

(51) International Patent Classification:
A61B 5/00 (2006.01)(21) International Application Number:
PCT/US2017/059297(22) International Filing Date:
31 October 2017 (31.10.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/415,996 01 November 2016 (01.11.2016) US(71) Applicant: POLYVAGAL SCIENCE LLC [US/US]; 305
Circle Park PL, Chapel Hill, North Carolina 27517 (US).(72) Inventor: PORGES, Stephen; 524 S. Highland Ave.,
Bloomington, Indiana 47401 (US).(74) Agent: ZELLER, Kyle; 155 Water St., Suite 6-6, Brook-
lyn, New York 11201 (US).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).**Published:**

— with international search report (Art. 21(3))

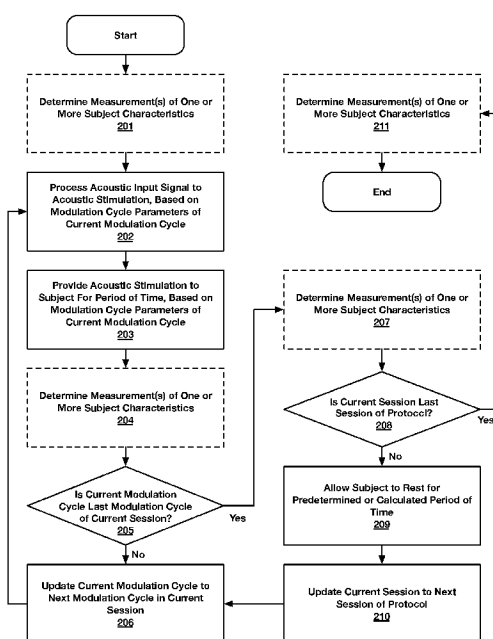
(54) Title: METHODS AND SYSTEMS FOR REDUCING SOUND SENSITIVITIES AND IMPROVING AUDITORY PRO-
CESSING, BEHAVIORAL STATE REGULATION AND SOCIAL ENGAGEMENT

FIG. 2

(57) Abstract: Various embodiments are described herein to reduce sound sensitivities, improve state regulation, and/or reduce auditory processing and social engagement deficits in individuals with such deficiencies by recruiting the anti-masking functions of the middle ear muscles in order to optimize the transfer function of the middle ear for the processing of human speech. In certain embodiments, an individual may be subjected to a training protocol comprising one or more training sessions. During each training session, acoustic stimuli are provided to a subject for a period of time, with or without accompanying visual stimulation. A user response may be determined, for example, before beginning the protocol, during a session, after a session, and/or upon completion of the protocol. Such user response may be employed to adjust the acoustic stimulation, and the adjusted acoustic stimulation may be provided to the subject during a subsequent training session (or at a subsequent time within the same training session). The training protocol may end after a predetermined number of training sessions or upon achieving a desired user response. The training session may be characterized by a fixed protocol during which continuous stimulation is presented for a fixed period of time or by an interactive protocol during which the stimulation presentation is dependent on the reactions of the subject.

**METHODS AND SYSTEMS FOR REDUCING SOUND SENSITIVITIES AND IMPROVING
AUDITORY PROCESSING, BEHAVIORAL STATE REGULATION AND SOCIAL
ENGAGEMENT**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. provisional patent application serial no. 62/415,996, titled “Methods and Systems For Reducing Sound Sensitivities and Improving Auditory Processing, Behavioral State Regulation and Social Engagement Behaviors,” filed November 1, 2016, which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] This specification relates generally to acoustic therapies for the treatment of various conditions, such as sound sensitivities, behavioral and autonomic state regulation difficulties, atypical social engagement behaviors and/or auditory processing deficits.

[0003] Sound sensitivities, difficulties in behavioral and autonomic state regulation, atypical social engagement behaviors and auditory processing deficits are prevalent symptoms in autism spectrum disorders (“ASD”) and other psychiatric diagnoses, such as Post-traumatic stress disorder (“PTSD”). These symptoms may also be present in individuals with developmental disabilities (e.g., Fragile X Syndrome, Prader Willi Syndrome), as well as in aging individuals and those who have been subjected to abuse or neglect.

[0004] Sound sensitivities may be experienced as a discomfort with background ambient sounds or a sensitivity to specific sounds. Such symptoms may be dependent or independent of sound source or the specific frequencies and/or loudness of sound. Problems in state regulation may be expressed as atypical autonomic regulation, atypical social and emotional behaviors, low reactivity thresholds, chronic pain, tantrums, difficulties in sustaining attention and/or sleep disorders. And auditory processing deficits may be

experienced as language and speech delays, difficulties in extracting human voice from background sounds and/or as a general compromise in social communication skills.

[0005] The mechanisms mediating sound sensitivities, autonomic and behavioral state regulation, social engagement and auditory processing are generally assumed to represent disparate response systems. From an empirical perspective, behavioral state regulation and social engagement are manifested in observable behaviors; autonomic regulation is observed in peripheral physiological reactions and medical systems; sound sensitivities are manifested through subjective experiences; and auditory processing is manifested in expressive and/or receptive language skills. Because sound sensitivities and deficits in state regulation, social engagement, and auditory processing lack diagnostic specificity, researchers who study the neurobiological and biobehavioral features of a specific psychiatric diagnosis (e.g., ASD, PTSD, etc.) or a genetic-based neurodevelopment disorder (e.g., Fragile X Syndrome, Prader Willi Syndrome, etc.) have not focused on these domains.

[0006] Moreover, sound sensitivities, behavioral and autonomic state regulation, social engagement and auditory processing are dependent on response systems that are studied by different scientific disciplines, which have little interaction and virtually no common language. For example, the study of psychiatric disorders (i.e., diagnoses), autonomic state regulation problems (e.g., symptoms manifested in visceral organs such as cardiovascular or digestive disorders), behavioral problems (e.g., state regulation and tantrums), psychological difficulties (e.g., emotional instability), sound sensitivities (e.g., a general or selective hypersensitivity to sounds), auditory processing disorders (e.g., difficulties understanding verbal instructions), and cognitive deficits (e.g., language delays) represent research domains investigated by separate disciplines. These distinctions contribute to conventional models of inquiry applied in clinical neuroscience, which rely on separate disciplines to categorize, investigate, treat, and explain the neurobiological mechanisms of clinical disorders.

[0007] One particular theory, the Polyvagal Theory, proposes a strategy that applies evolution as an organizing principle to understand a link between sound sensitivities, behavioral and autonomic state regulation, social engagement and auditory processing. According to the Polyvagal Theory, the well-documented phylogenetic shift in neural regulation of the autonomic nervous system provided mammals with a neural circuit that promotes social interactions in safe contexts by supporting calm physiological states and an ability to process relatively soft vocalizations in a frequency band distinct from the lower frequencies associated with reptilian predators. This “mammalian” circuit functions as the neural substrate for an integrated, social engagement system that dampens the functional impact of sounds outside the frequency band of vocalizations employed for social communication and regulates the neural circuits that optimize behavioral state, social engagement, and auditory processing.

[0008] An exemplary social engagement system according to the Polyvagal Theory is illustrated in **FIG. 1**. As shown, the social engagement system **100** includes a somatomotor component **140** with special visceral efferent pathways traveling through five cranial nerves **130** (i.e., the trigeminal nerve (V), facial nerve (VII), glossopharyngeal nerve (IX), vagus nerve (X) and accessory nerve (XI)) that regulate the striated muscles of the face and head (e.g., middle-ear muscles **141**, laryngeal muscles **142**, muscles of mastication **143**, facial muscles **144**, pharyngeal muscles **145** and head-turning muscles **146**). The somatomotor component **140** regulates the pitch of vocalizations, the tension on the middle-ear muscles to enhance detection and processing of vocalizations, and facial expressions that supplement communicated messages and allow a listener to provide feedback to a vocalizer.

[0009] The social engagement system **100** also includes a visceromotor component **150** with the myelinated vagus that regulates the heart **151** and bronchi **152** to adjust an individual's physiological state to be complement their facial and vocal signals of social communication. Thus, the visceromotor component **150** allows for an individual to project a physiological state of calmness or defense through voice and face. Coincident with this projection of physiological state, the middle-ear muscles change muscle tone to

either facilitate the processing of vocalizations (e.g., by dampening the transfer of acoustic energy representing low frequencies in the background) or enhance the processing of low frequency acoustic energy at the expense of dampening the ability to extract the acoustic information of vocalizations. Because, via evolution, low-frequency acoustic information signaled predator or environmental danger, this system requires cues of “safety.”

[0010] Based on the Polyvagal Theory, sound sensitivities and deficits in state regulation, social engagement and auditory processing may be paralleled by reduced vagal influences to the heart and bronchi via myelinated vagal pathways. Such a reduction is an adaptive response strategy to support mobilization (i.e., so-called “fight-flight” behaviors) in dangerous environments. Since the Polyvagal Theory articulates a hierarchy of neural circuits, the metabolic resources necessary for fight–flight behaviors are not efficiently available unless there is a retraction of the vagal brake—a calming mechanism that functions via the myelinated vagus to slow heart rate, optimize oxygenation of the blood, and to downregulate the sympathetic nervous system. This neurophysiological calming mechanism downregulates defensive states and enables social engagement behaviors to spontaneously occur. Thus, the neural mechanisms defining the social engagement system provide a plausible model to explain why sound sensitivities and both auditory processing and state regulation difficulties are prevalent in individuals with ASD and other clinical disorders. Consistent with this model, features of the social engagement system become windows of assessment and, due to the integrated nature of the system, these features may also be portals for possible intervention.

[0011] One particular portal of interest lies in the neural regulation of the middle-ear muscles. These muscles facilitate the extraction of human speech by dampening the transmission of low-frequency noise from the external environment to the inner ear. Sound enters the outer ear and travels, through the external auditory canal, to the eardrum where it is transduced by the structures of the middle ear (i.e., small bones comprising the ossicular chain) that connect the eardrum with the cochlea.

- [0012] The rigidity of the ossicular chain determines the stiffness of the eardrum, which, in part, determines the acoustic properties of sounds transmitted to the inner ear. The middle-ear muscles, via cranial nerves, regulate the position of the ossicles and stiffen or loosen the eardrum. When the eardrum is “tightened,” higher frequencies are absorbed and transmitted to the inner ear and the energy of lower frequencies is attenuated (i.e., reflected) before being encoded by the inner ear (i.e., the cochlea) and transmitted via the auditory nerve (i.e., cranial nerve VIII) to the cortex. Complementing the ascending pathways are descending pathways that regulate the middle-ear muscles, which functionally determine the energy (i.e., attenuate, pass, or amplify) of specific frequencies that reach the inner ear.
- [0013] The features describing the transformation of sound intensity from the outer ear to the inner ear defines the middle-ear transfer function. If the acoustic information in the frequency band associated with speech is distorted by an atypical middle-ear transfer function, the information coded by the inner ear (and subsequently transmitted to the cortex) may not contain sufficient information to enable accurate detection of speech sounds. In addition, there are descending pathways that regulate the hair cells in the cochlea to fine tune auditory perception, which is especially important in the development of language skills. If the acoustic information related to human speech that reaches the cortex via ascending pathways is distorted, then the descending pathways to the cochlea may also be atypical and will further distort the individual’s ability to process speech and to produce language.
- [0014] Atypical central regulation of peripheral middle-ear structures may pass low-frequency sounds that dominate the acoustic spectrum in our mechanized society (e.g., ventilation systems, traffic, airplanes, vacuum cleaners, and other appliances). This may result in both a hypersensitivity to sounds and a distortion or “masking” of the frequency components associated with human speech reaching the brain. Thus, an atypical middle-ear transfer function may be a potentially parsimonious explanation of both the auditory hypersensitivities and the difficulties in auditory processing frequently associated with autism.

[0015] There is a need in the art for systems and methods that can rehabilitate the integrated social engagement system via exercise of a specific portal, such as the middle-ear muscles.

SUMMARY

[0016] Various acoustic therapy systems and methods are described herein that are capable of treating various conditions, such as sound sensitivities, behavioral and autonomic state regulation difficulties, atypical social engagement behaviors and/or auditory processing deficits. Exemplary embodiments present processed acoustic stimuli to a subject in order to recruit and/or exercise neural regulation of the subject's middle-ear muscles.

[0017] It is an object of the embodiments to provide methods and systems for treating symptoms associated with aging, ASD, PTSD, and other clinical disorders, such as sound sensitivities, behavioral and autonomic state regulation deficiencies and/or auditory processing and social engagement deficits, by engaging neural regulation of specific structures described as part of the social engagement system (see **FIG. 1** at **100**).

[0018] It is another object of the embodiments to provide methods and systems for treating sound sensitivities, behavioral and autonomic state regulation deficiencies and/or auditory processing and social engagement deficits, the results of which may be measured through well-defined indices of auditory hypersensitivities and auditory processing, and through innovative indices of the middle-ear transfer function and/or physiological state (i.e., through measure of autonomic function).

[0019] It is another object of the embodiments to provide methods and systems for treating sound sensitivities, behavioral and autonomic state regulation deficiencies and/or auditory processing and social engagement deficits, wherein such embodiments are designed to engage and exercise the neural regulation of the middle-ear muscles, and provide an understanding of the transfer function of the middle-ear structures and the vulnerability of the fast twitch middle-ear muscles to fatigue.

[0020] It is yet another object of the embodiments to provide methods and systems for treating sound sensitivities, behavioral and autonomic state regulation deficiencies, auditory processing and social engagement deficits, chronic pain and associated conditions, anxiety disorders, blood sugar regulation deficiencies and/or conditions associated with aging, wherein a treatment protocol employs a noninvasive, acoustic vagal nerve stimulation to increase vagal activity to the heart via an auditory pathway.

[0021] In one embodiment, a method is provided wherein an acoustic input signal is processed according to processing parameters to produce acoustic stimuli during a session. The processing parameters may include a first frequency modulation cycle that includes a first initial modulation, a first widest modulation and a first final modulation. The first initial modulation may be defined by a first initial low-frequency limit of from about 600 Hz to about 900 Hz and a first initial high-frequency limit of from about 1,400 Hz to about 2,000 Hz. The first widest modulation may be defined by a first minimum low-frequency limit that is lower than the first initial low-frequency limit and a first maximum high-frequency limit that is higher than the first initial high-frequency limit. And the first final modulation may be defined by a first final low-frequency limit that is substantially similar to the first initial low-frequency limit and a first final high-frequency limit that is substantially similar to the first initial high-frequency limit.

[0022] The processing parameters may further include a second frequency modulation cycle that includes a second initial modulation, a second widest modulation and a second final modulation. The second initial modulation may be defined by a second initial low-frequency limit and a second initial high-frequency limit. The second widest modulation may be defined by a second minimum low-frequency limit that is lower than the second initial low-frequency limit and a second maximum high-frequency limit that is higher than the second initial high-frequency limit. And the second final modulation may be defined by a second final low-frequency limit that is substantially similar to the second initial low-frequency limit and a second final high-frequency limit that is substantially similar to the second initial high-frequency limit. The second minimum low-frequency limit of the second widest modulation may be lower than the first minimum low-

frequency limit of the first widest modulation of the first modulation cycle. Moreover, the second maximum high-frequency limit of the second widest modulation may be higher than the first maximum high-frequency limit of the first widest modulation of the first modulation cycle. It will be appreciated that the processing parameters may include any number of modulation cycles and each modulation cycle may include any number of modulations.

[0023] The method may further include transmitting the acoustic stimuli to the subject during the session to thereby recruit one or more anti-masking functions of one or more middle-ear muscles of the subject. And the method may also include determining that the subject has experienced a user response, such as one or more of reduced sound sensitivity, improved auditory processing, improved behavioral state regulation, improved autonomic state regulation, improved middle-ear transfer function and improved social engagement.

[0024] In certain embodiments, the method may include measuring one or more characteristics of the subject before processing the acoustic input signal to acoustic stimuli, wherein the one more characteristics are selected from the group consisting of: sound sensitivity, behavioral state regulation, autonomic state regulation, auditory processing, one or more social engagement skills, sucking, swallowing, breathing, one or more acoustic properties of vocalization of the subject, heart rate variability (“HRV”), respiratory sinus arrhythmia (“RSA”), heart rate, blood pressure, cognitive ability, pain level, anxiety level, blood sugar level, usage of one or more facial muscles, usage of one or more head-turning muscles and a middle-ear transfer function. Optionally, such measurements may be employed to adjust the processing parameters.

[0025] The details of one or more embodiments of the subject matter of this specification are set forth in the accompanying drawings and the description below. Other features, aspects, and advantages of the subject matter will become apparent from the description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] **FIG. 1** shows an exemplary social engagement system **100** according to the Polyvagal Theory.

[0027] **FIG. 2** shows a schematic diagram of an exemplary method according to an embodiment.

[0028] **FIG. 3** shows an exemplary middle-ear sound absorption (“MESA”) system **300** according to an embodiment.

[0029] **FIG. 4** shows a system architecture according to an exemplary embodiment.

[0030] **FIGs. 5-13** show graphical representations of exemplary frequency modulation cycles employed to process an acoustic input signal to acoustic stimuli that is transmitted to a subject during a first session (**FIG. 5**), second session (**FIG. 6**), third session (**FIG. 7**), fourth session (**FIG. 8**), fifth session (**FIG. 9**), sixth session (**FIG. 10**), seventh session (**FIG. 11**), eighth and ninth sessions (**FIG. 12**) and a tenth session (**FIG. 13**) of a training protocol according to an embodiment.

[0031] **FIGs. 14-16** show graphical representations of exemplary frequency modulation cycles employed to process an acoustic input signal to acoustic stimuli that is transmitted to a subject during three exemplary booster sessions according to an embodiment.

DETAILED DESCRIPTION

[0032] Various embodiments are described herein to reduce sound sensitivities, improve behavioral and autonomic state regulation, and/or reduce auditory processing and social engagement deficits in individuals with such deficiencies by recruiting the anti-masking functions of the middle-ear muscles in order to optimize the transfer function of the middle ear for the processing of human speech. In certain embodiments, an individual may be subjected to a training protocol comprising one or more training sessions. During each training session, modulated acoustic stimulation is provided to a subject, with or without accompanying, synchronized visual stimulation (e.g., video, virtual reality (“VR”) environment, etc.). A user response may be determined, for example, before

beginning the protocol, during one or more sessions, after one or more sessions and/or upon completion of the protocol. Such user response(s) may be employed to adjust one or more parameters of the protocol, including but not limited to: the total number of sessions, the length of one or more sessions and/or the acoustic stimulation provided during one or more sessions. Accordingly, each training session may comprise a predetermined period of time or a variable period of time based on user response. Similarly, the training protocol may end after a predetermined number of sessions or upon achieving a desired user response.

[0033] It has surprisingly been found that the exemplary methods and systems described herein may enhance the function of the social engagement system described by the Polyvagal Theory **100**, leading to improved auditory processing, reduced auditory hypersensitivities, changes in autonomic state characterized by increased vagal regulation of the heart (e.g., increases in HRV and RSA), and increased spontaneous social behaviors (e.g., sharing).

[0034] Without wishing to be bound to a particular theory, it is believed that the specific acoustic stimuli provided to a subject during training exercises the neural regulation of the middle-ear muscles. By modulating the frequency band associated with human vocalizations, the ascending pathways provide dynamically changing information that feeds back on the descending pathways regulating the middle-ear muscles. Metaphorically, exemplary methods described herein may be conceptualized as a “treadmill” exercise for the middle-ear muscles, where such muscles are engaged to listen and process features of dynamically changing acoustic stimuli. Accordingly, the exemplary methods may be employed to “rehabilitate” acoustic reflex functionality of the middle-ear muscles and/or to normalize the middle-ear transfer function.

[0035] It is believed the specifically selected and processed acoustic stimuli increases neural regulation of middle-ear structures to: dampen the perception of background low-frequency sounds, potentiate the extraction of human voice, functionally calm the behavioral and physiological state by increasing vagal regulation of the heart, and/or

promote more spontaneous social engagement behaviors. In this way, the disclosed systems and methods may trigger neural mechanisms that regulate the entire social engagement system, including enhanced vagal regulation of bodily organs.

[0036] Referring to **FIG. 2**, an exemplary method according to an embodiment is illustrated. As shown, acoustic stimuli are presented to a subject during any number of sessions of an exemplary listening protocol adapted to recruit the function of the subject's middle-ear muscles. Generally, one or more characteristics of the subject may be measured at various times before, during and/or after the protocol and one or more user responses (e.g., functional enhancement of neural regulation of the middle-ear muscles, improved auditory processing and/or any vagal regulation of the heart) may be determined by, for example, contrasting such measurements. As discussed in detail below, in certain embodiments, any of the measurements and/or determined user responses may be employed to dynamically adjust one or more protocol parameters, such as but not limited to: a total number of sessions, a duration of one or more sessions, and/or parameters of the acoustic stimuli presented to the subject during one or more sessions.

[0037] In a first optional step **201**, one or more of a subject's characteristics may be measured, observed or evaluated. In one embodiment, a structured questionnaire may be completed by, for example, a parent, guardian, teacher, doctor, or peer of the subject. Exemplary questionnaires may target specific categories of the subject's developmental and/or behavioral issues, including but not limited to, sound sensitivities and/or difficulties in interpreting the emotional state of others. Such questionnaires may focus on whether the subject has had difficulties in a specific behavioral area. Exemplary questionnaires may inquire about one or more of the following: sound sensitivity (e.g., exaggerated negative responses to common noises, such as crying or placing hands over the ears); spontaneous speech (e.g., non-prompted use of words to communicate thoughts and ideas); receptive speech (e.g., ability to understand instructions and/or phrases); spontaneity (e.g., non-prompted behaviors initiated by the subject); behavioral organization (e.g., ability to occupy oneself in a productive way when left alone); emotional control (e.g., ability to calm, ability to respond to unexpected changes without getting upset, etc.); affection

(e.g., behaviors reflective of warm emotional state, such as spontaneous kissing or hugging); listening (e.g., ability to focus on human speech without visual cues); eye contact (e.g., making and maintaining eye contact); and/or relatedness (e.g., understanding of joint partnership).

[0038] Additionally or alternatively, any number of deficits in the features of a subject's social engagement system may be determined via observation, inquiry and/or physical measurement. For example, the subject may be tested to determine such characteristics as: ingestive disorders; difficulties in listening (e.g., sound sensitivities, auditory processing deficits, extraction of human voice from background sounds and/or language delays); difficulties in coordinating sucking, swallowing, vocalizing, and/or breathing; atypical intonation during vocalization (e.g., lack vocal prosody); facial expression deficits (e.g., difficulties in gaze and/or flat affect); lack of head gestures; and/or reduced vagal influences to the heart via the myelinated vagus (e.g., measured by the amplitude of RSA).

[0039] In one embodiment, cognitive ability may be determined as part of the assessment. For example, a Kaufman Brief Intelligence Test ("KBIT") may be administered. *See* Kaufman, A. S. et al. "Kaufman Brief Intelligence Test Manual," American Guidance Service, Circle Pines, MN (1990) (incorporated by reference herein in its entirety). In other embodiments, a subject's level of pain may be evaluated, for example, by administering the McGill Pain Questionnaire. *See* Melzack, R. "The short-form McGill pain questionnaire," *Pain* 30.2 (1987): 191-197 (incorporated by reference here in its entirety).

[0040] In certain embodiments, the subject may be required to participate in a semi-structured, task-based, observational assessment to determine, for example, social engagement skills. The subject may be graded on a social interaction coding scale ("SICS"), an autism diagnostic observational scale ("ADOS") and/or an early social communication coding scale ("ESCS"). As a specific example, a child may be required to participate in a ten-

minute, semi-structured, play-based observational assessment with a therapist, which may be videotaped.

- [0041]** Auditory processing may be evaluated with a number of tests, such as the Filtered Words (“FW”) and/or Competing Words (“CW”) subtests from the SCAN Test for Auditory Processing Disorder. The FW subtest assesses a subject’s ability to decipher human speech from background sounds, which is a component of receptive language skills. The CW subtest is a dichotic listening task, which identifies developmentally delayed or damaged central auditory pathways. *See* Keith, R.W. “SCAN: A Screening Test for Auditory Processing Disorders,” The Psychological Corporation, San Antonio, TX (1986); and Keith, R.W. “SCAN-C: Test for Auditory Processing Disorders in Children—Revised,” The Psychological Corporation, San Antonio, TX (2000) (each of which are incorporated by reference herein in its entirety).
- [0042]** Acoustic properties of the subject’s vocalizations may be evaluated using frequency analyses (e.g., spectral analyses) and/or time-frequency analyses (e.g., modulation power spectrum analysis). These analyses can quantify the modulation of intonation (i.e., prosody) in the subject’s vocalizations—an important quality in social communication.
- [0043]** Additionally or alternatively, a number of tests may be conducted to assess characteristics of the subject’s physiological state. These tests may quantify neural regulation of autonomic state and may measure one or more of: blood pressure, heart rate, HRV, RSA and vasomotor activity. Moreover, in certain embodiments, one or more tests may be conducted to determine a level of anxiety or discomfort experienced by the patients.
- [0044]** A subject’s heart rate, HRV and/or RSA can be measured using contact sensors, such as an electrocardiogram (“ECG”) or a photoplethysmogram (“PPG”), and/or through noncontact methods. ECG may be assessed with, for example, a BIOPAC MP150 physiological acquisition system (Biopac Systems, Inc., Santa Barbara, CA), an EZ-IBI interbeat interval monitor (UFI, Morro Bay, CA), and/or a BIOLOG ambulatory heart rate monitor (UFI, Morro Bay, CA). A contact PPG may be assessed with, for example, a BIOPAC MP150 physiological acquisition system (Biopac Systems, Inc., Santa Barbara,

CA) and/or a noncontact PPG may be assessed via any of the systems described in U.S. Patent App. Pub. No. 20160317041 to Porges et al. (incorporated by reference herein in its entirety). Exemplary monitoring systems may sample ECG at around 1 kHz with minimal artifact and PPG at around 100 Hz with minimal artifact.

[0045] ECG and/or heart-period data from the monitoring device(s) may be visually inspected and/or edited. Editing may comprise, for example, integer arithmetic (e.g., dividing intervals between heart beats when detections of R-wave from the ECG or pulse waves from the PPG are missed, or adding intervals when spuriously invalid detections occur).

[0046] In one embodiment, RSA may be calculated via the method, described in U.S. Patent No. 4,510,944 to Porges (incorporated by reference herein in its entirety). This method quantifies the amplitude of RSA with age-specific parameters that are sensitive to the maturational shifts in the frequency of spontaneous breathing. In one embodiment, the method comprises the following steps: (1) R–R intervals or pulse-to-pulse intervals are timed to the nearest millisecond to produce a time series of sequential heart periods (i.e., the time between heart beats); (2) sequential heart periods are resampled into 250 ms intervals to produce time-based data; (3) the time-based series is detrended by a 51-point cubic moving polynomial that is stepped through the data to create a smoothed template and the template is subtracted from the original time-based series to generate a detrended residual series; (4) the detrended time series is bandpassed to extract the variance in the heart period pattern associated with spontaneous breathing (e.g., about 0.12 to about 1.0 Hz, depending on age); and (5) the natural logarithm of the variance of the bandpassed time series is calculated as the measure of the amplitude of RSA.

[0047] Heart period is a composite variable that is influenced by neural tone via both the parasympathetic and sympathetic branches of the autonomic nervous systems. This variable is, in part, determined by the size of the heart, which imposes limits on the temporal parameters of electrical potentials arising from a myocardium manifested in an ECG. The maturational increase in body size is paralleled by a decrease in heart rate (i.e., increase in heart period), reflecting the expanded time necessary to complete a heartbeat.

- [0048] In one embodiment, a subject's middle-ear transfer function may be assessed using a MESA system, as illustrated in **FIG. 3**. Generally, a MESA system **300** may be employed to characterize or evaluate a subject's middle-ear transfer function by measuring one or more properties (e.g., intensity, magnitude and/or phase shift) of a sound wave reflected off the subject's eardrum.
- [0049] As shown, an ear probe **310** having a speaker **311** and a microphone **312** may be placed within an ear **362** of a subject **360** such that the probe **310** is in sound-wave communication with the eardrum and middle-ear muscles of the ear **362**. Within the signal generator **313**, a series of sinusoidal signals may be combined by a digital processor to create a probe tone **340**. This digital signal, D_{in} , is converted to an analog voltage and driven through the speaker **311**, creating a pressure wave in the ear canal that reflects off the subject's ear **362**. A reflected sound wave **350** is detected by the microphone **312** and digitized to create a time synchronous representation of the reflected probe signal, D_{out} . An ear-muscle movement calculator **390** receives the two digital signals (D_{in} and D_{out}) and estimates a reflectance transfer function ("RTF"), which relates incoming sound energy within the ear canal to outgoing sound energy at the same position in the ear canal. Accordingly, the MESA system **300** allows for assessment of both supra- and sub-reflexive levels of contractions, measurement of changes in middle-ear muscle status in response to various acoustic challenges and/or determination of psychological state. In one embodiment, the MESA system disclosed in U.S. Patent App. Pub. No. 2013/0303941 to Porges et al. (incorporated by reference herein in its entirety) may be employed.
- [0050] Returning to **FIG. 2**, after initial measurements of one or more characteristics of the subject are determined in step **201**, a first treatment session may begin. As shown, an acoustic input signal may be processed by an audio processing device such that acoustic stimuli is produced **202** and eventually transmitted to the subject **203**. Generally, the acoustic input signal may be processed (i.e., modulated) to produce acoustic stimuli designed to exercise the neural regulation of the middle-ear structures and muscles of the subject.

- [0051]** In one embodiment, the acoustic input signal may comprise one or more of pre-recorded human speech, human singing, instrumental music, synthesized music and combinations thereof. For example, the input signal may have acoustic properties similar to a mother singing a lullaby to infant. Prerecorded vocal or instrumental music may be selected based on a number of variables, such as but not limited to: frequency band, modulation of intonation within the frequency band, tempo, volume and/or modulation of volume.
- [0052]** Certain soundtracks of animated movies (e.g., those created by The Walt Disney Company and its subsidiaries) provide an example of the optimal acoustic features for input acoustic stimulation. Such soundtracks emphasize melodic voices above middle C (i.e., 261.6 Hz), have an upbeat tempo, vary in volume within a comfortable range and minimize the inclusion of very low and very high acoustic frequencies. Other preferred acoustic input signals include, but are not limited to, lullabies, love songs, folk music and bluegrass ballads.
- [0053]** In another embodiment, the acoustic input signal may not be pre-recorded. Rather, the acoustic input signal may be an environmental acoustic signal, such as audio from a video being watched by the subject or speech of a person with whom the subject is interacting (e.g., a teacher, parent, therapist, medical professional or researcher). In such embodiments, the acoustic input signal may be dynamically processed into acoustic stimuli and output to a subject in real time or near real time such that the acoustic stimuli is synchronized to the video or interaction experiences. This may allow the subject to exercise neural regulation of the middle-ear muscles while, for example, listening to music, watching videos or dynamically interacting with others (e.g., in an educational, clinical or social context).
- [0054]** In each case, the selected input acoustic signal is processed to produce acoustic stimuli such that frequencies within a defined bandwidth are emphasized. To that end, the input acoustic signal may be processed to acoustic stimuli by attenuating frequencies outside an emphasized bandwidth (i.e., by filtering frequencies above a high-frequency limit and/or below a low-frequency limit).

- [0055] Generally, the frequency characteristics of the acoustic stimuli may be selected to emphasize the frequency band in which information related to human speech is conveyed, consistent and overlapping with the documented frequency band and weights associated with the Index of Articulation (“AI”) as defined in American National Standard ANSI S3.5-1997 American National Standard ANSI S3.5-1997 (“Methods for Calculation of the Speech Intelligibility Index”) and/or the Speech Intelligibility Index (“SII”) as described in Pavlovic, C. V. “Derivation of primary parameters and procedure’s for use in speech intelligibility predictions,” J. Acoust. Soc. Am. 82 (1987): 413-422 (each of which is incorporated by reference herein in its entirety). The AI is a quantified expression of the proportion of the average speech signal that is audible to a person in a given environment and is expressed on a scale of 0 to 1.0, with 1.0 representing perfect audible speech. The SII quantifies the intelligibility of speech and it is also expressed on a scale of 0 to 1.0.
- [0056] Such indices emphasize the relative importance of specific frequencies in conveying information related to cues about the human nervous system that are embedded in human vocalizations and that foster the regulation of autonomic and behavioral state. During “normal” listening to human speech, the middle-ear muscles are contracted to stiffen the ossicle chain and to optimize the extraction of human voice from background sounds (e.g., via descending central mechanisms). In a “normal” ear, acoustic energy within the primary frequencies of these indices is not attenuated (or is minimally attenuated) and may pass through the middle-ear structures to the inner ear.
- [0057] In one embodiment, the acoustic stimuli may be conceptualized as providing a “treadmill” exercise for the middle-ear muscles during which the demands to listen to, and process, the acoustic features of acoustic stimuli dynamically change. A traditional treadmill can dynamically adjust the walking and/or running speed and slope as the user of the treadmill is exercising. Treadmills can be programmed with a variety of exercise routines, with the speed and/or slope changing at defined times. Similarly, the acoustic stimuli may comprise dynamic challenges for the middle-ear muscles as the descending neural pathways adjust the middle-ear muscles in response to the changing processing

demands required by the input acoustic stimuli during a single session or across multiple sessions.

[0058] To that end, the acoustics stimuli provided to a subject may be adjusted continuously or discretely throughout a session (and across multiple sessions). In preferred embodiments the acoustic stimuli is processed from the input acoustic signal via a number of sequential, episodic bandwidth modulations or “modulation cycles.” Such modulation cycles may be seamlessly connected in time and implemented over the duration of a session.

[0059] Generally, each modulation cycle comprises at least an adjustment from a first modulation to any number of additional modulations, and an adjustment back to the first modulation. A modulation cycle may start with a minimum bandwidth and dynamically shift to broader bandwidths until a maximum bandwidth is reached. The modulation cycle may then continue to shift to narrower bandwidths until finally returning to the minimum bandwidth. For example, a modulation cycle may comprise: starting at a first, narrow modulation; adjusting from the first modulation to a wider, second modulation; adjusting from the second modulation to a widest, third modulation; adjusting from the third modulation back to the second modulation; and finally adjusting from the second modulation back to the first modulation.

[0060] Accordingly, modulation cycles may be defined by modulation cycle parameters, including: duration, a minimum frequency, a maximum frequency, a narrowest bandwidth, a widest bandwidth, individual changes in range of frequencies (i.e., modulations) and/or slope of the changes in frequencies. It will be appreciated that the minimum and maximum frequencies of a modulation within a given modulation cycle may define the modulation cycle’s bandwidth at any given time, and the duration of each modulation determines the slope of the modulation cycle.

[0061] In preferred embodiments, each modulation cycle may begin and end with a narrow frequency modulation bandwidth defined by a low-frequency limit of from about 600 Hz to about 900 Hz (e.g., about 800 Hz) and a high-frequency limit of from about 1,400 Hz

to about 2,000 Hz (e.g., about 1,500 Hz). Accordingly, the center frequency of each modulation cycle may be approximately equal to the resonant frequency of the middle ear in humans (i.e., about 800 Hz to about 1,200 Hz).

[0062] Exemplary modulation cycles may emphasize bandwidths within a low-frequency limit of from about 200 Hz to about 1,000 Hz (e.g., about 300 Hz, about 400 Hz, about 500 Hz, about 600 Hz, about 700 Hz, about 800 Hz, about 900 Hz or about 1,000 Hz) and a high-frequency limit of from about 1,200 Hz to about 5,000 Hz. A number of exemplary modulation cycles and corresponding emphasized bandwidths are shown in **FIGs. 5-16** and **Tables 1-12**, below. It will be appreciated that acoustic information in an input acoustic signal that is outside the emphasized bandwidth of any given modulation cycle may be attenuated (i.e., such information will not be included in the acoustic stimuli presented to the subject).

[0063] The modulation cycles employed in exemplary methods are generally selected to enable acoustic energy to be effectively transmitted across middle-ear structures of humans, regardless of the neural tone to the middle-ear muscles. However, it will be appreciated the described methods may also be useful for non-human subjects (e.g., for calming a dog or cat before a veterinary procedure) and such modulation cycles may be adapted for these non-human subjects by modifying the center frequency according to properties of their middle-ear structures. In such cases, the modulation cycles may comprise a bandwidth approximately defined by the following equation:

$$\pm 0.7 \times \log_{10}(\text{resonant frequency})$$

[0064] The duration of each modulation cycle may be framed within the timing of neural regulation of the autonomic nervous system that is inherent in the rhythms of normal homeostasis (e.g., respiration, blood pressure, intracranial fluid, and/or vasomotor activity). For example, the duration of a given modulation cycle may range from about 60 seconds (1 minute) to about 300 seconds (5 minutes) (e.g., about 60 seconds, about 90 seconds, about 120 seconds, about 150 seconds, about 180 seconds, about 210 seconds, about 240 seconds, about 270 seconds or about 300 seconds. And the duration of each

modulation within a modulation cycle may range from about 5 seconds to about 90 seconds, typically from about 10 seconds to about 30 seconds (e.g., about 10 seconds, about 15 seconds, about 20 seconds, about 25 seconds or about 30 seconds).

[0065] It will be appreciated that the number of modulation cycles and/or the parameters of each modulation cycle may vary within a session and across multiple session. Similarly, each modulation cycle may include any number of modulations comprising varying durations and/or bandwidths.

[0066] In one embodiment, the number of modulation cycles and/or the parameters of each modulation cycle within a session may be predetermined. In this case, the duration of each modulation cycle may be predetermined and informed by endogenous physiological rhythms associated with homeostatic processes (e.g., breathing, vasomotor and blood pressure oscillations). In other embodiments, the number of modulation cycles and/or the parameters of each modulation cycle within a session may be dynamically determined based on user response to the acoustic stimuli (e.g., measurement(s) of one or more characteristics of the subject and/or one or more determined subject results).

[0067] In any event, at step **202**, the acoustic input signal is processed to acoustic stimuli based on modulation cycle parameters of a first modulation cycle of a first session. As explained above, the modulation cycle parameters provide the algorithm to process acoustic stimuli. Importantly, such processing is independent of the input acoustic signal.

[0068] At step **203**, the acoustic stimuli processed according to the first modulation cycle parameters is provided to the subject (e.g., via a listening device). Exemplary listening device may include headphones, circumaural headphones, earphones, one or more external speakers, an integrated or external display and/or a virtual reality device. The listening device may be adapted to output acoustic stimuli to the subject with or without synchronized video.

[0069] In one embodiment, a listening device may be placed in electrical communication (e.g., wired or wireless) with an acoustic stimuli output device. The output device may receive an acoustic input signal, perform modulation, and output acoustic stimuli to the listening

device. Alternatively, the output device may simply read and/or receive pre-recorded acoustic stimuli and provide the same to the listening device without further modulation of the acoustic stimulation. The listening device may receive the acoustic stimulation and output the same to a subject via one or more speakers.

[0070] In another embodiment, a listening device may be configured to receive an acoustic input signal from an audio output device and/or via a microphone. The listening device may comprise electronic circuitry adapted to receive the acoustic input signal, perform modulation on the same, and output acoustic stimuli to a subject via one or more speakers. It will be appreciated that the listening device may process the input signal in substantially real time, according to the principles discussed above.

[0071] In certain embodiments, the acoustic stimuli may be either monophonic or stereophonic. In a monophonic mode, the same acoustic features are simultaneously delivered to both ears. In a stereophonic mode, human vocalization may be delivered to one ear (e.g., the right ear) and acoustic stimuli without human vocalization may be delivered to the other ear (e.g., the left ear). In this case, the acoustic stimuli provided to each ear may be processed to pass acoustic features in the same bandwidth or different bandwidths. Moreover, the relative loudness of the left and right channels may be manipulated by the system together or independently, as desired or required. This lateralization is consistent with the neurophysiology that supports a right-ear advantage for the processing of speech.

[0072] In one embodiment, the volume may not be manipulated, as vocal music already varies in volume. By varying the bandwidth, the total acoustic energy is varied in addition to the original volume shifts. Accordingly, equipment may be set to a peak sound pressure level (e.g., about 70 dB). In other embodiments, the volume may be varied as desired or required.

[0073] It will be appreciated that the context in which the protocol is performed influences the ability to actively recruit the neural regulation of the middle-ear muscles. The context should be quiet and safe to convey cues to the nervous system to calm the subject's

autonomic state. Cues and background noises can trigger shifts in autonomic state that support defense and adaptively reduce the neural tone to the middle ear muscles. In addition, social support, by a parent, friend, or therapist, may be necessary to send cues of safety to the subject's nervous system to facilitate the recruitment of the neural regulation of the middle muscles via the invention.

[0074] Generally, the duration of each session may be limited to ensure that the fast-twitch middle-ear muscles do not fatigue. In one embodiment, each session may be from about 10 minutes to about 90 minutes and, more specifically, from about 30 minutes to about 75 minutes (e.g., about 30 minutes, about 45 minutes, about 60 minutes or about 75 minutes). In certain embodiments, the length of each session may differ (e.g., the sessions may get progressively longer or shorter during the protocol). Similarly, each session may differ in one or more additional session parameters, such as: input audio signal characteristics and acoustic stimuli characteristics (e.g., number of modulation cycles and/or parameters of each modulation cycle).

[0075] In any event, upon completing the first modulation cycle (i.e., the “current modulation cycle”), a determination may be made as to whether the current modulation cycle is the last modulation cycle in the current session **205**. If the current modulation cycle is not the last modulation cycle in the current session, the method may update the current modulation cycle to the next modulation cycle in the current session (step **205**) and then return to step **202** to process the input acoustic signal according to the parameters of the next modulation cycle.

[0076] However, if the current modulation cycle is the last modulation cycle of the current session, the method may proceed to step **208**, where a determination is made as to whether the current session is the last session of a given protocol. Generally, the duration and timing of an exemplary protocol is designed to deal with fatigue and provide sufficient exercises over an entire selected bandwidth. Accordingly, in certain embodiments, the training protocol may end after a predetermined number of sessions or, as discussed in detail below, upon achieving a desired user response.

[0077] If the current session is not the last session of the protocol, the subject may be allowed or required to rest for a predetermined and/or calculated period of time (step **209**) before beginning the next session. Generally, one or more sessions may occur each day, and sessions may occur on sequential days or may be spaced apart by a certain number of days. As an example, a protocol may comprise five, one-hour sessions each separated by a rest period of at least 12 hours. As another example, a protocol may comprise ten, thirty-minute sessions, with two sessions occurring on each of five sequential days. In this example, a rest period of about 30 minutes to about 2 hours may be required between the two sessions on any given day.

[0078] The method may then proceed to step **210** by updating the current session to the next session in the protocol. The method then returns to step **206** to update the current modulation cycle to the first modulation cycle in the subsequent session (i.e., the updated current session) in order to process acoustic stimulation according to the parameters of the updated modulation cycle at step **202**.

[0079] However, if the current session is determined to be the last session of a protocol in step **208**, an updated measurement may be determined for one or more characteristics of the subject **211** (discussed below) and then the method may end.

[0080] As shown in **FIG. 2**, measurements of one or more characteristics of the subject may be observed or calculated at various times throughout the method (e.g., steps **201**, **204**, **207** and **211**) and such measurements may be compared/contrasted to determine one or more user responses to the training protocol. Generally, such measurements and user responses may be employed to adjust various protocol parameters, such as but not limited to a number of sessions, session parameters of one or more sessions (e.g., session duration, acoustic input signal selection and/or acoustic stimuli processing parameters).

[0081] As discussed in detail above, exemplary user responses may include, but are not limited to: changes in the transfer function of the middle ear structures (e.g., as measured by a MESA system **300**); changes in auditory processing (e.g., measured by the FW or CW SCAN subtests); changes in vocal prosody (e.g., measured by modulation power

spectrum analyses of vocalizations); changes in autonomic state (e.g., measured by HRV or RSA); changes in facial expressivity (e.g., measured by facial electromyograms or facial coding); changes in sleep pattern; changes in sound sensitivities; changes in self-reported affective state; changes in defensive self-protecting behaviors; and/or changes in other features of the social engagement system. Additionally or alternatively, subjective assessments may be employed to determine participant fatigue (i.e., from use of middle-ear muscles) and/or any itching in the participant's ear (i.e., from middle-ear bones moving and shifting the orientation of the ear drum).

[0082] It will be appreciated that useful information may be determined by simply testing functional and/or neurophysiological-based outcomes, in the absence of a comparison to other measurements. Functional outcomes include subjective and/or objective indices of auditory hypersensitivities and auditory processing, and may be tested as described above (e.g., via FW and CW tests). Neurophysiological-based outcomes include physiological state and the measurement of the middle-ear transfer function, and such outcomes may also be determined as described above.

[0083] In one embodiment, initial measurements may be determined at step **201** and such measurements may be employed in subsequent comparisons. In certain embodiments, the initial measurements may be employed to set up initial protocol parameters and/or initial session parameters.

[0084] Measurements and/or user responses may additionally or alternatively be determined at step **204**. Such information may be employed at step **205** to determine whether additional modulation cycles are desired or required. This information may also be used at step **202** or step **206** to dynamically modify parameters of the current session (e.g., parameters of one or more subsequent modulations cycles). Exemplary adjustments may comprise instantaneously or incrementally modifying: the parameters of one or more modulation cycles (e.g., range of frequencies, slope of the changes in frequencies, and/or duration of one or more cycles); the level of attenuation or amplification of the frequency range

inside or outside the bandwidth; and/or the level of attenuation or amplification for the left or right ears

[0085] Additionally or alternatively, measurements and/or user responses may be determined upon completion of one or more sessions (step **207**). This information may be used, for example, at step **208** to determine whether the subject requires additional sessions (e.g., in embodiments where the number of sessions is dynamically determined based on achieving a desired user response). Such information may also be employed to adjust parameters for a subsequent session.

[0086] Finally, measurements and/or user responses may be determined upon completion of the protocol. Such information may be employed to determine the overall effectiveness of the protocol in reducing sound sensitivities, improving behavioral and/or autonomic state regulation, and/or reducing auditory processing deficiencies and/or reducing social engagement deficiencies in the subject. Moreover, this information may be used to evaluate other plausible mechanisms leading to behavioral and autonomic state regulation difficulties, auditory hypersensitivities, and/or auditory processing difficulties).

[0087] Referring to **FIG. 4**, an exemplary system **400** according to an embodiment is illustrated. Generally, the system **400** is configured to present acoustic stimuli **460** to a subject **440**, optionally based on dynamic measures of physiological state that are used as part of a feedback system to inform the features of the stimuli being presented. This system comprises an audio processing means **420**, an audio output means **430** and a dynamic measurement means **450**. In one embodiment, the system may, optionally, comprise a video output means **470**.

[0088] The audio processing means **420** is configured to receive an acoustic input signal **410** (e.g., via an input **421**), such as but not limited to, pre-recorded or live human speech, human singing, and/or human vocal music. The acoustic input signal **410** may also be an environmental acoustic signal, such as audio synchronized to a video being currently watched by the subject, or speech of a person the subject with whom the subject is interacting (e.g., in real time or near real time).

- [0089] The audio processing means **420** processes the input acoustic signal **410** (e.g., via a processor **422**) according to the principles outlined herein to produce a processed acoustic signal **460**. As discussed in detail above, such processing may be dependent on dynamically changing parameters, including but not limited to: frequency bandwidth, range of bandwidth changes, slope of bandwidth changes, and/or duration of modulation. These parameters are based on the characteristics of the middle-ear structures and muscles, and may be tailored to the individual subject **440** or patient. The audio processing means may be further configured to process the acoustic input signal **410** based on the output of a dynamic measurement means **450**. Upon processing the input acoustic signal **410** to a processed acoustic signal **460**, the audio processing means may output the same to an audio output means **430** (e.g., via an output **423**).
- [0090] The audio output means **430** may be configured to present the processed acoustic signal **460** to a subject **440** during a protocol session. The audio output means **430** may comprise an input **431** to receive the processed acoustic signal **460** from the audio processing means **420**. The audio output means **430** may further comprise an output device **432**, such as but not limited to one or more output transducers or speakers. In certain embodiments, the audio output means **430** may be headphones, circumaural headphones and/or earphones.
- [0091] Although shown as separate components, it will be appreciated that any of the audio processing means **420**, audio output means **430** video output means **470** and/or dynamic measurement means **450** may be combined into a single device. For example, a combined audio processing / audio output device may be a pair of headphones with a processor configured to perform the required audio processing.
- [0092] As another example, in embodiments where the system comprises a video output means **470**, such as a television, computer monitor and or VR device (e.g., a 360° video platform), the video output means may provide the acoustic input signal **410** processed by the audio processing means **420**. Additionally or alternatively, the video output means **470** may comprise a processor configured to perform the required audio processing of the

audio processing means **420** and/or speakers to output the processed audio signal **460** to the subject **440**. Functionally, the simultaneous observation of facial and head movements, while listening to human vocalizations, may improve speech intelligibility. Accordingly, a VR environment may be provided wherein one or more humans are shown to be speaking or singing the acoustic stimuli **460** presented to the subject **440** with appropriate facial, head and/or hand movements. Such VR environment may require movements by the subject **440** to stimulate physiological states.

- [0093] The dynamic measurement means **450** may be configured to sense one or more physiological parameters of the subject **440**. As discussed above, these physiological parameters may include the subject's heart rate, RSA, vasomotor activity, and/or measures of the transfer function of the middle ear. For example, the transfer function of the middle ear may be tested using a MESA system (*see* **FIG. 3** at **300**), the subject's heart rate and RSA may be tested with an ECG or PPG, and vasomotor activity may be tested with a PPG.
- [0094] After an assessment of the subject is performed via the dynamic measurement means **450**, results of the assessment may be used to adjust the processing that occurs in audio processing means **420**. This adjustment may alter the bandwidth and other features of one or more modulation cycles and/or a sequence of modulation cycles within one or more sessions according to the principles discussed above.
- [0095] Referring to **FIGs. 5-13**, graphical representations of exemplary frequency modulation cycles employed to process an acoustic input signal to acoustic stimuli that is transmitted to a subject during a first session (**FIG. 5**), second session (**FIG. 6**), third session (**FIG. 7**), fourth session (**FIG. 8**), fifth session (**FIG. 9**), sixth session (**FIG. 10**), seventh session (**FIG. 11**), eighth and ninth sessions (**FIG. 12**) and a tenth session (**FIG. 13**) of a training protocol is illustrated. As shown, the x-axis of each graph (i.e., **500, 600, 700, 800, 900, 1000, 1200** and **1300**) represents time in seconds and the y-axis indicates frequency. The bandwidth of each modulation cycle may be defined by the low-frequency limit (**510, 610, 710, 810, 910, 1010, 1110, 1210** and **1310**) and the high-

frequency limit (520, 620, 720, 820, 920, 1020, 1120, 1220, 1320 and 1420) in each graph, respectively. Details of each of the modulation cycles shown in **FIGs. 5-13** are respectively provided in **Tables 1-9 of Appendix A**.

[0096] Referring to **FIGs. 14-16**, graphical representations of modulation cycles within a first booster session (**FIG. 14**), a second booster session (**FIG. 15**) and a third booster session (**FIG. 16**) are illustrated, where the x-axis of each graph (i.e., 1400, 1500 and 1600) represents time in seconds and the y-axis indicates frequency. In certain embodiments, a subject who has completed a protocol may be treated with one or more so-called “booster sessions” to re-engage the subject’s social engagement system. Such booster sessions may be appropriate if, for example, a subject experiences a loss of any of any benefits received from a previously completed protocol (e.g., after a long period of time and/or upon the occurrence of an event, such as a traumatic experience, fever or illness).

[0097] The bandwidth of each modulation cycle may be defined by the low-frequency limit (1410, 1510 and 1610) and the high-frequency limit (1420, 1520 and 1620) in each graph, respectively. And details of each of the modulation cycles shown in **FIGs. 14-16** are respectively provided in **Tables 10-12 of Appendix A**.

[0098] Because the described methods and systems deliver acoustic stimuli to subjects, they share some of the features of auditory intervention therapies (“AIT”). However, the disclosed methods and systems differ from traditional AIT in practice and theory. First, the methods and systems are based on the Polyvagal Theory and reflect a strategic attempt to engage neural regulation of specific structures involved in the social engagement system described by the Polyvagal Theory. Second, the methods and systems focus on features (e.g., sound sensitivities and difficulties in behavioral and autonomic state regulation, auditory processing, spontaneous social engagement, pain, anxiety etc.) that may be expressed by individuals with or without clinical diagnoses. Third, the effectiveness of the methods and systems may be measured through well-defined behavioral and physiological features of the social engagement system. Fourth, the methods and systems are designed with a number of unique features to engage and

exercise the neural regulation of the middle-ear muscles, including an understanding of the transfer function of the middle-ear structures and the vulnerability of the fast-twitch middle-ear muscles to fatigue. Fifth, the duration of the described procedures may be shorter (e.g., less than 5 hours) than most forms of AIT.

[0099] Moreover, there are several problems related to the evaluation of traditional AIT. First, the neurophysiological theory underlying conventional AIT is often not well developed or tested. Second, research has been frequently structured to ask questions of efficacy instead of developing protocols to test theoretically relevant components of AIT in order to understand the mechanisms and to refine the methodology. Third, since AIT are applied within a clinical setting, several experimental design parameters are difficult to control including: a constant protocol, limiting concurrent treatments (e.g., medication), and/or randomization.

[0100] Embodiments of the subject matter and the functional operations described in this specification can be implemented in one or more of the following: digital electronic circuitry; tangibly-embodied computer software or firmware; computer hardware, including the structures disclosed in this specification and their structural equivalents; and combinations thereof. Such embodiments can be implemented as one or more modules of computer program instructions encoded on a tangible non-transitory program carrier for execution by, or to control the operation of, data processing apparatus (i.e., one or more computer programs). Program instructions may be, alternatively or additionally, encoded on an artificially generated propagated signal (e.g., a machine-generated electrical, optical, or electromagnetic signal) that is generated to encode information for transmission to suitable receiver apparatus for execution by a data processing apparatus. And the computer storage medium can be one or more of: a machine-readable storage device, a machine-readable storage substrate, a random or serial access memory device, and combinations thereof.

[0101] As used herein, the term “data processing apparatus” comprises all kinds of apparatuses, devices, and machines for processing data, including but not limited to, a programmable

processor, a computer, and/or multiple processors or computers. Exemplary apparatuses may include special purpose logic circuitry, such as a field programmable gate array (“FPGA”) and/or an application specific integrated circuit (“ASIC”). In addition to hardware, exemplary apparatuses may comprise code that creates an execution environment for the computer program (e.g., code that constitutes one or more of: processor firmware, a protocol stack, a database management system, an operating system, and a combination thereof).

[0102] The term “computer program” may also be referred to or described herein as a “program,” “software,” a “software application,” a “module,” a “software module,” a “script,” or simply as “code.” A computer program may be written in any form of programming language, including compiled or interpreted languages, or declarative or procedural languages, and it can be deployed in any form, including as a standalone program or as a module, component, subroutine, or other unit suitable for use in a computing environment. Such software may correspond to a file in a file system. A program can be stored in a portion of a file that holds other programs or data. For example, a program may include one or more scripts stored in a markup language document; in a single file dedicated to the program in question; or in multiple coordinated files (e.g., files that store one or more modules, sub programs, or portions of code). A computer program can be deployed and/or executed on one computer or on multiple computers that are located at one site or distributed across multiple sites and interconnected by a communication network.

[0103] The processes and logic flows described in this specification can be performed by one or more programmable computers executing one or more computer programs to perform functions by operating on input data and generating output. The processes and logic flows can also be performed by, and apparatus can also be implemented as, special purpose logic circuitry, such as but not limited to an FPGA and/or an ASIC.

[0104] Computers suitable for the execution of the one or more computer programs include, but are not limited to, general purpose microprocessors, special purpose microprocessors,

and/or any other kind of central processing unit (“CPU”). Generally, CPU will receive instructions and data from a read only memory (“ROM”) and/or a random access memory (“RAM”). The essential elements of a computer are a CPU for performing or executing instructions and one or more memory devices for storing instructions and data. Generally, a computer will also include, or be operatively coupled to receive data from or transfer data to, or both, one or more mass storage devices for storing data (e.g., magnetic, magneto optical disks, and/or optical disks). However, a computer need not have such devices. Moreover, a computer may be embedded in another device, such as but not limited to, a mobile telephone, a personal digital assistant (“PDA”), a mobile audio or video player, a game console, a Global Positioning System (“GPS”) receiver, or a portable storage device (e.g., a universal serial bus (“USB”) flash drive).

- [0105]** Computer readable media suitable for storing computer program instructions and data include all forms of nonvolatile memory, media and memory devices. For example, computer readable media may include one or more of the following: semiconductor memory devices, such as erasable programmable read-only memory (“EPROM”), electrically erasable programmable read-only memory (“EEPROM”) and/or and flash memory devices; magnetic disks, such as internal hard disks or removable disks; magneto optical disks; and/or CD ROM and DVD-ROM disks. The processor and the memory can be supplemented by, or incorporated in, special purpose logic circuitry.
- [0106]** To provide for interaction with a user, embodiments may be implemented on a computer having any type of display device for displaying information to a user. Exemplary display devices include, but are not limited to one or more of: projectors, cathode ray tube (“CRT”) monitors, liquid crystal displays (“LCD”), light-emitting diode (“LED”) monitors and/or organic light-emitting diode (“OLED”) monitors. The computer may further comprise one or more input devices by which the user can provide input to the computer. Input devices may comprise one or more of: keyboards, a pointing device (e.g., a mouse or a trackball). Input from the user can be received in any form, including acoustic, speech, or tactile input. Moreover, feedback may be provided to the user via any form of sensory feedback (e.g., visual feedback, auditory feedback, or tactile feedback).

A computer can interact with a user by sending documents to and receiving documents from a device that is used by the user (e.g., by sending web pages to a web browser on a user's client device in response to requests received from the web browser).

[0107] Embodiments of the subject matter described in this specification can be implemented in a computing system that includes one or more of the following components: a backend component (e.g., a data server); a middleware component (e.g., an application server); a frontend component (e.g., a client computer having a graphical user interface (“GUI”) and/or a web browser through which a user can interact with an implementation of the subject matter described in this specification); and/or combinations thereof. The components of the system can be interconnected by any form or medium of digital data communication, such as but not limited to, a communication network. Non-limiting examples of communication networks include a local area network (“LAN”) and a wide area network (“WAN”), e.g., the Internet.

[0108] The computing system may include clients and/or servers. The client and server may be remote from each other and interact through a communication network. The relationship of client and server arises by virtue of computer programs running on the respective computers and having a client-server relationship to each other.

[0109] Various embodiments are described in this specification, with reference to the detailed discussed above, the accompanying drawings, and the claims. Numerous specific details are described to provide a thorough understanding of various embodiments. However, in certain instances, well-known or conventional details are not described in order to provide a concise discussion. The figures are not necessarily to scale, and some features may be exaggerated or minimized to show details of particular components. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims and as a representative basis for teaching one skilled in the art to variously employ the embodiments.

[0110] The embodiments described and claimed herein and drawings are illustrative and are not to be construed as limiting the embodiments. The subject matter of this specification is

not to be limited in scope by the specific examples, as these examples are intended as illustrations of several aspects of the embodiments. Any equivalent examples are intended to be within the scope of the specification. Indeed, various modifications of the disclosed embodiments in addition to those shown and described herein will become apparent to those skilled in the art, and such modifications are also intended to fall within the scope of the appended claims.

[0111] While this specification contains many specific implementation details, these should not be construed as limitations on the scope of any invention or of what may be claimed, but rather as descriptions of features that may be specific to particular embodiments of particular inventions. Certain features that are described in this specification in the context of separate embodiments can also be implemented in combination in a single embodiment. Conversely, various features that are described in the context of a single embodiment can also be implemented in multiple embodiments separately or in any suitable subcombination. Moreover, although features may 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 may be directed to a subcombination or variation of a subcombination.

[0112] 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 may be advantageous. Moreover, the separation of various system modules and 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 together in a single software product or packaged into multiple software products.

[0113] All cited references including patents, patent applications and publications are incorporated herein by reference in their entirety and for all purposes to the same extent

as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

APPENDIX A

Table 1: Session 1 (500)

Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	800	1500
Modulation Cycle 2			
100	20	800	1500
120	20	700	2000
140	20	700	2000
160	20	800	1500
Modulation Cycle 3			
180	20	800	1500
200	20	700	2000
220	20	700	2000
240	20	600	2500
260	20	600	2500
280	20	700	2000
300	20	700	2000
320	20	800	1500
Modulation Cycle 4			
340	20	800	1500
360	20	700	2000
380	20	700	2000
400	20	600	2500
420	20	600	2500
440	20	700	2000
460	20	700	2000
480	20	800	1500
Modulation Cycle 5			
500	20	800	1500
520	20	700	2000
540	20	700	2000
560	20	800	1500
Modulation Cycle 6			

580	20	800	1500
600	20	700	2000
620	20	700	2000
640	20	600	2500
660	20	600	2500
680	20	700	2000
700	20	700	2000
720	20	800	1500
Modulation Cycle 7			
740	20	800	1500
760	20	700	2000
780	20	700	2000
800	20	650	2500
820	20	650	2500
840	20	600	3000
860	20	600	3000
875	15	650	2500
890	15	650	2500
905	15	700	2000
920	15	700	2000
940	20	800	1500
Modulation Cycle 8			
960	20	800	1500
980	20	700	2000
1000	20	700	2000
1020	20	600	2500
1040	20	600	2500
1060	20	700	2000
1080	20	700	2000
1100	20	800	1500
Modulation Cycle 9			
1120	20	800	1500
1140	20	700	2000
1160	20	700	2000
1180	20	800	1500
Modulation Cycle 10			
1200	20	800	1500
1260	60	600	2500
1280	20	600	2500
1330	50	800	1500
Modulation Cycle 11			
1350	20	800	1500

1455	105	600	3000
1485	30	600	3000
1560	75	800	1500
Modulation Cycle 12			
1580	20	800	1500
1650	70	600	2500
1670	20	600	2500
1700	30	800	1500
Modulation Cycle 13			
1720	20	800	1500
1740	20	700	2000
1760	20	700	2000
1780	20	800	1500
1800	20	800	1500

Table 2: Session 2 (600)

Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	800	1500
Modulation Cycle 2			
100	20	800	1500
120	20	700	2000
140	20	700	2000
160	20	650	2500
180	20	650	2500
200	20	700	2000
220	20	700	2000
240	20	800	1500
Modulation Cycle 3			
260	20	800	1500
280	20	700	2000
300	20	700	2000
320	20	650	2500
340	20	650	2500
360	20	700	2000
380	20	700	2000

400	20	650	2500
420	20	650	2500
440	20	600	3000
460	20	600	3000
475	15	650	2500
490	15	650	2500
505	15	700	2000
525	20	700	2000
545	20	800	1500
Modulation Cycle 4			
565	20	800	1500
585	20	700	2000
605	20	700	2000
625	20	650	2500
645	20	650	2500
665	20	600	3000
685	20	600	3000
700	15	650	2500
715	15	650	2500
730	15	700	2000
750	20	700	2000
770	20	650	2500
790	20	650	2500
810	20	600	3000
830	20	600	3000
850	20	600	3500
870	20	600	3500
885	15	600	3000
900	15	600	3000
915	15	650	2500
930	15	650	2500
945	15	700	2000
960	15	700	2000
975	15	800	1500
Modulation Cycle 5			
995	20	800	1500
1015	20	700	2000
1035	20	700	2000
1055	20	650	2500
1075	20	650	2500
1095	20	600	3000
1115	20	600	3000

1130	15	650	2500
1145	15	650	2500
1160	15	700	2000
1175	15	700	2000
1190	15	800	1500
Modulation Cycle 6			
1210	20	800	1500
1270	60	650	2500
1290	20	650	2500
1310	20	700	2000
1330	20	700	2000
1400	70	600	3000
1430	30	600	3000
1495	65	800	1500
Modulation Cycle 7			
1515	20	800	1500
1640	125	600	3500
1670	30	600	3500
1715	45	650	2500
1735	20	650	2500
1780	45	800	1500
1800	20	800	1500

Table 3: Session 3 (700)

Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	800	1500
Modulation Cycle 1			
100	20	800	1500
120	20	700	2000
140	20	700	2000
160	20	800	1500
Modulation Cycle 2			
180	20	800	1500
200	20	700	2000
220	20	700	2000
240	20	600	2500

260	20	600	2500
280	20	700	2000
300	20	700	2000
320	20	800	1500
Modulation Cycle 3			
340	20	800	1500
360	20	700	2000
380	20	700	2000
400	20	600	2500
420	y 20	600	2500
440	20	700	2000
460	20	700	2000
480	20	800	1500
Modulation Cycle 4			
500	20	800	1500
520	20	700	2000
540	20	700	2000
560	20	800	1500
Modulation Cycle 5			
580	20	800	1500
600	20	700	2000
620	20	700	2000
640	20	600	2500
660	20	600	2500
680	20	700	2000
700	20	700	2000
720	20	800	1500
Modulation Cycle 6			
740	20	800	1500
760	20	700	2000
780	20	700	2000
800	20	600	2500
820	20	600	2500
840	20	500	3000
860	y 20	500	3000
875	15	600	2500
890	15	600	2500
905	15	700	2000
920	15	700	2000
940	20	800	1500
Modulation Cycle 7			
960	20	800	1500

980	20	700	2000
1000	20	700	2000
1020	20	600	2500
1040	20	600	2500
1060	20	700	2000
1080	20	700	2000
1100	20	800	1500
Modulation Cycle 8			
1120	20	800	1500
1140	20	700	2000
1160	20	700	2000
1180	20	800	1500
Modulation Cycle 9			
1200	20	800	1500
1260	60	600	2500
1280	20	600	2500
1330	50	800	1500
Modulation Cycle 10			
1350	20	800	1500
1455	105	500	3000
1485	30	500	3000
1560	75	800	1500
Modulation Cycle 11			
1580	20	800	1500
1650	70	600	2500
1670	20	600	2500
1700	30	800	1500
Modulation Cycle 12			
1720	20	800	1500
1740	20	700	2000
1760	20	700	2000
1780	20	800	1500
1800	20	800	1500

Table 4: Session 4 (800)

Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000

60	20	700	2000
80	20	800	1500
Modulation Cycle 2			
100	20	800	1500
120	20	700	2000
140	20	700	2000
160	20	600	2500
180	20	600	2500
200	20	700	2000
220	20	700	2000
240	20	800	1500
Modulation Cycle 3			
260	20	800	1500
280	20	700	2000
300	20	700	2000
320	20	600	2500
340	20	600	2500
360	20	550	3000
380	20	550	3000
395	15	600	2500
410	15	600	2500
425	15	700	2000
440	15	700	2000
455	15	800	1500
Modulation Cycle 4			
475	20	800	1500
495	20	700	2000
515	20	700	2000
535	20	600	2500
555	20	600	2500
575	20	550	3000
595	20	550	3000
610	15	600	2500
625	15	600	2500
640	15	700	2000
655	15	700	2000
670	15	800	1500
Modulation Cycle 5			
690	20	800	1500
715	25	700	2000
740	25	700	2000
765	25	600	2500

790	25	600	2500
815	25	550	3000
840	25	550	3000
865	25	500	3500
895	30	500	3500
910	15	550	3000
925	15	550	3000
940	15	600	2500
955	15	600	2500
970	15	700	2000
985	15	700	2000
1000	15	800	1500
Modulation Cycle 6			
1020	20	800	1500
1080	60	600	2500
1100	20	600	2500
1120	20	550	3000
1150	30	550	3000
1165	15	600	2500
1180	15	600	2500
1195	15	700	2000
1210	15	700	2000
1225	15	800	1500
Modulation Cycle 7			
1245	20	800	1500
1265	20	700	2000
1285	20	700	2000
1305	20	600	2500
1325	20	600	2500
1345	20	550	3000
1375	30	550	3000
1390	15	600	2500
1405	15	600	2500
1435	30	800	1500
Modulation Cycle 8			
1455	20	800	1500
1580	125	500	3500
1610	30	500	3500
1640	30	600	2500
1660	20	600	2500
1700	40	500	3500
1720	20	500	3500

1750	30	600	2500
1770	20	600	2500
1800	30	800	1500

Table 5: Session 5 (900)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	800	1500
Modulation Cycle 2			
100	20	800	1500
120	20	700	2000
140	20	700	2000
160	20	600	2500
180	20	600	2500
200	20	700	2000
220	20	700	2000
240	20	800	1500
Modulation Cycle 3			
260	20	800	1500
280	20	700	2000
300	20	700	2000
320	20	600	2500
340	20	600	2500
360	20	500	3000
380	20	500	3000
400	20	600	2500
420	20	600	2500
440	20	700	2000
460	20	700	2000
480	20	800	1500
Modulation Cycle 4			
500	20	800	1500
520	20	700	2000
540	20	700	2000
560	20	600	2500
580	20	600	2500

600	20	500	3000
620	20	500	3000
635	15	600	2500
650	15	600	2500
665	15	700	2000
680	15	700	2000
695	15	800	1500
Modulation Cycle 5			
715	20	800	1500
740	25	700	2000
765	25	700	2000
790	25	600	2500
815	25	600	2500
840	25	500	3000
865	25	500	3000
890	25	400	3500
920	30	400	3500
935	15	500	3000
950	15	500	3000
965	15	600	2500
980	15	600	2500
995	15	700	2000
1010	15	700	2000
1025	15	800	1500
Modulation Cycle 6			
1045	20	800	1500
1105	60	600	2500
1125	20	600	2500
1155	30	500	3000
1185	30	500	3000
1200	15	600	2500
1215	15	600	2500
1230	15	700	2000
1245	15	700	2000
1260	15	800	1500
Modulation Cycle 7			
1280	20	800	1500
1310	30	700	2000
1335	25	700	2000
1365	30	600	2500
1390	25	600	2500
1420	30	500	3000

1450	30	500	3000
1465	15	600	2500
1480	15	600	2500
1510	30	800	1500
Modulation Cycle 8			
1530	20	800	1500
1590	60	600	2500
1610	20	600	2500
1670	60	400	3500
1700	30	400	3500
1730	30	600	2500
1750	20	600	2500
1780	30	800	1500
1800	20	800	1500

Table 6: Session 6 (1000)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	600	2500
100	20	600	2500
120	20	500	3000
140	20	500	3000
160	20	600	2500
180	20	600	2500
200	20	700	2000
220	20	700	2000
240	20	800	1500
Modulation Cycle 2			
260	20	800	1500
280	20	700	2000
300	20	700	2000
320	20	600	2500
340	20	600	2500
360	20	500	3000
380	20	500	3000
400	20	400	3500

420	20	400	3500
440	20	500	3000
460	20	500	3000
480	20	600	2500
500	20	600	2500
520	20	700	2000
540	20	700	2000
560	20	800	1500
Modulation Cycle 3			
580	20	800	1500
605	25	700	2000
630	25	700	2000
655	25	600	2500
680	25	600	2500
705	25	500	3000
730	25	500	3000
755	25	450	3500
780	25	450	3500
805	25	400	4000
825	20	400	4000
840	15	450	3500
855	15	450	3500
870	15	500	3000
885	15	500	3000
900	15	600	2500
915	15	600	2500
930	15	700	2000
945	15	700	2000
960	15	800	1500
Modulation Cycle 4			
980	20	800	1500
1005	25	700	2000
1030	25	700	2000
1055	25	600	2500
1080	25	600	2500
1105	25	500	3000
1130	25	500	3000
1155	25	450	3500
1180	25	450	3500
1205	25	400	4000
1230	25	400	4000
1245	15	450	3500

1260	15	450	3500
1275	15	500	3000
1290	15	500	3000
1305	15	600	2500
1325	20	600	2500
1385	60	400	3500
1415	30	400	3500
1445	30	600	2500
1460	15	600	2500
1490	30	800	1500
Modulation Cycle 5			
1510	20	800	1500
1600	90	500	3000
1620	20	500	3000
1680	60	400	4000
1710	30	400	4000
1740	30	500	3000
1755	15	500	3000
1800	45	800	1500

Table 7: Session 7 (1100)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	600	2500
100	20	600	2500
120	20	500	3000
140	20	500	3000
160	20	600	2500
180	20	600	2500
200	20	700	2000
220	20	700	2000
240	20	800	1500
Modulation Cycle 2			
260	20	800	1500
280	20	700	2000
300	20	700	2000
320	20	600	2500

340	20	600	2500
360	20	500	3000
380	20	500	3000
400	20	400	3500
420	20	400	3500
440	20	500	3000
460	20	500	3000
480	20	600	2500
500	20	600	2500
520	20	700	2000
540	20	700	2000
560	20	800	1500
Modulation Cycle 3			
580	20	800	1500
605	25	700	2000
630	25	700	2000
655	25	600	2500
680	25	600	2500
705	25	500	3000
730	25	500	3000
755	25	400	3500
780	25	400	3500
805	25	300	4000
825	20	300	4000
840	15	400	3500
855	15	400	3500
870	15	500	3000
885	15	500	3000
900	15	600	2500
915	15	600	2500
930	15	700	2000
945	15	700	2000
960	15	800	1500
Modulation Cycle 4			
980	20	800	1500
1005	25	700	2000
1030	25	700	2000
1055	25	600	2500
1080	25	600	2500
1105	25	500	3000
1130	25	500	3000
1155	25	400	3500

1180	25	400	3500
1205	25	300	4000
1230	25	300	4000
1245	15	400	3500
1260	15	400	3500
1275	15	500	3000
1290	15	500	3000
1305	15	600	2500
1325	20	600	2500
1385	60	400	3500
1415	30	400	3500
1445	30	600	2500
1460	15	600	2500
1490	30	800	1500
Modulation Cycle 5			
1510	20	800	1500
1600	90	500	3000
1620	20	500	3000
1680	60	300	4000
1710	30	300	4000
1740	30	500	3000
1755	15	500	3000
1800	45	800	1500

Table 8: Sessions 8 and 9 (1200)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	600	2500
100	20	600	2500
120	20	500	3000
140	20	500	3000
160	20	600	2500
180	20	600	2500
200	20	700	2000
220	20	700	2000
240	20	800	1500
Modulation Cycle 2			

260	20	800	1500
280	20	700	2000
300	20	700	2000
320	20	600	2500
340	20	600	2500
360	20	500	3000
380	20	500	3000
400	20	400	3500
420	20	400	3500
440	20	500	3000
460	20	500	3000
480	20	600	2500
500	20	600	2500
520	20	700	2000
540	20	700	2000
560	20	800	1500
Modulation Cycle 3			
580	20	800	1500
640	60	600	2500
660	20	600	2500
680	20	500	3000
700	20	500	3000
720	20	400	3500
740	20	400	3500
760	20	300	4000
780	20	300	4000
800	20	400	3500
820	20	400	3500
840	20	500	3000
860	20	500	3000
880	20	600	2500
900	20	600	2500
960	60	800	1500
Modulation Cycle 4			
980	20	800	1500
1080	100	500	3000
1100	20	500	3000
1120	20	400	3500
1140	20	400	3500
1160	20	300	4000
1180	20	300	4000
1200	20	200	4500

1220	20	200	4500
1240	20	300	4000
1260	20	300	4000
1280	20	400	3500
1300	20	400	3500
1320	20	500	3000
1340	20	500	3000
1405	65	800	1500
Modulation Cycle 5			
1425	20	800	1500
1515	90	500	3000
1535	20	500	3000
1575	40	300	4000
1595	20	300	4000
1615	20	200	4500
1645	30	200	4500
1665	20	300	4000
1685	20	300	4000
1725	40	500	3000
1745	20	500	3000
1800	55	800	1500

Table 9: Session 10 (1300)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
Modulation Cycle 1			
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	600	2500
100	20	600	2500
120	20	500	3000
140	20	500	3000
160	20	400	3500
180	20	400	3500
195	15	500	3000
210	15	500	3000
225	15	600	2500
240	15	600	2500
255	15	700	2000

Modulation Cycle 2			
275	20	700	2000
295	20	600	2500
315	20	600	2500
335	20	500	3000
355	20	500	3000
375	20	400	3500
395	20	400	3500
415	20	300	4000
435	20	300	4000
450	15	400	3500
465	15	400	3500
480	15	500	3000
495	15	500	3000
510	15	600	2500
525	15	600	2500
540	15	700	2000
555	15	700	2000
575	20	800	1500
Modulation Cycle 3			
595	20	800	1500
615	20	700	2000
635	20	700	2000
655	20	600	2500
675	20	600	2500
695	20	500	3000
715	20	500	3000
735	20	400	3500
755	20	400	3500
775	20	300	4000
795	20	300	4000
815	20	250	4500
835	20	250	4500
850	15	300	4000
865	15	300	4000
895	30	500	3000
910	15	500	3000
955	45	800	1500
Modulation Cycle 4			
975	20	800	1500
1065	90	500	3000
1085	20	500	3000

1175	90	250	4500
1195	20	250	4500
1215	20	200	5000
1245	30	200	5000
1260	15	250	4500
1275	15	250	4500
1320	45	500	3000
1335	15	500	3000
1365	30	700	2000
Modulation Cycle 5			
1385	20	700	2000
1475	90	400	3500
1495	20	400	3500
1585	90	200	5000
1615	30	200	5000
1680	65	400	3500
1700	20	400	3500
1780	80	800	1500
1800	20	800	1500

Table 10: Booster 1 (1400)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
0	20	800	1500
20	20	800	1500
40	20	700	2000
60	20	700	2000
80	20	600	2500
100	20	600	2500
120	20	500	3000
140	20	500	3000
160	20	400	3500
180	20	400	3500
195	15	500	3000
210	15	500	3000
225	15	600	2500
240	15	600	2500
255	15	700	2000
275	20	700	2000
295	20	600	2500
315	20	600	2500

335	20	500	3000
355	20	500	3000
375	20	400	3500
395	20	400	3500
415	20	300	4000
435	20	300	4000
450	15	400	3500
465	15	400	3500
480	15	500	3000
495	15	500	3000
510	15	600	2500
525	15	600	2500
540	15	700	2000
555	15	700	2000
575	20	800	1500
600	25	800	1500

Table 11: Booster 2 (1500)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
0	15	800	1500
15	15	700	2000
35	20	700	2000
55	20	600	2500
75	20	600	2500
95	20	500	3000
115	20	500	3000
135	20	400	3500
155	20	400	3500
175	20	300	4000
195	20	300	4000
215	20	250	4500
235	20	250	4500
250	15	300	4000
265	15	300	4000
295	30	500	3000
310	15	500	3000
355	45	800	1500
375	20	800	1500
465	90	500	3000
485	20	500	3000

575	90	250	4500
600	25	250	4500

Table 12: Booster 3 (1600)

Start Time (s)	Duration (s)	Low-Frequency Limit (Hz)	High-Frequency Limit (Hz)
0	30	200	5000
30	30	200	5000
45	15	300	4500
60	15	300	4500
105	45	500	3000
120	15	500	3000
150	30	800	2000
170	20	800	2000
260	90	400	3500
280	20	400	3500
370	90	200	5000
400	30	200	5000
465	65	400	3500
485	20	400	3500
565	80	800	1500
600	35	800	1500

CLAIMS

What is claimed is:

1. A method comprising:

processing an acoustic input signal to produce acoustic stimuli during a session, wherein the processing is based on processing parameters comprising:

a first frequency modulation cycle comprising:

a first initial modulation comprising:

a first initial low-frequency limit of from about 600 Hz to about 900 Hz;
and

a first initial high-frequency limit of from about 1,400 Hz to about 2,000 Hz;

a first widest modulation comprising:

a first minimum low-frequency limit that is lower than the first initial low-frequency limit; and

a first maximum high-frequency limit that is higher than the first initial high-frequency limit; and

a first final modulation comprising:

a first final low-frequency limit that is substantially similar to the first initial low-frequency limit; and

a first final high-frequency limit that is substantially similar to the first initial high-frequency limit; and

a second frequency modulation cycle comprising:

a second initial modulation comprising:

a second initial low-frequency limit; and

a second initial high-frequency limit;

a second widest modulation comprising:

a second minimum low-frequency limit that is lower than the second initial low-frequency limit; and

a second maximum high-frequency limit that is higher than the second initial high-frequency limit; and

a second final modulation comprising:

a second final low-frequency limit that is substantially similar to the second initial low-frequency limit; and

a second final high-frequency limit that is substantially similar to the second initial high-frequency limit,

wherein the second minimum low-frequency limit is lower than the first minimum low-frequency limit and/or the second maximum high-frequency limit is higher than the first maximum high-frequency limit;

transmitting the acoustic stimuli to the subject during the session to thereby recruit one or more anti-masking functions of one or more middle-ear muscles of the subject; and

determining that the subject has experienced a user response comprising one or more of: reduced sound sensitivity, improved auditory processing, improved behavioral state regulation, improved autonomic state regulation, and improved social engagement.

2. A method according to claim 1, further comprising:

measuring one or more characteristics of the subject before processing the acoustic input signal to acoustic stimuli,

wherein the one more characteristics are selected from the group consisting of: sound sensitivity, behavioral state regulation, autonomic state regulation, auditory processing, one or more social engagement skills, sucking, swallowing, breathing, one or more

acoustic properties of vocalization of the subject, HRV, RSA, heart rate, blood pressure, cognitive ability, pain level, anxiety level, blood sugar level, usage of one or more facial muscles, usage of one or more head-turning muscles and a middle-ear transfer function.

3. A method according to claim 2, wherein:

the one or more characteristics comprises the middle-ear transfer function, and
the measuring comprises using a middle-ear sound absorption (“MESA”) system.

4. A method according to claim 2, further comprising adjusting one or more of the processing parameters based on the one or more measured characteristics.

5. A method according to claim 2, further comprising:

determining an updated measurement of the one or more measured characteristics during or after the transmitting the acoustic stimuli to the subject,
wherein the determining that the subject has experienced the user response is based on the updated measurement.

6. A method according to claim 1, further comprising:

processing a second acoustic input signal to produce second acoustic stimuli during a second session,

wherein the processing is based on second processing parameters comprising a plurality of frequency modulation cycles, and

wherein at least one of the frequency modulation cycles comprises a bandwidth that is wider than any bandwidth associated with any of the modulation cycles of the processing parameters of the first session; and

transmitting the second acoustic stimuli to the subject during the second session.

7. A method according to claim 6, wherein the second acoustic input signal is different than the first acoustic input signal.

8. A method according to claim 6, wherein the second session comprises a duration that is substantially similar to a duration of the first session.
9. A method according to claim 1, wherein the acoustic input signal comprises one or more of human speech, human singing, instrumental music and synthesized music.
10. A method according to claim 9, wherein the acoustic input signal is selected from the group consisting of animated movie soundtracks, lullabies, love songs, folk songs and bluegrass ballads.
11. A method according to claim 9, wherein the acoustic input signal comprises melodic voices above about 261.6 Hz and a varying volume level.
12. A method according to claim 1, wherein the first and second frequency modulation cycles are seamlessly connected in time.
13. A method according to claim 1, wherein:
 - the second initial low-frequency limit is substantially similar to the first initial low-frequency limit, and
 - the second initial high-frequency limit is substantially similar to the first initial high-frequency limit.
14. A method according to claim 1, wherein:
 - the first initial low-frequency limit is 800 Hz, and
 - the first initial high-frequency limit is 1,500.
15. A method according to claim 1, wherein:
 - each of the first and second minimum low-frequency limits comprises a frequency of from about 300 Hz to about 1,000 Hz, and

each of the first and second maximum high-frequency limits comprises a frequency of from about 1,500 Hz to about 5,000 Hz.

16. A method according to claim 1, wherein each of the first initial modulation, first widest modulation, first final modulation, second initial modulation, second widest modulation and second final modulation comprises a duration of from about 5 seconds to about 60 seconds.
17. A method according to claim 1, wherein each of the first and second frequency modulation cycles comprises a duration of from about 60 seconds to about 300 seconds.
18. A method according to claim 1, wherein the session comprises a duration of from about 30 minutes to about 60 minutes.
19. A method according to claim 1, further comprising:
 - displaying visual stimuli to the subject during the first session,
 - wherein the visual stimuli and the acoustic stimuli are synchronized.
20. A method according to claim 19, wherein the visual stimuli comprises a virtual reality environment.
21. A method according to claim 20, wherein the acoustic stimuli noninvasively stimulates a vagal nerve of the subject causing increased vagal activity to a heart of the subject.
22. A method according to claim 1, wherein the subject is a human.
23. A method according to claim 1, wherein the subject is a non-human mammal.

1 / 10

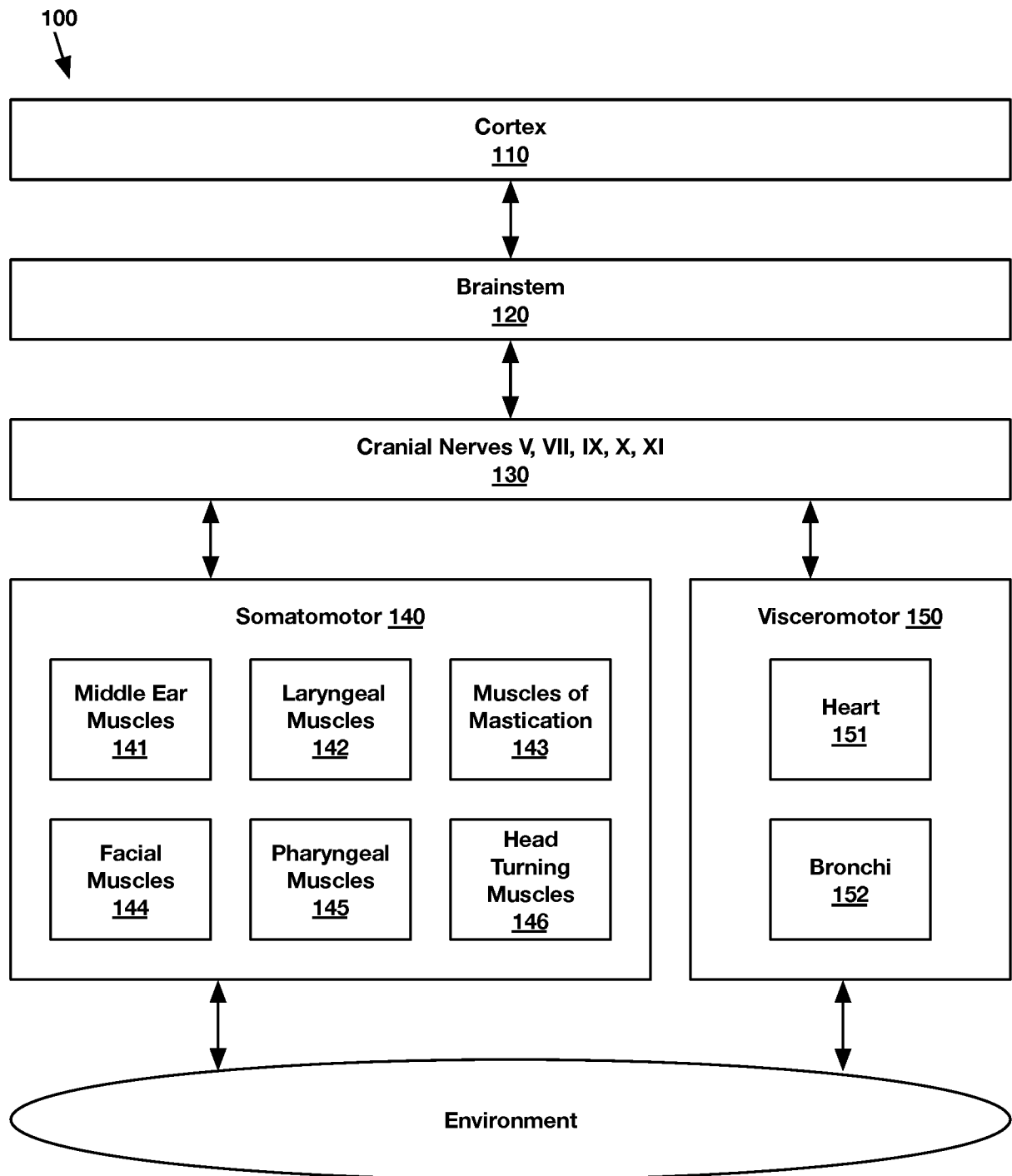


FIG. 1

(Prior Art)

2 / 10

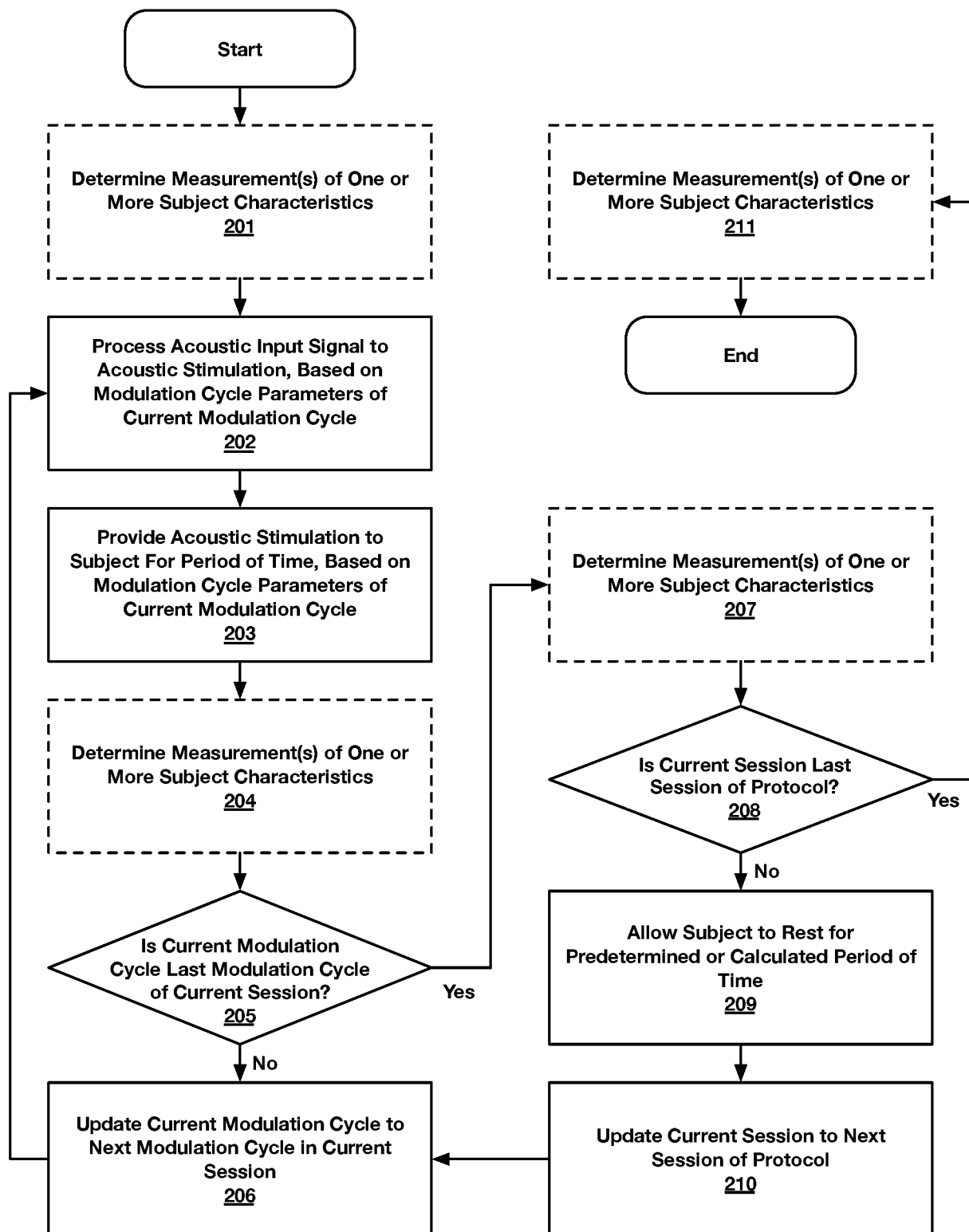


FIG. 2

3 / 10

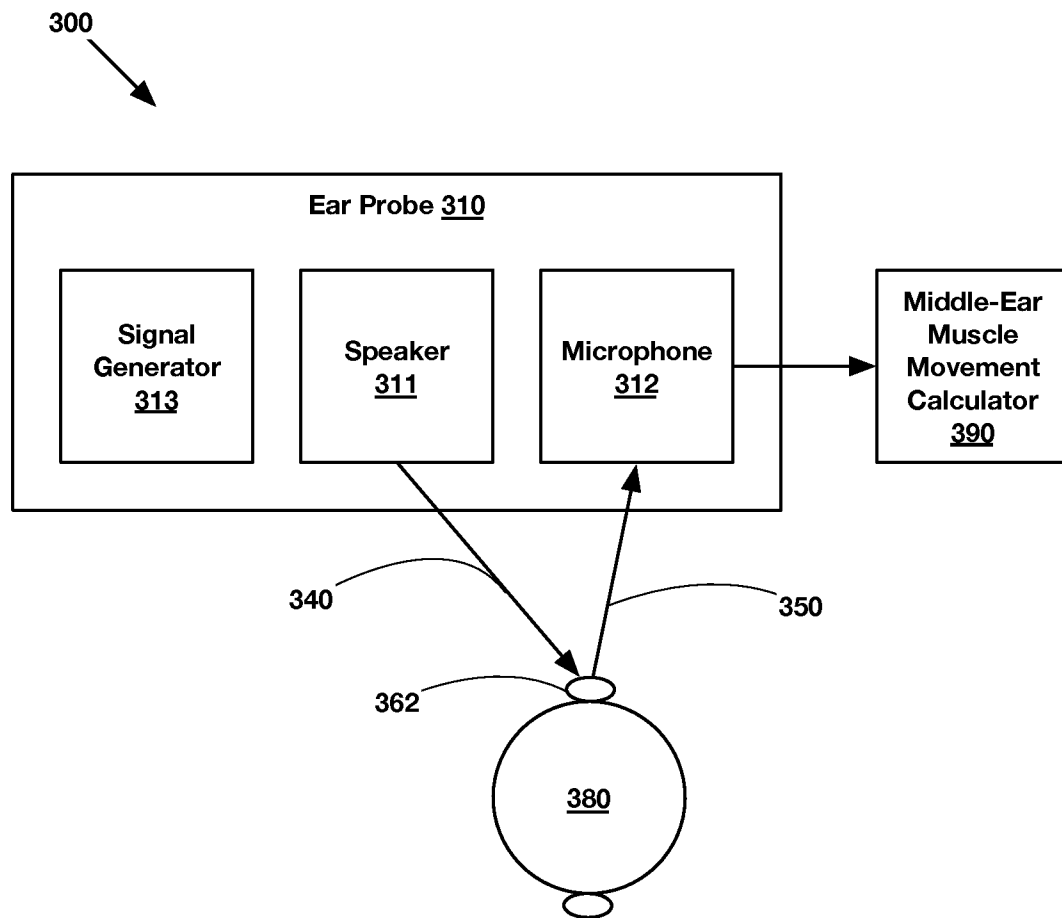


FIG. 3
(Prior Art)

4 / 10

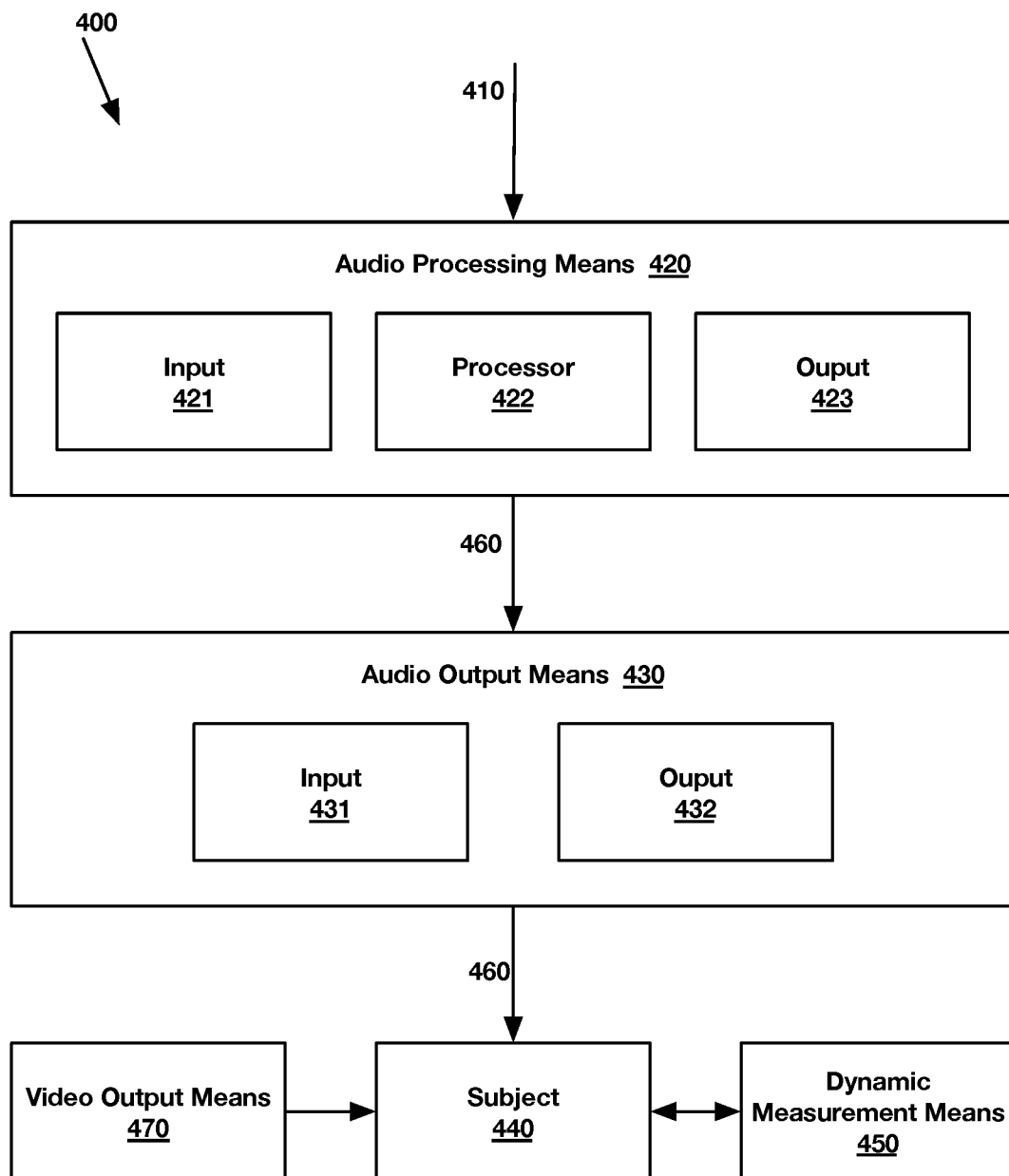


FIG. 4

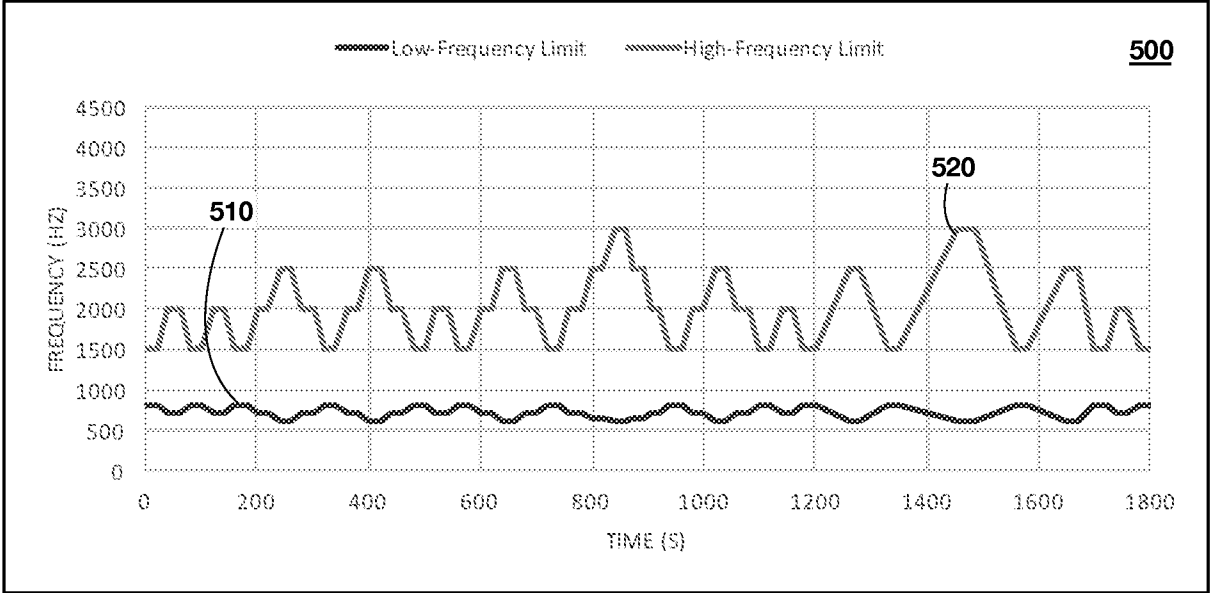


FIG. 5

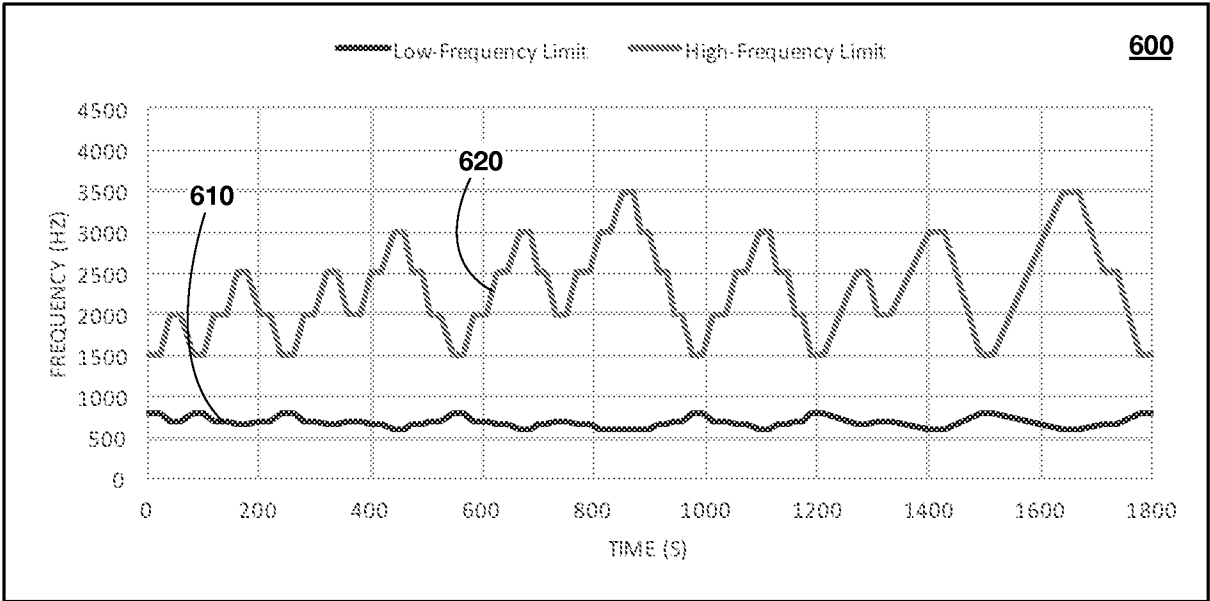


FIG. 6

6 / 10

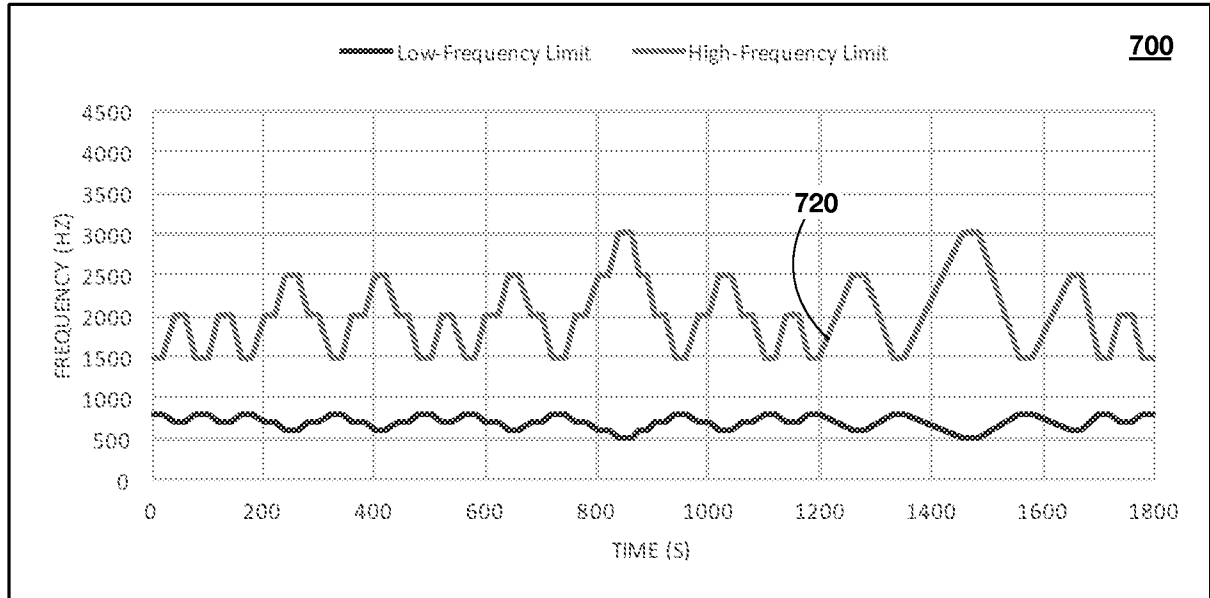


FIG. 7

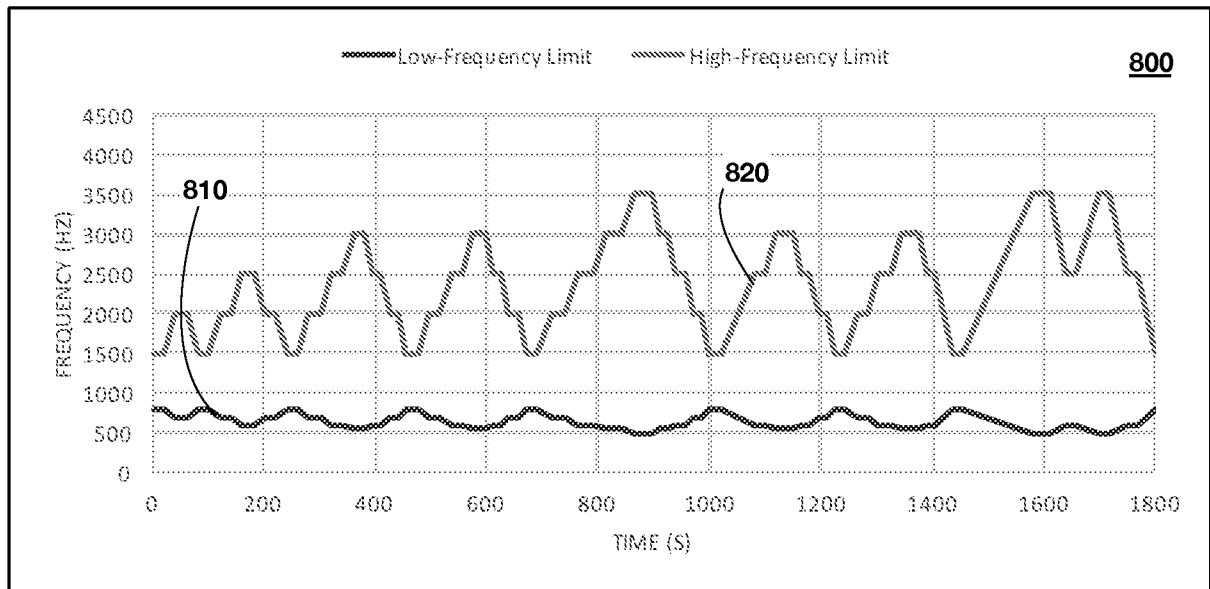


FIG. 8

7 / 10

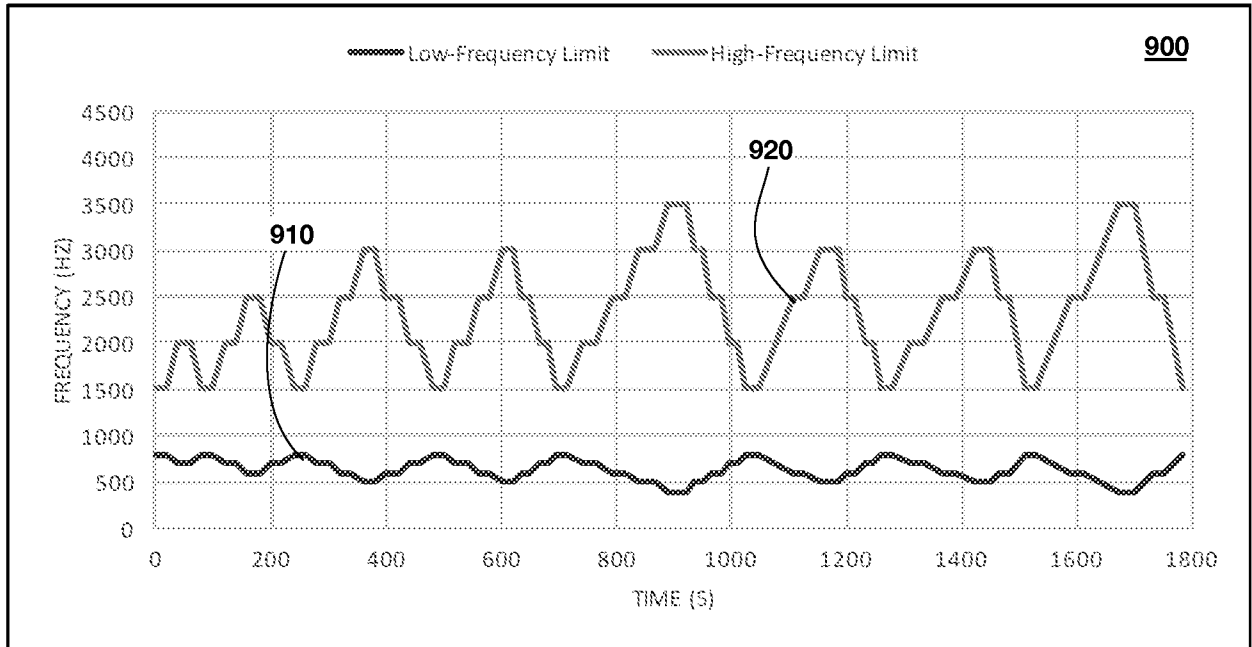


FIG. 9

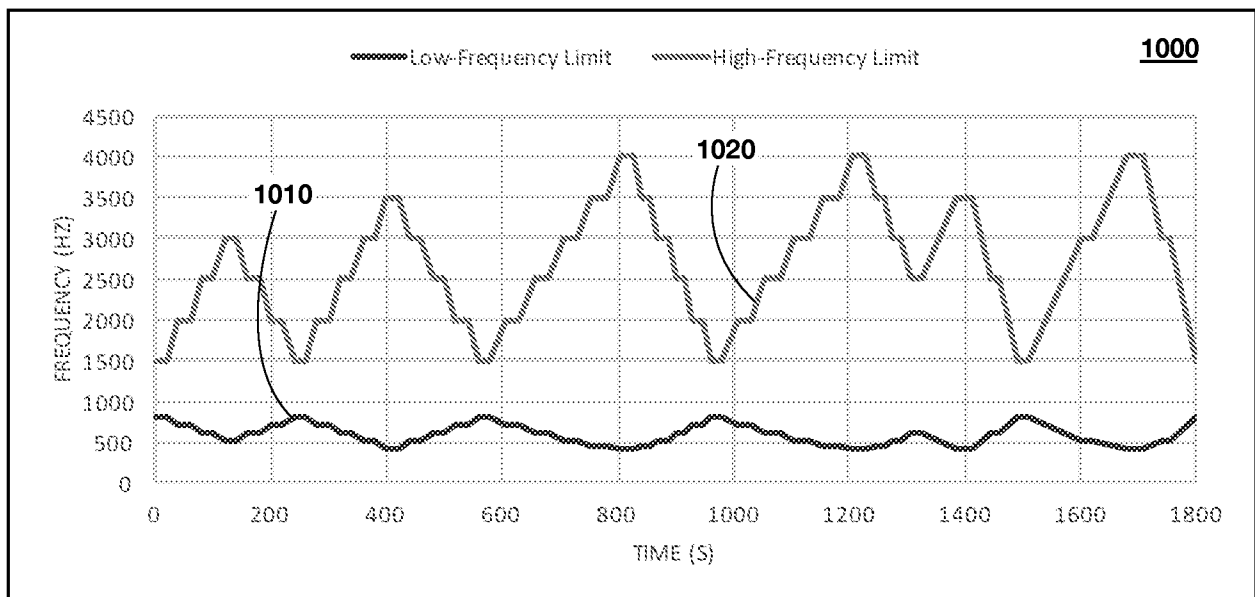


FIG. 10

8 / 10

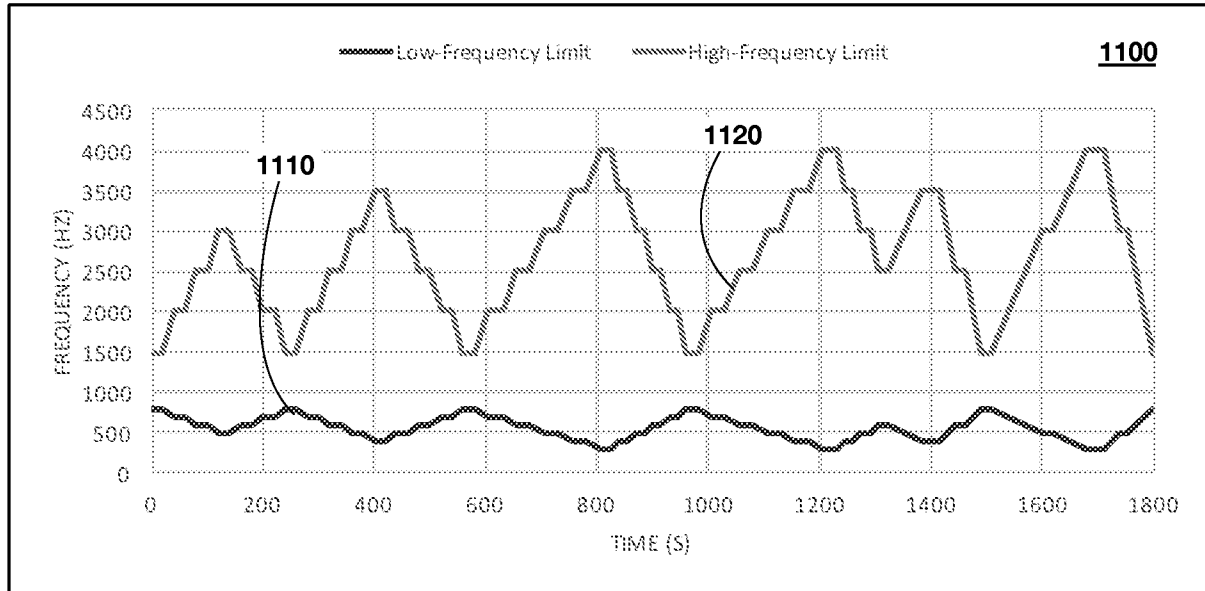


FIG. 11

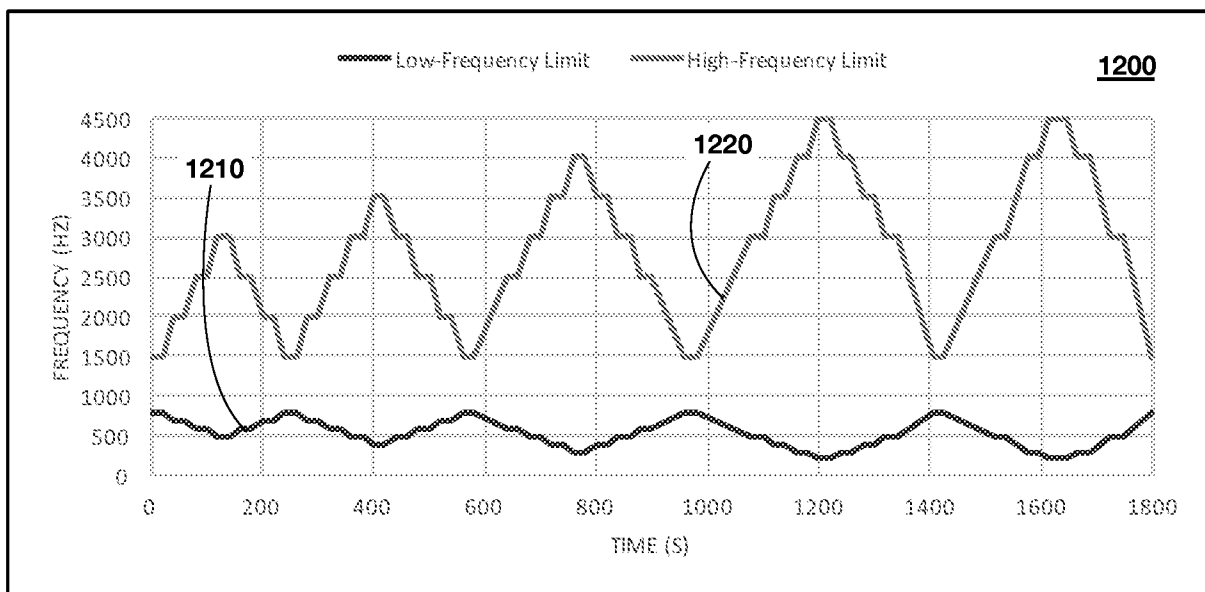


FIG. 12

9 / 10

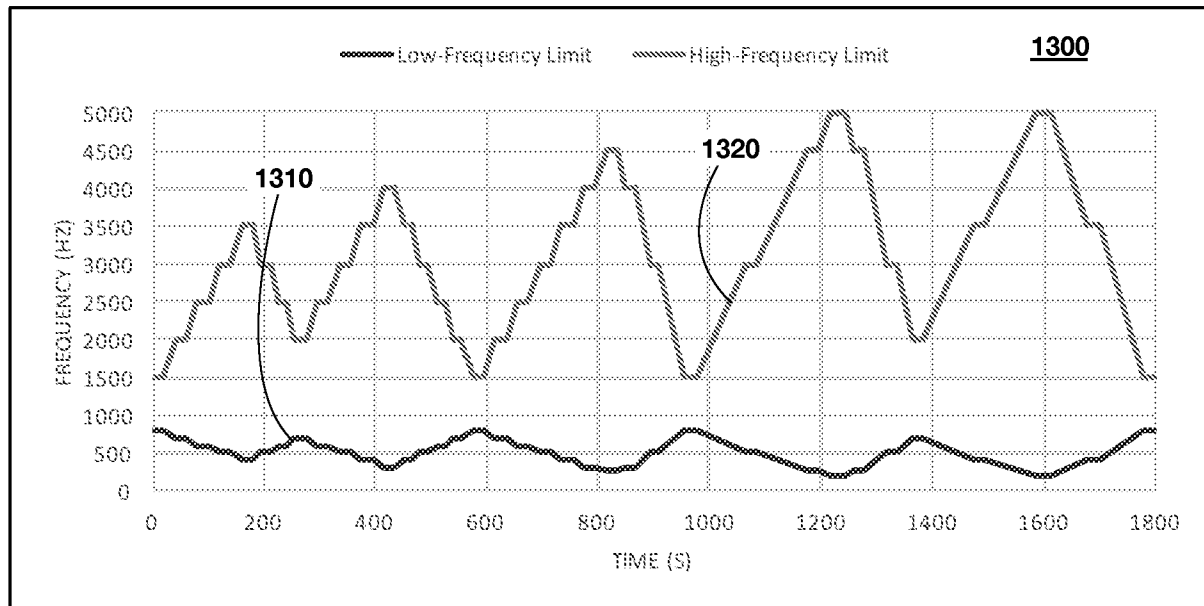


FIG. 13

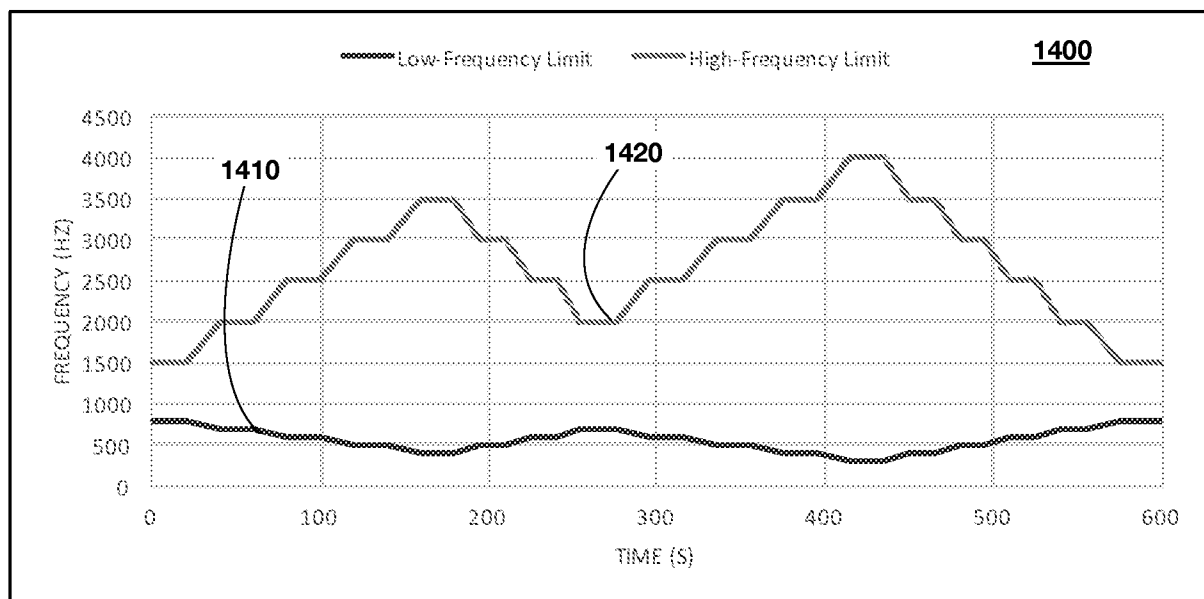


FIG. 14

10 / 10

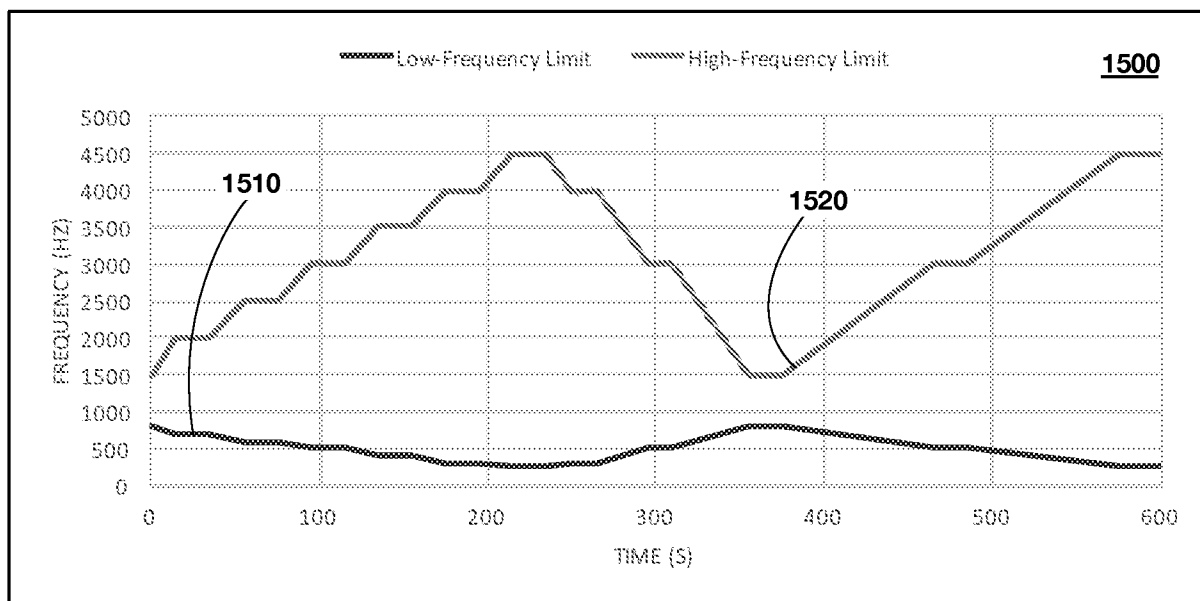


FIG. 15

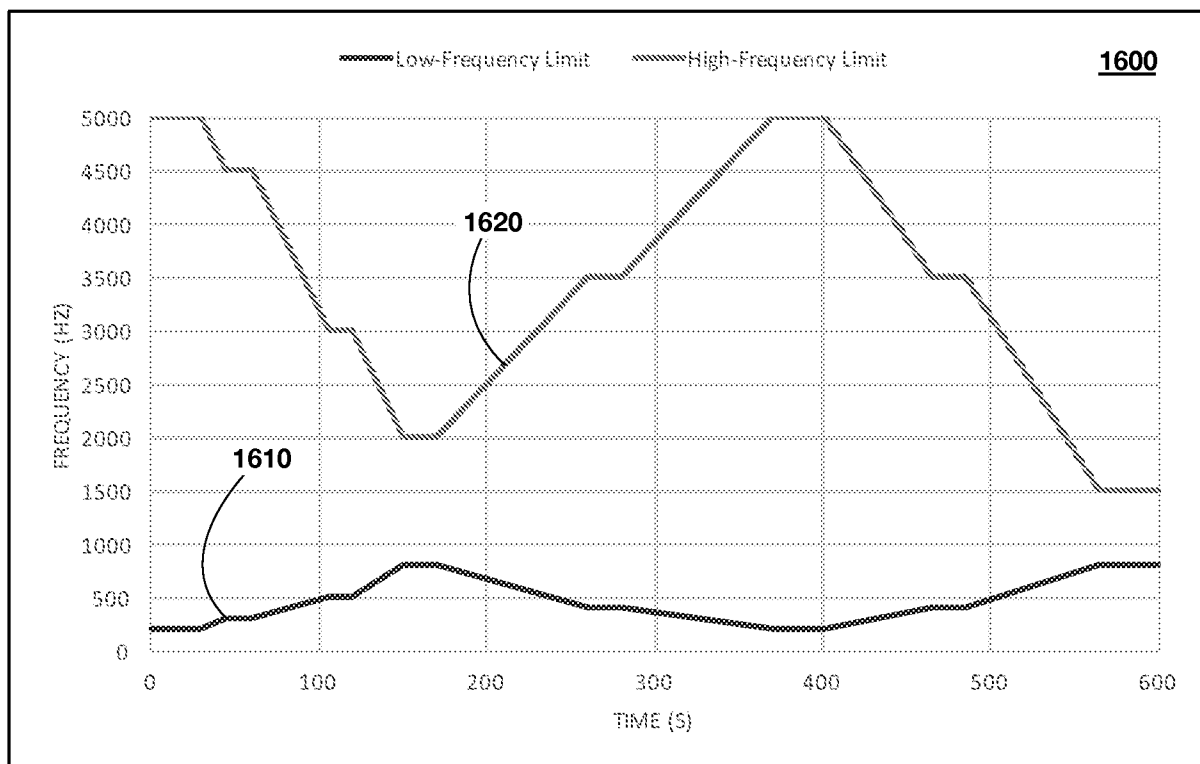


FIG. 16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/59297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 5/00 (2018.01)

CPC - A61B 5/121, A61B 5/126, A61B 5/125, A61B 5/123

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0303941 A1 (Porges et al.) 14 November 2013 (14.11.2013) entire document (especially para [0009], [0014], [0076], [0120], [0133], [0150]-[0151], [0204]-[0208])	1-23
A	US 2010/0016755 A1 (Henry et al.) 21 January 2010 (21.01.2010) (para [0054], [0063]-[0064])	1-23
A	US 2013/0060159 A1 (Bromwich et al.) 07 March 2013 (07.03.2013) (para [0025], [0027])	1-23
A	US 2009/0208044 A1 (NEHER) 20 August 2009 (20.08.2009) entire document	1-23
A	US 2015/0264492 A1 (LAUDANSKI et al.) 17 September 2015 (17.09.2015) entire document	1-23
A	US 9,333,372 B2 (Otis) 10 May 2016 (10.05.2016) entire document	1-23
A	US 8,737,631 B2 (Boretzki et al.) 27 May 2014 (27.05.2014) entire document	1-23
A	US 2013/0203027 A1 (De Villers-Sidani et al.) 08 August 2013 (08.08.2013) entire document	1-23

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

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 January 2018 (22.01.2018)

Date of mailing of the international search report

01 FEB 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

专利名称(译)	降低声音灵敏度并改善听力过程,行为规范和社会参与度的方法和系统		
公开(公告)号	EP3534778A4	公开(公告)日	2020-07-01
申请号	EP2017866994	申请日	2017-10-31
[标]发明人	PORGES STEPHEN		
发明人	PORGES, STEPHEN		
IPC分类号	A61B5/00		
CPC分类号	A61B5/12 A61B5/125 A61B5/486 A61M21/00 A61M2021/0027 A61M2205/3303 A61M2205/3331 A61M2205/3375 A61M2205/3553 A61M2205/50 A61M2205/581 A61M2205/582 A61M2205/583 A61M2230/04		
代理机构(译)	GILL JENNINGS & EVERY LLP		
优先权	62/415996 2016-11-01 US		
其他公开文献	EP3534778A1		
外部链接	Espacenet		

摘要(译)

本文描述了各种实施方案,以通过募集中耳肌肉的抗掩蔽功能来优化听觉敏感度,改善状态调节和/或减少患有此类缺陷的个体的听觉处理和社交参与缺陷,从而优化中耳肌肉的传递功能。中耳用于处理人类语音。在某些实施例中,个体可以经受包括一个或多个训练课程的训练方案。在每次训练期间,在一段时间内,伴有或不伴有视觉刺激的情况下,向受试者提供听觉刺激。可以例如在开始协议之前,会话期间,会话之后和/或协议完成时确定用户响应。可以采用这种用户响应来调整声刺激,并且可以在随后的训练期间(或在同一训练期间内的随后时间)向受试者提供调整的声刺激。训练协议可以在预定数量的训练会话之后或在达到期望的用户响应时结束。训练课程的特征可以在于在固定时间段内呈现连续刺激的固定协议,或在刺激时间段内依赖于受试者反应的交互协议。