first and last 12-week period were used for assessing efficacy of NS treatment on sleep (N=7 Treatment, N=6 Sham). To avoid subjects with more data dominating comparisons across periods, the first six weeks of available data closest to the study start and the last six weeks closest to the study end were considered for each subject. Actigraphy recordings from a single patient in the treatment group are shown in **FIG. 38**, displaying during 5 subsequent nights prior and during treatment period. The X-axis of **FIG. 38** shows the time of day, and the Y-axis shows the activity level (in log scale). The black tracings represent the continuous activity levels, and the light gray horizontal bars represent the intervals identified as sleep in each night. The dark gray horizontal bars represent the longest movement periods within each night. The letters A through E correspond to five consecutive nights prior to treatment. The imposed curve shows a smooth (median filtered) activity level, with long movement intervals observed. Letters F through J correspond to five consecutive nights during treatment period. The imposed curve shows a smooth (median filtered) activity level. Compared to the pre-treatment period, patient showed fewer and shorter movement periods during treatment. In overall, nighttime active durations were significantly ($p<0.03$) reduced in the treatment group, whereas active durations were significantly ($p<0.03$) increased in patients of the sham group. Comparison of between treatment and sham groups were also done using normalized nighttime active durations. This normalization is done by dividing each active duration by the duration of the corresponding nighttime period. This measure eliminates potential variation in length of total sleep duration impacting numbers or durations of active periods. This analysis further confirmed opposite changes in nighttime active durations between treatment and sham groups. Changes in normalized active periods between the first and second 12-weeks period showed a significant ($p<0.001$) reduction in patients of the treatment group, in contrast to a significant increase ($p<0.001$) in patients of the sham group (**FIG. 40**). These findings demonstrate a reduction in nighttime active durations in response to NS treatment, leading to reduction in sleep fragmentation and improvement in sleep quality, while the opposite can be assessed in the sham group.

[0672] *Effects of NS Treatment on Sleep Quality Determined by Continuous Actigraphy*

Recordings. MMSE changes were different in the treatment (n=13) and sham (n=8) groups. Initial assessment showed an MMSE value of 19.9 ± 2.9 , which did not change significantly during the duration of the treatment, showing an MMSE value of 19.3 ± 3.4 , measured at week 24.

In contrast, the sham group showed the expected a significant decline in MMSE scored: initial score of 18.5 ± 2.7 dropped to 16.8 ± 5.7 ($p < 0.05$).

[0673] *Maintenance of Functional Ability Assessed by ADCS-ADL*. Effects of NS treatment on patients' the ability to perform activities of daily living were assessed at baseline and regular monthly intervals during the 24-week treatment period using the clinically proven ADCS-ADL scale via structured interview with care partner. Average ADCS-ADL scores were calculated from the first 12-week and second 12-week periods in both treatment ($n=14$) and sham ($n=8$) groups (**FIG. 41**). The ADCS-ADL is a well-established instrument for testing function of mild to moderate AD patients, and numerous clinical trials have reported a significant decline in the ADCS-ADL scores in this patient population over a 6-month period (Loy, C. and L. Schneider (2006). "Galantamine for Alzheimer's disease and mild cognitive impairment." Cochrane Database Syst Rev(1): CD001747; Peskind, E. R., S. G. Potkin, N. Pomara, B. R. Ott, S. M. Graham, J. T. Olin and S. McDonald (2006). "Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial." Am J Geriatr Psychiatry 14(8): 704–715). In our study, each patient in the sham group showed a decline in ADCS-ADL scores, resulting in this patient group significant ($p < 0.001$), approximately 3 points decline over the trial period. In contrast, 9 out of 14 patients in the treatment group maintained or even showed improvement in their ADCS-ADL scores. Therefore, the average ADSC-ADL score in the treatment group significantly ($p < 0.035$) increased during the treatment period. Accordingly, **FIG. 41** demonstrates that changes in daytime activities showed a significant improvement in the treatment group and a significant decline in the sham group.

DISCUSSION

[0674] This interim analysis of the Overture trial (NCT03556280) demonstrates a beneficial outcome of daily use of the NS therapy over a six-month period in mild to moderate AD patients: NS treatment resulted in improved sleep quality and maintained quality of daily living as compared to subjects in the control arm of the study.

[0675] Results, based on the collected actigraphy data over a 6-month period, demonstrate that NS therapy can reduce sleep fragmentation, leading to significantly reduced active periods during night in mild to moderate AD patients. In contrast, patients in the sham group did not show improvement in sleep characteristics. Given the well-recognized architecture of human physiological sleep, consisting subsequent periods of different NREM stages starting from superficial to deep slow wave sleep and REM sleep period in a strictly subsequent order, it is obvious that sleep fragmentation can dramatically disrupts sleep architecture and consequently effectiveness of sleep. Sleep fragmentation, as a symptom of sleep disorders have multiple impact on human physiology, including dysfunction not only in the nervous system, but also

overall health by impairing body metabolism or immune defense system. Nevertheless, decremental cognitive impacts of sleep abnormalities are particularly worrisome in MCI and AD patients. Therefore, application of NS therapy offers novel intervention for in AD patients for improving sleep quality. Available clinical data revealed that this therapy is safe and can be applied daily in an extended period of time in patients. Considering that sleep disorders are contributing to impaired function and cognition, effective treatments for improving sleep quality potentially have multiple benefits in MCI and AD patients.

[0676] The clinical benefits of NS therapy on sleep is particularly relevant, since pathomechanisms underlying sleep dysfunction in MCI and AD patients are not well understood, therefore developing specific sleep therapies are not feasible currently. AD-related pathological proteins, such as A β - and tau- oligomers are known to disrupt sleep, though their mode of action is unknown. From an early stage of the disease brainstem ascending neurons considered to play in role in sleep-wake regulation, including cholinergic, serotonergic and norepinephrine neurons show profound degeneration (Smith, M. T., C. S. McCrae, J. Cheung, J. L. Martin, C. G. Harrod, J. L. Heald and K. A. Carden (2018). "Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment." *J Clin Sleep Med* 14(7): 1209-1230; Tiepolt, S., M. Patt, G. Aghakhanyan, P. M. Meyer, S. Hesse, H. Barthel and O. Sabri (2019). "Current radiotracers to image neurodegenerative diseases." *EJNMMI Radiopharm Chem* 4(1): 17; Kang, S. S., X. Liu, E. H. Ahn, J. Xiang, F. P. Manfredsson, X. Yang, H. R. Luo, L. C. Liles, D. Weinshenker and K. Ye (2020). "Norepinephrine metabolite DOPEGAL activates AEP and pathological Tau aggregation in locus coeruleus." *The Journal of Clinical Investigation* 130(1): 422-437). Similarly, suprachiasmatic nucleus containing neurons playing the key role in regulating circadian rhythms also shows neurodegeneration early in the disease Van Erum, J., D. Van Dam and P. P. De Deyn (2018). "Sleep and Alzheimer's disease: A pivotal role for the suprachiasmatic nucleus." *Sleep Med Rev* 40: 17-27). There are only limited treatment options for sleep abnormalities in MCI and AD patients, and pharmacological treatments currently include antidepressant, antihistamines, anxiolytics, and sedative-hypnotic drugs such as benzodiazepines (Vitiello, M. V. and S. Borson (2001). "Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment." *CNS Drugs* 15(10): 777-796; Deschenes, C. L. and S. M. McCurry (2009). "Current treatments for sleep disturbances in individuals with dementia." *Curr Psychiatry Rep* 11(1): 20-26; Ooms, S. and Y. E. Ju (2016). "Treatment of Sleep Disorders in Dementia." *Curr Treat Options Neurol* 18(9): 40). Some of the most frequently used anxiolytics/sedative-hypnotic drugs in the general clinical practice are GABAA positive allosteric modulators, which are contraindicated in MCI and AD

patients due to their negative effects on cognitive function, interference with motor behavior and addiction-forming profile. Recently, suvorexant, an orexin receptor antagonist has been approved as a sleep medication for AD patients having clinically diagnosed insomnia. The main effects of suvorexant are a prolonged total sleep time and delayed wake after sleep onset, without impacting sleep fragmentation or altering sleep architecture (Herring, W. J., P. Ceesay, E. Snyder, D. Bliwise, K. Budd, J. Hutzelmann, J. Stevens, C. Lines and D. Michelson (2020). "Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial." *Alzheimers Dement* 16(3): 541-551). Non-pharmacological treatments include behavioral measures such as sleep hygiene education, exercise regimens, and reduction of noise during sleeping hours. Bright light therapy is one of the non-pharmacologic modalities that offers recommendations from the American Academy of Sleep Medicine for use in sleep disturbances due to circadian disorders. Clinical tests of light therapy in AD patients resulted in conflicting findings (Ouslander, J.G., Connell, B.R., Bliwise, D.L., Endeshaw, Y., Griffiths, P. and Schnelle, J.F. (2006). "A Nonpharmacological Intervention to Improve Sleep in Nursing Home Patients: Results of a Controlled Clinical Trial." *Journal of the American Geriatrics Society*. 54: 38-47; Deschenes et al., 2009), and currently no approved device or therapeutic intervention exists.

[0677] The current findings demonstrate a beneficial effect of NS therapy in mild to moderate AD patients, prolonging nighttime undisturbed restful periods, indicating a reduced sleep fragmentation. There are no proved therapies for reducing sleep fragmentation which could improve sleep quality in MCI or AD patients, and frequently used sedative-hypnotic drugs are decremental on the physiological architecture of sleep. Having monthly interviews with patients and caregivers about everyday activities and sleep habits, there was not an indication that NS treatment leads to daytime sleepiness or grogginess, which are typical side effects of most sleep medication, including the orexin receptor antagonist suvorexant. Furthermore, in the present trial clinically diagnosed sleep abnormality such as insomnia has not been a requirement, consequently beneficial effects of NS treatment are not limited to AD patients suffering from clinically recognized sleep problems.

[0678] The present findings demonstrate that NS treatment not only improves sleep quality but also helps to maintain functional ability reflected in activity of daily living in mild to moderate AD patients. Although some pharmacological treatments, such as the acetylcholine esterase inhibitor donepezil, delay decline in activity of daily living, currently there are no approved non-pharmacological therapies achieving this effect. Based on scientific and clinical observations demonstrating a close relationship between sleep quality and activity of daily living, it can be presumed that improving sleep quality in AD patients would provide multiple benefits: better

sleep will enhance patients' daytime performance, including cognitive function, and reduce daytime sleepiness. In line with this hypothesis, patients on NS treatment maintained functional activity as reflected by their unchanged ADSC-ADL score over the six-month treatment period. In contrast, ADSC scores of sham group patients dropped similarly to changes of placebo group patients in clinical trials (Doody, R. S., R. Raman, M. Farlow, T. Iwatsubo, B. Vellas, S. Joffe, K. Kieburtz, F. He, X. Sun, R. G. Thomas, P. S. Aisen, C. Alzheimer's Disease Cooperative Study Steering, E. Siemers, G. Sethuraman, R. Mohs and G. Semagacestat Study (2013). "A phase 3 trial of semagacestat for treatment of Alzheimer's disease." *N Engl J Med* 369(4): 341-350; Doody, R. S., R. G. Thomas, M. Farlow, T. Iwatsubo, B. Vellas, S. Joffe, K. Kieburtz, R. Raman, X. Sun, P. S. Aisen, E. Siemers, H. Liu-Seifert, R. Mohs, C. Alzheimer's Disease Cooperative Study Steering and G. Solanezumab Study (2014). "Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease." *N Engl J Med* 370(4): 311-321). Even though the close relationship between sleep and daily activity is well documented, it is unknown at present whether improved sleep quality is the main factor contributing to the maintenance of ADSC-ADL scores in NS treated patients, or improvement in sleep and continuation of functional ability are unrelated positive outcomes from the therapy.

[0679] Currently, the underlying mechanisms of improved sleep and maintained functional ability of AD patients in response to GSS treatment are not known. Preclinical studies indicate that 40 Hz sensory stimulation reverses A β and tau pathologies leading to improved cognitive function in transgenic mice (Iaccarino, Singer et al. 2016; Adaikkan, C., S. J. Middleton, A. Marco, P. C. Pao, H. Mathys, D. N. Kim, F. Gao, J. Z. Young, H. J. Suk, E. S. Boyden, T. J. McHugh and L. H. Tsai (2019). "Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection." *Neuron* 102(5): 929-943 e928; Martorell, Paulson et al. 2019). Although human AD-related biomarker studies are in progress, at the moment it is unknown if the same biochemical and neuroimmunology mechanisms are activated in AD patients as identified in mice. The bidirectional interaction between sleep and disease progression (Wang and Holtzman 2020) supports the notion that improved sleep in response to GSS treatment could also slow down disease progression.

CONCLUSION

[0680] The present study's findings indicate that NS treatment helps maintain everyday activity and quality of life of AD patients. Since measurements of both sleep fragmentation and ADSC-ADL were determined in the same patient cohort, the data suggest a positive treatment effect of maintaining ability to complete daily activities in patients having improved sleep quality. NS treatment consists of a non-invasive sensory stimulation; with exceptional safety profile, its long-

term, chronic application is feasible. Expanded and longer trials will uncover additional clinical benefits and potentially disease-modifying properties of NS treatment.

Example 3. Randomized Controlled Trial with Greater Amount of Participants

BACKGROUND

[0681] An additional randomized controlled trial was performed, with patients maintaining the same methods and inclusion criteria as the interim analysis of the trial disclosed herein, in Example 2. This trial involved a greater number of participants than that which was subject to the interim analysis.

METHODS

[0682] Patients with mild-to-moderate AD (MMSE 14-26, inclusive; n=74) were randomized to receive either 40Hz noninvasive audio-visual stimulation or sham stimulation over a 6-month period. Functional abilities of patients were measured by Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale at baseline and every four weeks during the study and follow-up period. Sleep quality was assessed from nighttime activities of a subgroup of patients (n=7 in treatment, n=6 in sham groups) who were monitored continuously via a wrist worn actigraphy watch throughout the 6-month period.

RESULTS

[0683] The sham group contained 19 patients, and the treatment group contained 33 patients. Adjusted ADCS-ADL scores from beginning and the end of the trial were compared in patients who completed the trial. Over the 6-month period, patients in the sham group (n=19) showed the expected decline, a 5.40-point drop in ADCS-ADL scores, whereas patients in the treatment group (n=33) receiving therapy exhibited only a 0.57-point decline. Changes in ADCS-ADL scores were statistically significant between the sham and treatment groups ($P<0.01$). Nighttime active durations in the treatment group were significantly ($p<0.03$) reduced in the second 3 months compared to the first 3-months but such durations increased in the sham group. To evaluate the impact on active durations, normalization is done by dividing duration of each active period by the duration of the matching entire nighttime period. Analysis of normalized active durations by the corresponding nighttime period of each patient further confirmed opposite changes in nighttime active durations between treatment and sham groups ($p<0.001$), with the treatment group experiencing reduced nighttime active durations, and the sham group experiencing increased nighttime active durations.

CONCLUSION

[0684] This trial confirmed that patients in gamma stimulation therapy maintained their activities of daily living and showed an improved sleep quality over a 6-month treatment period; two

outcome measures, functional ability and sleep quality known to be strongly linked in AD.

Maintenance of functional ability represents an important treatment and management goal for AD patients, reducing formal and informal care, and delaying time to institutionalization.

Example 4. White Matter Atrophy and Myelination

OBJECTIVES

[0685] The present study evaluated whether gamma sensory stimulation for a 6-month period could affect white matter atrophy and myelination in patients on AD spectrum.

METHODS and MATERIALS

[0686] The neuroimaging data used in this study is collected in Cognito Therapeutics' Overture, a randomized, placebo-controlled feasibility study (NCT03556280) in patients (age of 50 years or older and Mini-Mental State Examination (MMSE) 14-26) on AD spectrum. In this study, participants in the active treatment arm received 1-hour daily, at-home, 40Hz simultaneous auditory-visual sensory stimulation for a 6-month period while the placebo arm subjects received sham stimulation. Structural magnetic resonance imaging (MRI) data was acquired at baseline, month 3 and month 6 visits using 1.5 Tesla MRI. 38 participants (25 Treatment and 13 Placebo) who fulfilled the requirement of sufficient T1w image quality were included in the analysis.

Volume assessments on multiple white matter structures were done using T1 MRI, and myelination assessments were done using T1w/T2w ratio. One treatment group and one placebo group participant were excluded from myelination analysis owing to T2w image quality. Patient characteristics at baseline are summarized in Table 2. Bayesian linear mixed effects modeling was used to assess the changes from baseline. Changes in white matter volume and myelination were compared between treatment group and placebo group participants after 6 months of treatment.

[0687] Table 2: Demographic and clinical characteristics of the treatment and the placebo group participants at baseline.

	Treatment (n=25)	Placebo (n=13)	p-value
Age in years, mean $\pm$ SD	68.36 $\pm$ 7.69	76.62 $\pm$ 9.97	0.02
Sex (Male/Female)	7(Male)/18(Female)	8(Male)/5(Female)	0.10
MMSE score, mean $\pm$ SD	20.64 $\pm$ 3.15	19.77 $\pm$ 3.27	0.44
ADCS-ADL scale, mean $\pm$ SD	64.88 $\pm$ 7.95	66.23 $\pm$ 10.83	0.70
Number (%) of APOE ϵ 4 positive	13(52.00%)	7(53.85%)	1

Abbreviations: MMSE, Mini-Mental State Exam; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living; APOE, apolipoprotein E.

[0688] Therapy Device. The device used in this study is a gamma sensory stimulation device developed by Cognito Therapeutics, Inc. It consists of a handheld controller, an eye-set for visual stimulation and headphones for auditory stimulation. All the components work in synchrony to provide precisely timed non-invasive 40Hz stimulation to evoke steady-state gamma brainwave activity. Prior to study, a physician determines the tolerable range of stimulus parameters for the participant. During the therapy, participants can also adjust the brightness of the visual stimulation and the volume of the auditory stimulation using push buttons on the controller. If assistance is needed, they can communicate with a care partner. The device captures usage information and adherence data. All the information is uploaded to a secured cloud server for remote monitoring.

[0689] MRI Data Acquisition. In Overture feasibility study, structural magnetic resonance imaging (MRI) data were acquired at Baseline, month 3 and month 6 using 1.5 Tesla MRI scanner. The study adopted a ADNI1 comparable standardized MRI scan protocol. For T1w, it included 1.25×1.25 mm in-plane spatial resolution, 1.2 mm thickness, TR 2400 ms and TE 3.65 ms for Siemens Espree scanner, 0.94×0.94 mm in-plane spatial resolution, 1.2-mm thickness, TR ~3.9 ms and TE 1.35 ms in General Electric scanner Signa HDxt and 0.94×0.94 mm in-plane spatial resolution, 1.2-mm thickness, TR 9.5 ms and TE ~3.6 or 4 ms in Philips Ingenia scanner or Philips Achieva scanner. For T2w, it included 1×1 mm in-plane spatial resolution, 4 mm thickness, TR 3000 ms and TE 96 ms for Siemens and GE scanners and 1×1 mm in-plane spatial resolution, 4 mm thickness, TR 3000 ms and TE 92 ms for Philips scanner (Jack et al. 2008).

[0690] Image Analysis. The FreeSurfer pipeline is used to process and automatically parcellate T1 MRI into predefined cortical structures and segment the volume into predefined subcortical structures (Dale et al., 1999; Fischl et al., 2001; Fischl et al., 2008; Fischl et al., 2002; Fischl et al., 1999a; Fischl et al., 1999b; Ségonne et al., 2005; Desikan et al., 2006). Here, we focus on total 52 white matter structures to assess volumetric changes and evaluate myelin content.

[0691] Myelin Sensitive Imaging. A non-invasive myelin-sensitive imaging was employed by using T1w/T2w ratio to acquire a myelin-reflecting contrast (Glasser and Van Essen, 2011; Glasser et al., 2014, 2016). This process included co-registration of the T2w images to the T1w images using rigid transformation, inhomogeneity correction for both T1w and T2w images and linear calibration of image intensity using non-brain tissue masks to create T1w/T2w ratio images corresponding to myelin content (Ganzetti et al., 2014, 2015). T1w/T2w ratio was processed using MRTTool (v. 1.4.3, <https://www.nitrc.org/projects/mrtool/>), the toolbox

implemented in the SPM12 software (University College London, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>).

[0692] Statistical Methods. Demographic and biomarker data of the treatment group participants and the placebo group participants were compared using two-sample T tests for numerical data or chi-square tests for categorical data. For efficacy analysis, a Bayesian linear mixed effects model was used to assess the changes in the volumetric data and myelination for each of the white matter structures. Fixed effects of the model include total intracranial volume, baseline MMSE score, baseline age, visit (as number of days from the start of the treatment), group, baseline MRI measures (volume for white matter atrophy assessment and sum of T1w/T2w ratio for myelination assessment), group-visit interaction and baseline MRI measures-visit interaction. Random effects of the model include subject and site information. The Kenward-Roger approximation of the degrees of freedom was used. For volumetric analysis, volume change (% change from baseline) and for myelination analysis, sum of T1w/T2w ratio change (% change from baseline) were assessed for each studied white matter structure. All statistical analyses were conducted using R (R version 4.1.1).

RESULTS

[0693] With respect to baseline levels, it was observed that the treatment group demonstrated a $0.17 \pm 1.08\%$ increase and the placebo group demonstrated a $-2.54 \pm 1.38\%$ decrease in total cerebral white matter volume after a 6-month period. The difference between these two groups was statistically significant ($p < 0.038$). See **FIG. 44**.

[0694] **FIG. 44** provides white matter volume change from baseline (%) after 40Hz gamma sensory stimulation therapy for a 6-month period favors the treatment group. LS Mean volume changes for the total cerebral white matter show the significant difference ($p < 0.038$) between the Treatment group participants (dark gray) and the Placebo group participants (light gray), favoring the Treatment group. Error bars indicate SE.

[0695] It was also observed that the treatment group demonstrated a $-1.42 \pm 2.35\%$ decrease and the placebo group demonstrated a $-6.19 \pm 2.63\%$ decrease in myelination as assessed by summing the ratio of T1 weighted (T1w) and T2 weighted (T2w) intensities across the MRI images. This difference was also statistically significant ($p < 0.025$) between groups. See **FIG. 45**. **FIG. 45** provides T1w/T2w ratio change in white matter (% change from baseline) after 40Hz gamma sensory stimulation therapy for a 6-month period favors the treatment group. LS Mean sum of T1w/T2w ratio changes for the total cerebral white matter show the significant difference ($p < 0.025$) between the Treatment group participants (dark gray) and the Placebo group participants (light gray), favoring the Treatment group. Error bars indicate SE.

[0696] Next, the structures that respond to treatment the most, in volume and myelin-reflecting T1w/T2w ratio changes among 52 white matter structures, were examined. All statistically significant changes favored the treatment group. Compared to the placebo group, significant ($p<0.05$) attenuation in volume loss was identified in 12 of 52 structures: the entorhinal region, left cingulate lobe, parstriangularis region, cuneus region, lateral occipital region, postcentral region, left occipital lobe, left frontal lobe, left parietal lobe, occipital lobe, left temporal lobe and caudal middle frontal region (sorted in ascending order by p value) for the treatment group after 6 months of treatment (**FIG. 46A**). Forty Hz gamma sensory stimulation therapy administered over a 6-month period most significantly reduced white matter atrophy in entorhinal region. The treatment group demonstrated a $5.14\pm3.66\%$ ($0.08\pm0.06\text{ cm}^3$) increase, while the placebo group demonstrated a $-7.60\pm4.35\%$ ($-0.13\pm0.07\text{ cm}^3$) decrease in volume. The difference between these two groups was statistically significant ($p<0.002$). The treatment also trended in the direction of preventing volume loss ($0.05\leq p<0.1$) in the precentral region, paracentral region, lingual region, fusiform region, frontal lobe, rostral anterior cingulate region, inferior temporal region, right occipital lobe, parietal lobe, rostral middle frontal, precuneus region, medial orbitofrontal region and temporal lobe (sorted in ascending order by p value) (**FIG. 46B**).

[0697] **FIG. 46A** and **FIG. 46B** provide white matter structures volume change from baseline (%) after 40Hz gamma sensory stimulation therapy for a 6-month period favors the treatment group. LS Mean volume changes for the white matter structures (**FIG. 46A**, sorted in ascending order by p value) show the significant difference ($p<0.05$) between the Treatment group participants (dark gray) and the Placebo group participants (light gray), favoring the treatment group. **FIG. 46B** (sorted in ascending order by p value) shows LS Mean volume changes for the white matter structures with the marginal difference ($0.05\leq p<0.1$) between the Treatment group participants (dark gray) and the Placebo group participants (light gray), favoring the Treatment group. Error bars indicate SE. * $p<0.05$, ** for $p<0.01$, and • for $0.05<p<0.1$.

[0698] Compared to the placebo group, significantly less myelin damage (T1w/T2w ratio) was observed in entorhinal region, parstriangularis region, postcentral region, left parietal lobe, lateral occipital region, paracentral region, rostral middle frontal region, supramarginal region, precentral region, parietal lobe, right occipital lobe, fusiform region, occipital lobe, left frontal lobe, cuneus region, precuneus region, inferior parietal region, frontal lobe, lingual region, left occipital lobe, left temporal lobe, right parietal lobe and parsorbitalis region (**FIG. 47A**, white matter structures sorted in ascending order by p value), indicating significant differences ($p<0.05$) between the treatment group and the placebo group. Within the 52 studied white matter structures, the most significant myelin-reflecting T1w/T2w ratio change was also in the entorhinal region. The treatment group participants exhibit a $+2.78\pm4.97\%$ increase from

baseline on sum of T1w/T2w ratio while the placebo group participants exhibit a -10.59 ± 5.63 % decrease from baseline on sum of T1w/T2w ratio ($p < 0.003$), suggesting that 40Hz gamma sensory stimulation therapy for a 6-month period can significantly protect myelin damage in this brain region. The treatment can also trend towards slowing down demyelination ($0.05 \leq p < 0.1$) in right frontal lobe, caudal middle frontal region, rostral anterior cingulate region, superior frontal region, temporal lobe, medial orbitofrontal region, posterior cingulate region, superior parietal region, left cingulate lobe, superior temporal region, cingulate lobe and temporal pole region (**FIG. 47B**, white matter structures sorted in ascending order by p value).

[0699] **FIG. 47A** and **FIG. 47B** provide T1w/T2w ratio change in white matter structures (% change from baseline) after 40Hz gamma sensory stimulation therapy for a 6-month period favors the treatment group. LS Mean sum of T1w/T2w ratio changes in the white matter structures (Panel A, sorted in ascending order by p value) shows the significant difference ($p < 0.05$) between the Treatment group participants (dark gray) and the Placebo group participants (light gray), favoring the treatment group. Panel B (sorted in ascending order by p value) shows LS Mean sum of T1w/T2w ratio changes in the white matter structures with the marginal difference ($0.05 \leq p < 0.1$) between the Treatment group participants (dark gray) and the Placebo group participants (light gray), favoring the Treatment group. Error bars indicate SE. * $p < 0.05$, ** for $p < 0.01$, and • for $0.05 < p < 0.1$.

[0700] These results suggest that 40Hz gamma sensory stimulation therapy for a 6-month period can reduce white matter atrophy and the changes are accompanied by significantly less demyelination in the treatment group compared to placebo group.

CONCLUSIONS

[0701] Administration of 40 Hz gamma sensory stimulation for a 6-month period led to beneficial effects on total and regional white matter volume along with reduction in myelin damage. Among all white matter structures analyzed, the most significant changes were observed in the entorhinal region: The treatment group demonstrated a $5.14 \pm 3.66\%$ increase, while the placebo group demonstrated a $-7.60 \pm 4.35\%$ decrease in volume. The difference between these two groups was statistically significant ($p < 0.002$). The treatment group demonstrated a 2.78 ± 4.97 % increase and the placebo group demonstrated a -10.59 ± 5.63 % decrease in the myelin-reflecting T1w/T2w measurements. This difference was also statistically significant ($p < 0.003$) between groups.

[0702] All white matter structures with statistically significant changes were in the treatment group and the most significant change was in the entorhinal region. Given its afferent connections to the hippocampus and the entorhinal cortex, and its relevance in AD pathology,

reduction in white matter atrophy and myelin damage in entorhinal region can play an important role to prevent disease progression.

Example 5. Portable Systems, Devices and Associated Methods of Use

[0703] In some embodiments, stimulation via a portable system or single headset device as disclosed herein induces a gamma oscillation in a brain region of the subject. In some embodiments, the stimulation comprises a frequency of about 20 Hz to about 60 Hz. In some embodiments, the stimulation comprises a frequency of about 40 Hz. In some embodiments, the portable system or single headset device comprises a visual source with an open view or transparent lens (open view visual stimulation)

[0704] In some embodiments, the open view visual stimulation provided by the portable system or single headset device provides advantages over an identical device comprising an opaque lens (closed view visual stimulation). For example, the induction of gamma oscillation in a brain region can be more effective when using open view visual stimulation than when using closed view visual stimulation. Additionally, from the perspective of a subject wearing the device, the open view visual stimulation can allow the subject to readily converse and carry out other cognitive tasks and voluntary movements such as holding the hand of their caregiver while remaining seated. Additionally, the open view visual stimulation can allow the subject to receive a regimen of gamma stimulation while performing other tasks, such as and not limited to, activities of daily living.

[0705] Instructions for use are included with each device. The devices are designed for ease of use for subjects, with no requirements for high dexterity manipulation of the devices and are accompanied by simple visual instructions in large print.

[0706] The device includes a hand-held controller which allows the subject, with the assistance from a caregiver if needed, to turn the device on, independently adjust the output amplitude of the stimulation, and to pause and resume the stimulation during a session.

Example 6. Human Clinical Study of Safety, Efficacy, and Results of Treatment using a Portable System with Open View Visual Stimulation

[0707] Recent studies highlight significant neurocognitive benefits from steady-state gamma sensory stimulation. Notably, a 6-month, daily, home-based treatment regimen demonstrated significant slowing of disease progression in mild to moderate Alzheimer's disease. This trial used an investigational medical product for treatment administration, which provides the visual component of stimulation through an eye set with opaque (closed view visual stimulation) lenses. The investigational medical product comprises a portable system as disclosed herein, i.e., the

portable system comprises a first stimulus emitting component comprising a visual source configured to emit a visual stimulus having a frequency of about 20 Hz to about 60 Hz; and a second stimulus emitting component comprising an audio source configured to emit an auditory stimulus having a frequency of about 20 Hz to about 60 Hz, wherein said visual source and said audio source are operatively connected and comprise a single headset device, and wherein said visual source is rotatable about said audio source and wherein the visual source comprises glasses comprising a lens that opaque.

[0708] This current study aimed to determine if allowing participants to view through a translucent (open view visual stimulation) lens during stimulation elicits comparable acute, sensory-evoked brain oscillations.

[0709] Thirty-one cognitively intact older adults (mean age 59.7 ± 8.3 years, 52% female) underwent visual tolerance and EEG-based gamma response testing. Visual (40 Hz) stimulation was delivered using both open view visual stimulation and closed view visual stimulation eye sets (3 minutes per lens configuration). Twenty-nine participants returned for a second visit one week later.

[0710] EEG data was acquired with a 32-channel cap (ANT-Neuro). Preprocessing and artifact removal were performed using EEGLAB (MATLAB). Power spectral densities of the EEG signals were computed and (globally/regionally) averaged across channels. The evoked Gamma Response was estimated as the peak power at 40Hz relative to the power at surrounding frequencies (38-39 & 41-42Hz).

[0711] One participant was excluded from analysis due to a pre-existing medical condition. Gamma Response comparisons between open view visual stimulation and closed view visual stimulation were conducted at Visit 1 (N=30) and Visit 2 (N=28) using paired t-tests and 2-way mixed effects models (GraphPad). Both global and regional brain responses were assessed. Due to the exploratory nature of this analysis, corrections for multiple comparisons were not applied.

[0712] Comparing open view visual stimulation and closed view visual stimulation within each visit separately, the mean global Gamma Response was greater for open view visual stimulation vs. closed view visual stimulation at both visits ($\Delta\text{GR}_{v1}=0.569$ dB, $p=0.111$; $\Delta\text{GR}_{v2}=0.856$ dB, $p=0.044$), but only Visit 2 reached statistical significance. The 2-way repeated measures similarly showed a significant effect of lens ($p=0.027$), while no visit or interaction effects were observed. Consistent results were observed for regional Gamma Responses, with a significant lens effect in the frontal ($p=0.047$) and temporal ($p=0.009$) regions and no visit or interaction effects.

[0713] This study demonstrates that open view visual stimulation produces a slightly greater evoked response compared to the closed view visual stimulation in a non-clinical population. As the open view visual stimulation can promote adoption and ease at-home use future studies in

clinical populations can support interchangeability of lens configurations for administration of gamma treatment.

Example 7. Human Clinical Study of Safety, Efficacy, and Results of Treatment Using a Portable System with Open View Visual Stimulation

[0714] Methods and Study Design

[0715] A clinical study is performed to assess the safety, tolerability, and efficacy of long-term, daily use of a portable system with a non-opaque visual source (open view visual stimulation) on cognition, functional ability, and biomarkers in a group of experimental subjects. In some embodiments, experimental subjects include subjects with mild-to-moderate AD. The clinical study is a multi-center, randomized controlled trial evaluating daily use of the device, with therapy to be received at home for a 6-month treatment period. Subjects included in the study are adults and adults 50 years and older with a clinical diagnosis of mild to moderate AD (MMSE: 14-26, inclusive), a reliable care partner, and successful tolerance and screening via EEG. Key exclusion criteria include profound hearing or visual impairment, use of memantine, major psychiatric illness, clinically relevant history of seizure, or contraindication to imaging studies.

[0716] Study Participants and Design.

[0717] A total number of patients are assessed for eligibility to participate in the study. Patients are first given a screening EEG, and then split into groups. One group is a sham control group that is not given treatment; the other is a group that is subjected to 1 hour of therapy, which involves subjecting the subject to visual stimulation with a non-opaque lens at a frequency of about 30 Hz to about 60 Hz, at least once per day. Of those assessed for eligibility, patients are randomized between an active open view visual stimulation group and a closed view visual stimulation control group.

[0718] The study employs various clinical outcome assessment scales to assess cognitive decline or dysfunction. These include the Neuropsychiatric Inventory (NPI), Clinical Dementia Rating-Sum of Boxes (CDR-sb), the Clinical Dementia Rating-Global Score (CDR global), the Mini-Mental State Exam (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale-14 (ADAS-Cog14), and a variation of the Alzheimer's Disease Composite Score (ADCOMS) as optimized for patients with mild or moderate Alzheimer's Disease. NPI examines 12 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities. The NPI can be used to screen for multiple types of dementia, and it involves giving the caregiver of a subject the questions and

then, based on the answers, rating the frequency of the symptoms, their severity, and the distress the symptoms cause on a three, four, and five-point scale, respectively.

[0719] CDR global is calculated based on testing performed for six different cognitive and behavioral domains: memory, orientation, judgment, and problem solving, community affairs, home and hobbies performance, and personal care. To test these areas, an informant is given a set of questions about a subject's memory problem, judgment and problem-solving ability of the subject, community affairs of the subject, home life and hobbies of the subject, and personal questions related to the subject. The subject is given another set of questions that includes memory-related questions, orientation-related questions, and questions about judgment and problem-solving ability. The CDR global score is calculated based on the results of those questions, and it is measured using a scale of 0 to 3, with 0 representing no dementia, 0.5 indicating very mild dementia, 1 indicating mild dementia, 2 indicating moderate dementia/cognitive impairment, and 3 indicating severe dementia/cognitive impairment. CDR-sb is a clinical outcome assessment that looks at functional impact of cognitive impairment: memory, executive function, instrumental and basic activities of daily living and assesses them based on interviews with an informant and the patient. The CDR-sb score is based on assessment of items including memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care. The CDR-sb is scored from 0 to 18, with higher scores representing greater severity of cognitive and functional impairment.

[0720] The MMSE looks at 11 items to assess memory, language, praxis, and executive function based on a cognitive assessment of the patient. Items assessed include registration, recall, constructional praxis, attention and concentration, language, orientation time, and orientation place. The MMSE is scaled from 0 to 30, with higher scores representing lower severity of cognitive dysfunction. The ADAS-Cog14 assesses memory, language, praxis, and executive function. The score is based on a cognitive assessment of the patient and assesses fourteen items: spoken language, maze, comprehension spoken language, remembering word recognition test instructions, ideational praxis, commands, naming, word finding difficulty, constructional praxis, orientation, digit cancellation, word recognition, word recall, and delayed recall. A score is based on points allocated to each item, and the maximum total score is 90, with higher numbers indicating greater severity of cognitive dysfunction. The Alzheimer's Disease Composite Score (ADCOMS) considers items from all of the above-discussed scores: items from Alzheimer's Disease Assessment Scale-cognitive subscale items, MMSE items, and all of the CDR-sb items. ADCOMS combines portions of the ADAS-cog, Clinical Dementia Rating (CDR) scale, and MMSE that have been shown to change the most over time in people who do not have functional

impairment yet. MADCOMS, which is used in the present example, optimizes the scale instead by combining items more significant for mild and moderate dementia.

[0721] The study design involves primary efficacy endpoints of MADCOMS, ADAS-cog14, and CDR-sb. Unlike ADCOMS, MADCOMS is optimized for patients with moderate or mild Alzheimer's Disease. These are optimized for AD-specific decline. A separate optimization is done for moderate and mild AD. Secondary efficacy endpoints consist of ADCS-ADL, ADCOMs (adjusted), MMSE, CDR-global score and the Neuropsychiatric Inventory (NPI). Of the secondary endpoints, ADCS-ADL is measured monthly and MMSE is measured at the last time point.

[0722] The efficacy endpoints are analyzed by applying a linear model of analysis or a separate means model of analysis. The linear model of analysis involves employing a linear fit model to determine a value at T0 based on the difference from baseline in conditions at the end of the study. The separate means analysis employs estimates of mean values at each timepoint, which is either a monthly timepoint or at three and six months after treatment begins, depending on the score that is being analyzed. In evaluating MADCOMS composite score, for example, the separate means analysis is applied using mean values that are estimated at three and six months. The linear model is applied by using the estimates of treatment difference at the end of the study and connecting a straight line to 0.

[0723] To assess biomarkers, researchers use MRI, volumetric analyses, EEG, Amyloid positron emission tomography (PET), actigraphy, and plasma biomarkers. In some embodiments the study measures gamma oscillations within brain regions, levels of tau phosphorylation, levels of amyloid- β (A β) peptide, levels of at least one of C-terminal fragments (CTFs) and N-terminal fragments (NTFs) of amyloid precursor protein (APP), numbers of endosomes, or a combination thereof. The study employs structural MRIs, taken before any treatment begins and at the end of six months and assesses these for volume-base morphology. Volumetric changes for the hippocampus, lateral ventricles, whole cortex (cerebral cortical gray matter) and whole brain (cerebrum and cerebellum) are determined, and the rate of atrophy is compared for active and sham groups using a linear model. To analyze for safety and tolerability, researchers look for adverse events and presence of amyloid related imaging abnormalities (ARIA) on MRI. Therapy adherence is also analyzed. Blinding effectiveness for subjects, care partners, and assessors are prospectively analyzed by assessing baseline and follow up ascertainment of whether the care partner, assessor, or patient thought the patient is on active or sham treatment. In some embodiments, levels of the measured biomarkers are maintained or reduced in active treatment groups as compared to groups receiving sham treatment.

[0724] Results

[0725] The subjects are randomized between open view visual stimulation and closed view visual stimulation. The safety population for the study includes subjects who received at least one treatment, and the modified intent to treat (mITT) population includes subjects who complete the 6-month study, which form the basis for analysis of outcome measures. **FIG. 19** demonstrates an example efficacy summary chart for a modified intent to treat (mITT) population, including hypothesized p-values, difference, confidence intervals (CI), and a hypothesized standardized estimate of efficacy based on the values.

[0726] Demographic and Baseline Characteristics

[0727] In terms of demographic and baseline characteristics of the mITT population, following randomization, the populations are balanced across gender, baseline MMSE, ApoE4 status, activities of daily living (ADL), and PET amyloid standardized uptake value ratio (SUVR) status; imbalances between the two groups are categorized with differences in age, ADAS-Cog11, and CDR-sb scores at baseline being noted. Statistical models include covariates for age and MMSE at baseline.

[0728] Safety and Tolerability

[0729] The gamma oscillation inducing waveform stimulus is safe and well-tolerated in the mild and moderate AD subjects. The active group is hypothesized to have a lower rate of treatment emergent adverse events (TEAE) than the sham group.

[0730] Treatment related AEs (TRAEs) deemed definitely, probably, and possibly related to the therapy is hypothesized to be elevated in the active group versus the sham group. Of the randomized subjects, withdraw rates are hypothesized to be similar between both groups including withdraw rates due to adverse events. TEAEs that occur most often in the active group are hypothesized to be tinnitus, delusions, and broken bones. TEAEs that occur most often in the sham group are hypothesized to be upper respiratory infection, confusion, anxiety, and dizziness.

[0731] Clinical Assessments

[0732] Over the treatment period of 6-months, subjects are evaluated in-clinic and via phone visits for cognitive, functional, and biomarker changes on multiple measures.

[0733] The primary efficacy endpoints are hypothesized to demonstrate effects favoring the active group on the MADCOMS and CDR-sb and favoring the Sham group on the ADAS-cog14.

[0734] Selected secondary endpoints demonstrate significant effects favoring the treatment (active) group. The active group has significant benefit on functional ability as measured by the ADCS-ADL. The active group demonstrates significant benefit on the MMSE, which represents slowing in the rate of decline versus the Sham group. The active group (open view visual stimulation) is hypothesized to demonstrate maintained or increased recognition, discrimination, spatial memory, working memory, and attention as compared to the sham group (closed view

visual stimulation). Examples of such hypothesized results are demonstrated in **FIGs. 20-24 and 26**.

[0735] Biomarker Changes—MRI

[0736] Structural MR imaging is analyzed for volume-base morphometry using an automated image processing pipeline (Biospective, Montreal, Canada). Volumetric changes of the hippocampus, lateral ventricles, whole cortex (cerebral cortical gray matter) and whole brain (cerebrum and cerebellum, no cerebrospinal fluid (CSF)) for each subject are determined; no manual corrections are performed. The active group is hypothesized to demonstrate maintained or increased volumetric changes as compared to the sham group. An example of hypothesized magnetic resonance imaging (MRI) results is demonstrated in **FIG. 25**.

[0737] Conclusions

[0738] Open view visual stimulation is hypothesized to be safe and well tolerated in accordance with previous studies. Primary efficacy outcomes (MADCOMS, CDR-sb) are hypothesized to favor the active group over the sham group. Selected secondary endpoints will demonstrate that active treatment with gamma stimulation therapy leads to significant benefits in the ability to perform activities of daily living via the ADCS-ADL and cognition via the MMSE, representing important treatment and management objectives for AD patients. Quantitative MR analysis is hypothesized to demonstrate slowing of brain atrophy as measured by whole brain volume in the active group. The combined clinical and biomarker findings are hypothesized to suggest the beneficial effects of open view visual stimulation for AD subjects can be facilitated via differentiated pathways.

Example 8: Use of a Portable System for Preserving Corpus Callosum Structure in AD

Abstract

[0739] Objective: To examine the impact of 40Hz gamma stimulation using a portable system on the preservation of the corpus callosum, a critical structure for interhemispheric connectivity, in people with mild cognitive impairment or Alzheimer's Disease.

[0740] Methods: OVERTURE (NCT03556280) participants were randomized 2:1 (Active:Sham) to receive daily, 1-hour, 40-Hz gamma sensory stimulation or sham treatment for six months. Structural magnetic resonance imaging data were analyzed to assess changes in corpus callosum area (N=50; 33 for active, 17 for sham). Bayesian linear mixed-effects modeling was used to assess differences in longitudinal changes of corpus callosum area between the two treatment groups. **Results:** All observed differences in corpus callosum area favored the active treatment group. Differences were observed in the total corpus callosum area ($2.28 \pm 0.87\%$, $p < .02$) and its subregions, including genu/rostrum ($2.36 \pm 0.90\%$, $p < .02$), anterior-body

($2.64 \pm 1.26\%$, $p < .04$), mid-body ($2.79 \pm 1.18\%$, $p < .03$), posterior-body ($2.87 \pm 1.41\%$, $p < .05$), and splenium ($1.58 \pm 0.73\%$, $p < .04$). Total corpus callosum area and some of the sub-regional differences, such as genu/rostrum and splenium, were observed as early as 3 months after commencement of treatment.

[0741] Interpretation: The structural magnetic resonance imaging results from the OVERTURE Phase 2 study suggest that six months of non-invasive 40Hz stimulation reduces the rate of atrophy of the corpus callosum in individuals with Alzheimer's Disease. The preservation of structural integrity in the corpus callosum, crucial for interhemispheric communication and cognitive function, can be achievable through this non-invasive approach, potentially providing a promising disease-modifying alternative in Alzheimer's Disease management.

[0742] Introduction

[0743] Alzheimer's disease (AD) is marked by neuronal death, synaptic loss, and compromised white matter structural integrity. Current AD therapies primarily focus on reducing amyloid protein accumulation, with limited focus on directly preventing neurodegeneration. Our prior research indicated that 40Hz gamma sensory stimulation can prevent atrophy in individuals with mild cognitive impairment (MCI) or AD, showing reductions in white matter volume loss. However, our previous work did not specifically examine the corpus callosum. Notably, earlier studies, some over two decades old, reported more than eightfold reduction in the midsagittal area of the corpus callosum, the principal white matter fiber bundle connecting the brain's hemispheres, in AD patients compared to controls. Building on these findings, this study explored the effects of 40Hz gamma sensory stimulation therapy specifically on the preservation of the corpus callosum.

[0744] The corpus callosum plays a crucial role in interhemispheric functional integration, with over 300 million fibers transmitting information across the network. Corpus callosum atrophy is particularly pronounced in AD and preventing it can have important consequences for neuronal communication and neural network function. Corpus callosum atrophy is more severe in the anterior and posterior thirds, where there are more small, myelinated fibers. Although the regional pattern and degree of corpus callosum atrophy correlates with dementia severity in individuals with AD, the development of therapeutic interventions for AD have not focused on preventing or mitigating corpus callosum atrophy. Recent findings indicate that noninvasive 40Hz gamma sensory stimulation can induce neuronal oscillations, potentially preventing synaptic loss, neurodegeneration, and brain atrophy. This stimulation can also mitigate demyelination and promote the generation of new oligodendrocytes. Furthermore, clinical studies suggest that 40Hz gamma stimulation can enhance functional connectivity and reduce potentially

harmful cytokines in the nervous system, slow cognitive decline, and improve activities of daily living.

[0745] Methods

[0746] Study Sample and Design This study used data from the OVERTURE clinical trial (NCT03556280), a randomized, placebo-controlled study aimed at evaluating the safety, tolerability, adherence, and efficacy estimate of daily, 1-hour sessions using a portable system as disclosed herein, i.e., a portable system comprising a first stimulus emitting component comprising a visual source configured to emit a visual stimulus having a frequency of about 20 Hz to about 60 Hz; and a second stimulus emitting component comprising an audio source configured to emit an auditory stimulus having a frequency of about 20 Hz to about 60 Hz, wherein said visual source and said audio source are operatively connected and comprise a single headset device, and wherein said visual source is rotatable about said audio source to generate combined 40Hz visual and auditory evoked gamma oscillations for six months in individuals who are clinically diagnosed as MCI or AD (N=74). The trial protocols were approved by the Advarra institutional review board (FDA IORG#0000635, OHRA IRB Registration #00000971), and informed consent was obtained from all participants or their legally authorized representatives. The exclusion criteria included comorbid neurological conditions, profound sensory impairments, seizure history, or those on anti-seizure/anti-epileptic medication. Participants who were already taking cholinesterase inhibitors continued a consistent dosage; however, the use of memantine was exclusionary. Although not part of the inclusion criteria, amyloid pathology was assessed using Amyvid [¹⁸F] florbetapir PET imaging.

[0747] Therapeutic System The treatment used a portable system as disclosed herein, featuring a handheld controller, and a single headset device comprising a visual source comprising glasses, and headphones for auditory stimulation (See e.g., FIGs 66-78). The device allowed participants to adjust the visual and auditory stimulation levels for comfort and was equipped with a communication feature for assistance from a care partner if required. Usage and adherence data were automatically captured and transmitted to a secure cloud server for remote monitoring purposes.

[0748] MRI Data Acquisition Structural magnetic resonance imaging (MRI) was performed at baseline, month 3, and month 6 using 1.5 Tesla MRI scanners across multiple sites. The imaging protocol was harmonized with the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI1) protocol to ensure consistency in data acquisition. The protocol specifics for T1-weighted images were as follows: on Siemens Espree scanners, images were acquired with an in-plane spatial resolution of 1.25×1.25mm, slice thickness of 1.2mm, repetition time (TR) of 2400ms, and echo time (TE) of 3.65ms; on General Electric Signa HDxt scanners, the resolution was 0.94×0.94mm,

slice thickness 1.2mm, TR approximately 3.9ms, and TE 1.35ms; and on Philips Ingenia or Achieva scanners, the protocol was set to 0.94×0.94mm resolution, 1.2-mm slice thickness, TR of 9.5ms, and TE approximately 3.6 or 4ms.

[0749] MRI Analysis Among the 74 participants who enrolled in the study, MRI analyses were conducted based on specific exclusion criteria to ensure the quality and reliability of the data. The exclusion criteria were as follows: **Insufficient Image Quality:** Participants whose T1-weighted (T1w) MRI images were deemed inadequate for analysis due to excessive motion artifacts or insufficient contrast between gray matter and white matter were also excluded. This criterion resulted in the exclusion of 10 participants from the Active group and 7 participants from the Sham group. **Incomplete Data:** Participants who failed to complete baseline structural MRI assessments or at least one follow-up visit by the end of the study period (Month 6) were excluded. This criterion led to the exclusion of 3 participants from the Active group and 4 participants from the Sham group. After applying these exclusion criteria, the final sample comprised 50 participants, with 33 in the Active group and 17 in the Sham group (See Table 4 for a comparison of the baseline characteristics of the Active and Sham groups in this sample). These participants were included in the longitudinal area assessments of the corpus callosum.

[0750] Table 4. Demographic Characteristics

	Active (n=33)	Sham (n=17)	χ^2	T value	95% CI	P value
AGE in years, mean ± SD	69.21 ± 7.54	75.06 ± 11.26	n.a	1.93	-0.41, 12.11	0.07
SEX, Male/Female	10/23	10/7	2.71	n.a	n.a.	0.10
Number (%) of APOE^ε_ε 4	16 (50%)	8 (47%)	0	n.a.	n.a.	1
Number (%) of PET SUVR§ >1.12	23 (77%)	11 (65%)	.78	n.a.	n.a.	0.5
MMSE† score, mean ± SD	21.15 ± 3.45	18.88 ± 3.33	n.a	-2.25	-4.32, -0.22	0.03

ADCS-ADL scale, mean $\pm$ SD	65.30 $\pm$ 9.47	62.94 $\pm$ 11.77	n.a	-0.72	-9.12, 4.41	0.48
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*Abbreviations: *From participants with corpus callosum data ¶APOE, apolipoprotein E. ‡APOE status for one, and §PET SUVR (F18-AV-45 Positron Emission Tomography, Standard Uptake Value Ratio, whole cerebellum reference)², for three active treatment participants are missing. tMMSE, Mini-Mental State Examination. †ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living. n.a. Not Applicable*

[0751] Corpus Callosum Midsagittal Area Analysis To delineate midsagittal area of the corpus callosum, we used a segmentation process using the Yuki module within the Automated Registration Toolbox (ART), which was applied to T1-weighted MRI images to define the boundaries and calculate the area within the midsagittal plane (MSP). Subsequently, the MSP of the corpus callosum was parcellated into five subregions (genu/rostrum, anterior body, mid body, posterior body, and splenium) using an automated image analysis streamline. For baseline comparisons between the two groups, the area of interest for each individual was normalized by the total intracranial volume raised to the two-thirds power to account for the dimensional difference between volume and area.

[0752] Statistical Methods A longitudinal analysis was conducted to assess percent changes in midsagittal plane corpus callosum area and in the areas of its five midsagittal plane subregions. The percent change was computed using the formula: *Percent Change* = $100 \times (\text{Area at Follow-up} / \text{Area at Baseline 1}) \%$ where *Area* represents the studied corpus callosum area at the respective time points. These changes were analyzed with a Bayesian linear mixed-effects model, incorporating non-informative priors for all model parameters. The model accounted for baseline Mini-Mental State Examination (MMSE) score, age at baseline, time of visit, treatment group allocation, baseline MRI measures of corpus callosum area, two-thirds power of total intracranial volume (as a covariate for area), group and visit interaction, and interactions between baseline area and visit. Random effects in the model included inter-subject and inter-site variability. The Kenward-Roger approximation was used to estimate the model's degrees of freedom. The percent change from baseline was evaluated for the total corpus callosum and each of the five subregions. All statistical analyses were performed using the statistical computing software R, version 4.1.1.

[0753] Data Availability The data are not publicly available due to information that could compromise the confidentiality of research participants.

[0754] Results

[0755] Demographic characteristics

[0756] There were no differences in age, sex, apolipoprotein E4 (APOE4) status, or baseline Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scores between active and sham groups (Table 4). However, MMSE scores were higher in the active group. This difference was accounted for and adjusted in all the models studied.

[0757] **Assessment of Corpus Callosum Structure at Baseline** The two treatment groups did not differ in total or subregion corpus callosum area at baseline (Table 5).

[0758] **Table 5. Normalized Area Assessments for Corpus Callosum and its Subregions at Baseline**

	Active (n=33) Mean $\pm$ SD (%)	Sham (n=17) Mean $\pm$ SD (%)	t-value	95% CI	p-value
Total Corpus Callosum	4.17 $\pm$ 0.52	3.91 $\pm$ 0.55	-1.66	-0.59 - 0.06	0.108
Genu/Rostrum	1.19 $\pm$ 0.15	1.14 $\pm$ 0.18	-0.98	-0.16 - 0.05	0.334
Anterior-Body	0.61 $\pm$ 0.11	0.56 $\pm$ 0.09	-1.58	-0.10 - 0.01	0.123
Mid-Body	0.55 $\pm$ 0.09	0.50 $\pm$ 0.08	-1.95	-0.10 - 0.00	0.059
Posterior-Body	0.57 $\pm$ 0.12	0.52 $\pm$ 0.11	-1.22	-0.11 - 0.03	0.230
Splenium	1.26 $\pm$ 0.19	1.18 $\pm$ 0.16	-1.56	-0.18 - 0.02	0.127

[0759] **Changes in Total Corpus Callosum Following Treatment** The active treatment group exhibited preservation of the corpus callosum, in contrast to the sham group, which demonstrated atrophy (see **FIG. 81**): After 6 months of treatment, the active group exhibited a corpus callosum area change of 0.20 $\pm$ 0.70%, whereas the sham group showed a change of -2.08 $\pm$ 0.87%. The difference between the two groups was significant (2.28 $\pm$ 0.87%, $p < 0.02$). The differences were detectable after 3 months as well: The active treatment group had a change of 0.20 $\pm$ 0.62% while the sham group had a change of -1.34 $\pm$ 0.75%. The difference between the groups was also significant after 3 months (1.54 $\pm$ 0.68%, $p < 0.03$).

[0760] **Changes in Corpus Callosum Subregional Areas** **FIG. 82** illustrates the changes in the areas of the corpus callosum subregions. At 6 months, the active treatment group exhibited preservation or reduced atrophy in all studied subregions whereas the sham group showed atrophy in all subregions. The differences between the two groups were significant: Genu/Rostrum (2.36 $\pm$ 0.90%, $p < 0.02$), Anterior-Body (2.64 $\pm$ 1.26%, $p < 0.04$), Mid-Body (2.79 $\pm$ 1.18%, $p < 0.03$), Posterior-Body (2.87 $\pm$ 1.41%, $p < 0.05$), and Splenium (1.58 $\pm$ 0.73%, $p < 0.04$). Furthermore, at the 3-month assessment, preservation of area in the anterior and posterior subregions of the corpus callosum was observed in the active treatment group. This preservation is reflected by the following differences in area change compared to the sham group: Genu/Rostrum (1.59 $\pm$ 0.70%, $p < 0.03$) and Splenium (1.24 $\pm$ 0.54%, $p < 0.03$).

[0761] Annual Atrophy Rates in the Corpus Callosum Several longitudinal studies have documented annual reductions in the corpus callosum area in patients with AD, particularly affecting the genu-rostrum and splenium regions. These are the same regions where we observed the effects of the treatment within 3 months. We compared the one-year projected atrophy rates of the corpus callosum area of participants in the OVERTURE study with those reported for people with and without AD in the literature. Our findings consistently demonstrate either preservation of the corpus callosum area (total, genu/rostrum, anterior, mid, and posterior body) or reduced atrophy (splenium) compared to the rates reported in the literature (Table 6). Observed rates of corpus callosum reduction in the sham group in OVERTURE were in line with previously reported rates of atrophy in people with AD.

[0762] Table 6. Comparison of Corpus Callosum Changes in Literature

REFERENCE	ESTIMATED CHANGE (per year)	POPULATION	N (M/F)	AGE Mean $\pm$ SD (Range)	MMSE TOTAL Mean $\pm$ SD (Range)	CORPUS CALLOSUM	GENU ROSTRUM	ANTERIOR BODY	MID BODY	POSTERIOR BODY	SPLENIUM
OVERTURE	%	Sham	17 (10/7)	75.06 $\pm$ 11.26 (51-91)	18.88 $\pm$ 3.33 (14-25)	-3.46 $\pm$ 1.39	-3.68 $\pm$ 1.45	-3.68 $\pm$ 1.99	-4 $\pm$ 1.89	-3.85 $\pm$ 2.23	-2.7 $\pm$ 1.23
		Active	33 (10/23)	69.21 $\pm$ 7.54 (56-79)	21.15 $\pm$ 3.45 (14-26)	0.22 $\pm$ 1.03	0.12 $\pm$ 1.09	0.44 $\pm$ 1.48	0.88 $\pm$ 1.38	1.23 $\pm$ 1.66	-0.48 $\pm$ 0.91
Elahi et al., 2015	%	MCI-NC	57 (46/11)	74.1 $\pm$ 7.4	27.7 $\pm$ 1.7	0.64 $\pm$ 0.29 (M only) 0.02 $\pm$ 0.60 (F only)	0.98 $\pm$ 0.59 (M only) 0.02 $\pm$ 1.20 (F only)	0.73 $\pm$ 0.63	0.43 $\pm$ 0.62	0.02 $\pm$ 0.69	0.41 $\pm$ 0.47 (M only) 0.02 $\pm$ 0.96 (F only)
		MCI-C	81 (51/30)	74.1 $\pm$ 6.9	26.7 $\pm$ 1.8	0.75 $\pm$ 0.28 (M only) 1.22 $\pm$ 0.36 (F only)	-1.23 $\pm$ 0.56 (M only) 2.03 $\pm$ 0.73 (F only)	0.59 $\pm$ 0.53	0.09 $\pm$ 0.52	0.04 $\pm$ 0.58	-0.82 $\pm$ 0.44 (M only) 1.75 $\pm$ 0.58 (F only)
Teipel et al., 2002	%	NC	10 (6/4)	65.4 $\pm$ 7.2 (52-76)	29.8 $\pm$ 0.4 (29-30)	0.9 $\pm$ 5.0	1.6 $\pm$ 6.3	3.9 $\pm$ 12.1	1.6 $\pm$ 9.5	3.7 $\pm$ 12.7	0.7 $\pm$ 3.6
		AD	21 (11/10)	69.2 $\pm$ 8.2	17.4 $\pm$ 6.7 (1-28)	7.7 $\pm$ 6.7	12.1 $\pm$ 15.1	10.3 $\pm$ 18.8	3.0 $\pm$ 10.6	4 $\pm$ 10	7.3 $\pm$ 9.3

				(54-87)						±18.1	
Zhu et al., 2014	%	NC	72 (22/50)	75.4 3 ±8.23 n.a.	29.19 ±0.85 n.a.	-1.69 ±1.44	n.a.	n.a.	n.a.	n.a.	n.a.
		Decliner	14 (4/10)	77.0 7 ±7.69 n.a.	29.36 ±0.93 n.a.	-1.37 ±0.79	n.a.	n.a.	n.a.	n.a.	n.a.
		AD	51 (30/21)	74.9 6 ±6.23 n.a.	25.92 ±3.09 n.a.	-3.86 ±2.81	n.a.	n.a.	n.a.	n.a.	n.a.
Bachman et al., 2014	Mm ²	NC	75 (21/54)	75.5 n.a. (60-93)	29.2 n.a. (26-30)	-1.50 ±1.56	-0.81 ±0.71	- 0.5 2 ±0.39	-0.09 ±0.40	-0.02 ±0.50	-0.25 ±0.51
		AD-VM	51 (29/22)	75.7 n.a. (61-90)	26.9 n.a. (17-30)	-3.20 ±1.86	-1.61 ±0.84	- 0.43 ±0.45	-0.13 ±0.46	0. 02 ±0.60	-0.95 ±0.59
		AD-M	21 (11/10)	73.4 n.a. (64-83)	23.5 n.a. (19-30)	-4.07 ±3.54	-2.04 ±1.70	0.36 ±1.00	0.22 ±1.03	0. 26 ±1.08	-2.91 ±1.31

NC, Normal Controls; AD, Alzheimer's Disease; AD-VM, Very Mild Alzheimer's Disease; AD-M, Mild Alzheimer's Disease; MCI-C, Mild Cognitive Impairment Converted to Alzheimer's Disease; MCI-NC, Mild Cognitive Impairment NOT Converted to Alzheimer's Disease; M, Male; F, Female; n.a., data not available; $\bar{x}$, mean $\pm$ 95% CI; $\bar{x}$, mean $\pm$ SD; LS_mean $\pm$ SE (one-year projection). See Teipel SJ, Bayer W, Alexander GE, et al. Progression of corpus callosum atrophy in Alzheimer disease. Arch Neurol. 2002 Feb;59(2):243-8; Bachman AH, Lee SH, Sidtis JJ, Ardekani BA. Corpus callosum shape and size changes in early Alzheimer's disease: a longitudinal MRI study using the OASIS brain database. J Alzheimers Dis. 2014;39(1):71-8; Elahi S, Bachman AH, Lee SH, Sidtis JJ, Ardekani BA, Alzheimer's Disease Neuroimaging I. Corpus callosum atrophy rate in mild cognitive impairment and prodromal Alzheimer's disease. J Alzheimers Dis. 2015;45(3):921-31; Zhu M, Wang X, Gao W, et al. Corpus callosum atrophy and cognitive decline in early Alzheimer's disease: longitudinal MRI study. Dement Geriatr Cogn Disord. 2014;37(3-4):214-22.

[0763] Discussion

[0764] We assessed the effects of 40Hz gamma stimulation using a portable system as disclosed herein on the area of the corpus callosum in individuals with clinical MCI and AD. Our findings indicate that after six months, participants receiving active treatment exhibited either preservation or a reduction in atrophy of the corpus callosum compared to those receiving sham treatment. These results constitute an extension of our previous findings that demonstrated that 40Hz

simultaneous audio-visual sensory stimulation preserves white matter integrity. The beneficial effects of 40Hz gamma stimulation can be mediated by stimulation-evoked neuronal oscillatory activity, which potentially enhances white matter plasticity, promoting oligodendrogenesis and adaptive myelination.

[0765] Accelerated loss of corpus callosum area in AD patients is well documented and considered to indicate either axonal loss or loss of myelination of existing interhemispheric axons. Brain atrophy reflects neurodegeneration, but the underlying mechanisms that promote atrophy are not fully understood. Intracellular accumulation of toxic hyperphosphorylated tau likely contributes to neurodegeneration in AD. Hyperphosphorylated tau accumulates in axons and disrupts axonal transport, perhaps accounting for the white matter volume loss that is present at a very early stage of AD progression.

[0766] Preclinical studies demonstrated a protective effect of 40Hz steady-state oscillation, due to optogenetic or non-invasive sensory stimulation. Reduced neurodegeneration and brain volume loss are observed in AD-related transgenic mice when steady-state gamma oscillations are evoked over several weeks due to upregulation of cytoprotective proteins and reduced DNA damage. Furthermore, in ischemic stroke models, there are also neuroprotective effects of gamma oscillation evoked by either optogenetic or sensory stimulations. Recent clinical findings revealed protective effects of sensory-evoked gamma oscillation on brain atrophy in AD patient. Evoked gamma oscillation reduced hippocampal volume loss after 3 months of treatment and whole brain volume loss after 6 months of treatment. Notably, attenuated cortical thinning of the occipital cortex was also observed, a region that has profound steady state oscillation in response to visual stimulation. Reduced neuronal loss due to evoked gamma oscillation can prevent axonal loss as well as decline in corpus callosum structure.

[0767] Neuroprotective effects of evoked gamma oscillations on myelin were also observed in preclinical and clinical studies. A recent study reported that sensory-evoked gamma oscillation prevented demyelination in cuprizone multiple sclerosis model by promoting new oligodendrocyte generation and reducing brain inflammation by decreasing levels of proinflammatory molecules.

[0768] These findings are in line with previous results demonstrating that optogenetic activation of neurons promotes oligodendrocyte differentiation and remyelination of axons in the damaged brain tissue by enhancing axon-oligodendroglia interactions. Our recent findings showed that 40Hz sensory-evoked gamma oscillation preserved various white matter structures in OVERTURE trial participants. Therefore, it is reasonable to consider that preservation of corpus callosum area could be due to both reduced neurodegeneration and demyelination associated with AD progression.

[0769] In conclusion, we demonstrate that 40Hz noninvasive gamma sensory stimulation using a portable system is a promising intervention to preserve corpus callosum integrity.

CLAIMS

WHAT IS CLAIMED IS:

1. A portable neurostimulation system for use by a subject in need thereof, said portable system comprising:
 - a. a first stimulus emitting component comprising a visual source configured to emit a visual stimulus having a frequency of about 20 Hz to about 60 Hz; and
 - b. a second stimulus emitting component comprising an audio source configured to emit an auditory stimulus having a frequency of about 20 Hz to about 60 Hz,wherein said visual source and said audio source are operatively connected and comprised in a single headset device, and wherein said visual source is rotatable about said audio source.
2. The portable system of claim 1, wherein use of said system induces gamma oscillations in a brain region of said subject, thereby slowing progression of a mild cognitive impairment or dementia in said subject.
3. The portable system of claim 1 or 2, wherein said visual source comprises a light emitting diode that projects said visual stimulus towards a screen, wherein said visual stimulus comprises light pulses.
4. The portable system of any one of the preceding claims, wherein said visual source comprises a light emitting diode driver.
5. The portable system of any one of the preceding claims, wherein said audio source comprises a set of headphones.
6. The portable system of claim 5, wherein said audio source comprises supra-aural headphones.
7. The portable system of claim 6, wherein said supra-aural headphones further comprise a removable headband configured to secure said portable system to said head of said subject.
8. The portable system of claim 1, wherein said light pulses have a frequency of about 40 Hz to about 60 Hz.
9. The portable system of claim 8, wherein said light pulses have a frequency of about 35 Hz to about 45 Hz.
10. The portable system of claim 9, wherein said light pulses have a frequency of about 40 Hz.
11. The portable system of claim 1, wherein said auditory stimulus has a frequency of about 40 Hz to about 60 Hz.
12. The portable system of claim 11, wherein said auditory stimulus has a frequency of about 35 Hz to about 45 Hz.

13. The portable system of claim 12, wherein said auditory stimulus has a frequency of about 40 Hz.
14. The portable system of any one of the preceding claims, wherein said visual source comprises glasses.
15. The portable system of claim 14, wherein said glasses comprise a lens that is not opaque.
16. The portable system of claim 15, wherein said lens comprises a translucent lens.
17. The portable system of claim 16, wherein said lens comprises a transmittance of about 0% to about 100%.
18. The portable system of claim any one of the preceding claims, further comprising a third stimulus emitting component comprising a haptic source, wherein said haptic source produces a haptic stimulus.
19. The portable system of claim 18, wherein said haptic stimulus has a frequency of about 40 Hz to about 60 Hz.
20. The portable system of claim 19, wherein said haptic stimulus has a frequency of about 35 Hz to about 45 Hz.
21. The portable system of claim 20, wherein said haptic stimulus has a frequency of about 40 Hz.
22. The portable system of any one of claims 18-21, wherein said haptic stimulus comprises a vibration.
23. The portable system of any one of claims 1-22, further comprising an input device comprising a hand-held controller.
24. The portable system of claim 23, wherein said hand-held controller receives and transmits a signal dictating a dosing parameter corresponding to a frequency of said visual stimulus, a duration of said visual stimulus, a brightness of said visual stimulus, a color of said visual stimulus, a duration of said audio or haptic stimulus, an intensity of said audio or haptic stimulus, a frequency of said audio or haptic stimulus, or any combination thereof.
25. The portable system of claim 24, wherein said hand-held controller further comprises an independent power supply comprising batteries.
26. The portable system of claim 25, wherein said hand-held controller further comprises a rechargeable battery.
27. The portable system of any one of claims 23-26, wherein said hand-held controller is operably connected to receive and transmit said signal to said portable system using Wi-Fi or Bluetooth signals.
28. The portable system of any one of claims 23-27, wherein said portable system further comprises adjustable inputs.

29. The portable system of claim 28, wherein said adjustable input for said portable system comprises an input for powering on and powering off said portable system.
30. The portable system of claim 28 or 29, wherein said adjustable input for said portable system comprises an input for pausing said visual, haptic, or audio stimulus.
31. The portable system of any one of the preceding claims, wherein said portable system further comprises adjustable inputs for said audio source.
32. The portable system of claim 31, wherein said adjustable inputs for said audio source comprise an adjustable volume input.
33. The portable system of any one of the preceding claims, wherein said portable system further comprises adjustable inputs for said haptic source.
34. The portable system of claim 33, wherein said adjustable inputs for said haptic source comprise an adjustable intensity input.
35. The portable system of any one of the preceding claims, wherein said portable system further comprises adjustable inputs for said visual source.
36. The portable system of claim 35, wherein said adjustable inputs for said visual source comprise an adjustable brightness input.
37. The portable system of any one of claims 28-36, wherein said hand-held controller comprises said adjustable inputs.
38. The portable system of any one of claims 28-36, wherein said visual source comprises said adjustable inputs.
39. The portable system of claim 38, wherein said visual source comprises a pair of glasses.
40. The portable system of any one of the preceding claims, wherein said single headset device provides improved comfort, portability, patient adherence, ease of use, or cognitive function of said subject's brain as compared to a portable system for benefiting a cognitive state or function of a brain of a subject comprising a visual source and an audio source that are not operatively configured to comprise a single headset device.
41. The portable system of any one of the preceding claims, wherein said portable system further comprises a rechargeable battery.
42. The portable system of any one of the preceding claims, wherein said portable system further comprises a base.
43. The portable system of claim 42, wherein said base is configured to house said portable system and a hand-held controller.
44. The portable system of claim 43, wherein said base is configured to provide a charge for said rechargeable battery of said portable system and a hand-held controller.

45. The portable system of any one of the preceding claims, wherein use of said system slows progression of a neurological disease.
46. The portable system of claim 45, wherein said neurological disease is Alzheimer's disease.
47. The portable system of claim 45, wherein said neurological disease is Parkinson's disease.
48. The portable system of claim 45, wherein said neurological disease is dementia.
49. The portable system of any one of the preceding claims, wherein said portable system is configured to transmit data to a clinician.
50. The portable system of claim 49, wherein said data comprises records of said subject's use of the portable system, dosing parameters used by said subject, said subject's cognitive state or function, or a combination thereof.
51. The portable system of any one of the preceding claims, wherein said portable system further comprises:
 - c. a processor;
 - d. a memory device; and
 - e. a feedback sensor,wherein said processor receives an indication of a physiological assessment, cognitive assessment, neural assessment, or physical assessment of said subject through said feedback sensor and instructs said first stimulus-emitting component, said second stimulus-emitting component, or said third stimulus-emitting component based on said indication to adjust at least one parameter associated with said auditory, visual, or haptic stimulus.
52. The portable system of claim 51, wherein said adjustment of at least one parameter associated with said auditory, visual, or haptic stimulus comprises an adjustment that induces gamma oscillations in a brain region of said subject.
53. The portable system of claim 51 or 52, wherein said physical assessment of said subject involves ascertaining at least one of said subject's: compliance with proper use and positioning of said system, eye status, alert or sleep status, or environment and surroundings.
54. The portable system of any one of claims 51-53, wherein said neural assessment of said subject is received using brain wave sensors, an electroencephalography (EEG) device, an electrooculography (EOG) devices, or a magnetoencephalography (MEG) device.

55. The portable system of any one of claims 51-54, wherein said cognitive assessment of said subject is obtained through questions posed to said subject, activities and tasks performed by said subject in response to a prompt, or behaviors exhibited by said subject.
56. The portable system of any one of claims 51-55, wherein said processor further instructs said stimulus-emitting component to lengthen or shorten a duration of stimulation in response to said indication of said physiological, cognitive, neural, and/or physical assessment.
57. The portable system of any one of claims 51-56, wherein said physical assessment of said subject is performed to determine hearing of said subject.
58. The portable system of any one of claims 51-57, wherein said system is used to treat, prevent, or mitigate cognitive dysfunction in said subject.
59. The portable system of any one of the preceding claims, wherein use of said portable system comprises inducing one or more improvements in said brain region of said subject.
60. The portable system of claim 59, wherein said one or more improvements comprises maintaining or improving cognitive function in said brain region of said subject.
61. The portable system of claim 60, wherein said maintaining or improving cognitive function comprises maintaining or improving recognition, discrimination, spatial memory, working memory, attention, or a combination thereof.
62. The portable system of claim 60 or 61, wherein said one or more improvements comprises maintaining or reducing tau phosphorylation in said brain region of said subject.
63. The portable system of any one of claims 60-62, wherein said one or more improvements comprises maintaining or reducing an amount of amyloid- β ($A\beta$) peptide in said brain region of said subject.
64. The portable system of any one of claims 60-63, wherein said one or more improvements comprises maintaining or reducing an amount of C-terminal fragments (CTFs) of amyloid precursor protein (APP) in said brain region of said subject.
65. The portable system of any one of claims 60-64, wherein said one or more improvements comprises maintaining or reducing cleavage of APP into CTFs and NTFs by β -secretase (BACE1) in said brain region of said subject.
66. The portable system of any one of claims 60-65, wherein said one or more improvements comprises maintaining or reducing cleavage of APP into CTFs and NTFs by γ -secretase in said brain region of said subject.

67. The portable system of any one of claims 60-66, wherein said one or more improvements comprises maintaining or reducing a number of endosomes in said brain region of said subject.
68. The portable system of any one of claims 60-67, wherein said one or more improvements comprises promoting clearance of A β peptide in said brain region of said subject.
69. The portable system of any one of claims 60-68, wherein said one or more improvements comprises increasing uptake of A β peptide by microglia in said brain region of said subject.
70. The portable system of any one of claims 60-69, wherein said dementia comprises Alzheimer's disease, vascular dementia, Lewy body dementia, Pick's disease, fronto-temporal dementia (FTD), AIDS dementia, age-related cognitive impairments, and age-related memory impairments.
71. The portable system of any one of claims 60-70, wherein said one or more improvements are increased by about 1% to about 100% in said subject as compared to a subject that does not use said portable system.
72. The portable system of claim 2, wherein said brain region comprises an entorhinal cortex, a hippocampus, a cerebral cortex, a visual association cortex, an auditory association cortex, a cingulate lobe, an amygdala, a thalamic nucleus, a cingulate lobe, a pons, a brainstem, a cerebellum, a lateral ventricle, an occipital lobe, a parietal lobe, a temporal lobe, a midbrain, a striatum, a basal ganglia, a globus pallidus, a substantia nigra, or any combination thereof.
73. A method comprising: stimulating a subject with said visual, auditory, or haptic stimulus generated by said portable system of any one of claims 1-72, thereby inducing gamma oscillations in a brain region of said subject.
74. A method of benefiting a cognitive state or function of a brain of a subject, comprising providing a subject said portable system of any one of claims 1-73, and stimulating said subject with said visual, auditory, or haptic stimulus, wherein use of said system induces gamma oscillations in at least one brain region of said subject and causes an improvement in one or more cognitive functions of said subject's brain, thereby slowing progression of mild cognitive impairment or Alzheimer's disease in said subject.
75. The method of claim 73 or 74, wherein said gamma oscillations comprise synchronized gamma oscillations.
76. The method of any one of claims 73-75, wherein said visual, auditory, or haptic stimulus is administered to said subject for about 10 minutes, about 30 minutes, about 45 minutes, about 1 hour, or more than about 1 hour per day.

77. The method of any one of claims 73-76, wherein said visual, auditory, or haptic stimulus is administered to said subject at least once, twice, three times, or more than three times per day.
78. The method of any one of claims 73-77, wherein said subject comprises a mammal.
79. The method of claim 78, wherein said mammal comprises a non-human primate.
80. The method of claim 78, wherein said mammal comprises a human.
81. The method of any one of claims 73-80, wherein said method further comprises a) identifying an activity being performed by a subject; and b) administering said visual, auditory, or haptic stimulus to said subject during said activity to induce a gamma oscillation in a brain region of said subject.