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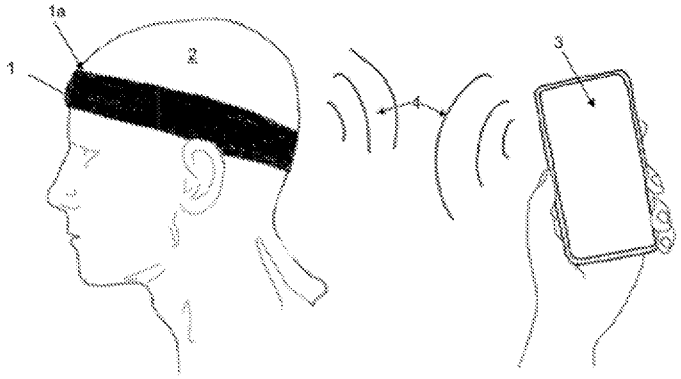
(54) Title: A BRAIN STIMULATION SYSTEM AND A HEADWEAR SUITABLE FOR CLOSED-LOOP BRAIN STIMULATION

Fig. 1



(57) Abstract: The invention comprises a brain stimulating system for transcranial magnetic stimulation (TMS), preferably to provide a closed loop brain stimulation and a headwear (1) for performing TMS. The headwear comprises a number of conductor coils (12c) for generating a magnetic field to induce the TMS and a power system (11) for supplying current to the respective plurality of coils (12c). The brain stimulating system comprises a sensor system (13) comprising at least one primary physiological sensor (13b) adapted for detecting a physiological parameter in response to a brain stimulation and a computer system comprising a controller (11) configured for receiving stimulation data representing a set of stimulation parameters of a stimulation protocol, converting the received stimulation data to a set of current parameters according to a converting protocol and controlling the power arrangement, comprising supplying current to one or more of said conductor coils (12c) according to the set of current parameters for inducing the brain stimulation according to the stimulation protocol. The computer system is further configured detecting the physiological parameter using the primary physiological sensor, and determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, and if not, adjusting the converting protocol.

[Continued on next page]

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A BRAIN STIMULATION SYSTEM AND A HEADWEAR SUITABLE FOR CLOSED-LOOP BRAIN STIMULATION

TECHNICAL FIELD

The invention relates to a brain stimulation system suitable for closed-loop transcranial magnetic stimulation (TMS) and a headwear for performing such brain stimulation.

BACKGROUND ART

Transcranial magnetic stimulation (TMS) is a non-invasive treatment technique that uses a magnetic field to influence brain activity. The TMS technique has been widely accepted and used as an effective treatment option for a wide range of brain conditions. TMS requires neither surgery nor medications. It involves an electromagnetic induction using an insulated coil placed over the scalp, focused on an area of the brain thought to play an important role in brain diseases or mental health disorders. The TMS treatment may thereby be applied for regulating brain activity in order to treat brain disorders or otherwise achieve certain desired brain states.

TMS may for example be used to treat users with certain psychiatric or neurological disorders, such as depression, obsessive-compulsive disorder (OCD), and Parkinson's disease. TMS treatment may also have an effect in other types of treatments such as in pain treatment, e.g. for improving chronic pain conditions. The article "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)", by Lefaucheur et al. Clinical Neurophysiology 131 (2020) 474–528. https://doi.org/10.1016/j.clinph.2019.11.002 is a review article showing the therapeutic efficacy of repetitive transcranial magnetic stimulation.

WO 2022/204725 describes a system and method for providing transcranial magnetic stimulation (TMS) based on electroencephalogram (EEG) data. The system and method may include a portable neuro-electroencephalogram synchronization therapy (NEST) system for capturing EEG data from a user. The system and method may also include an electrophysiology database and customized TMS treatment system for receiving the EEG data from the portable NEST system. The electrophysiology database and customized TMS treatment system may determine a TMS treatment protocol based on the received EEG data. The portable NEST system may provide synchronized TMS based on the determined TMS treatment.

Over the years, various TMS protocols have been developed targeting different brain disorders or brain conditions. TMS stimulation is usually based on treatment based on protocols that are selected based on symptoms of the user and optionally in dependence on measured brain activities of a user.

US 2019/0261877 describes a method for enhancing cognitive function based on individual cognitive frequency resonance that intentionally and selectively enhances a specific cognitive function by resonating with brain waves through brain stimulation using an electric current of the same frequency or waveform as individual cognitive frequency generated during a cognitive task by using Transcranial Current Stimulation (tCS), Transcranial Magnetic Stimulation or Focused Ultrasound Stimulation (FUS).

US2016008620 describes a therapeutic or diagnostic system comprising a non-invasive TMS brain stimulation device configured to stimulate a user's brain or nervous system by emitting electromagnetic pulses according to stimulation parameters. It is taught that in particular, stimulation pulses may be delivered at a frequency of between 12 and 40 Hertz with a 3 to 5 ratio as compared with burst repetition frequency, or at other specific patterns within that range. The therapeutic brain stimulation system includes a feedback device to measure brain activity or activity relating thereto. Measurements obtained from the feedback device can be used to adjust stimulation parameters to maximize treatment benefit or may be used to determine optimal parameters individualized or customized for a given user. The TMS brain stimulation device may be configured to receive input from the feedback device and may operate to adjust stimulation parameters of the treatment protocol in real time.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide a brain stimulation system that is configured for providing a very effective brain stimulation that can be adapted to individual users.

In an embodiment, it is an objective to provide a brain stimulation system with a high reliability for reaching a desired treatment outcome.

In an embodiment, it is an objective to provide a brain stimulation system that is configured for running a selected stimulation protocol with high precision and optionally for adjusting the stimulation protocol.

In an embodiment, it is an objective to provide a brain stimulation system that may be used with a high degree of flexibility according to a user's needs.

In an embodiment, it is an objective to provide a brain stimulation system that provides a high degree of safety for a user.

In an embodiment, it is an objective to provide a brain stimulation system which requires no manual clinical adjustment during use or even prior to use.

In an embodiment, it is an objective to provide a headwear constituting or forming part of a brain stimulation system, wherein the head wear is portable by a user during treatment.

In an embodiment, it is an objective to provide a headwear for a brain stimulation system that may be provided at an attractively low cost.

These and other objectives have been solved by the invention or embodiments thereof as defined in the claims and/or as described herein below.

It has been found that the invention or embodiments thereof have a number of additional advantages, which will be clear to the skilled person from the following description.

The brain stimulating system of the invention is configured for transcranial magnetic stimulation (TMS). The brain stimulating system comprises a headwear with a head facing surface configured for being in contact with a user's head and defining a treatment scene. The headwear comprises

- a plurality of conductor coils, wherein the conductor coils are located at selected locations, wherein each of the conductor coils is orientated to generate a magnetic field at the treatment scene adapted for inducing an electric field at the cortex of a user
- a power arrangement for supplying current to the respective plurality of conductor coils.

The brain stimulating system comprises a sensor system comprising at least one primary physiological sensor adapted for detecting a physiological parameter in response to a brain stimulation. It should be noted that the at least one primary physiological sensor may in addition be adapted for detecting one or more physiological parameters which are not in direct response to a brain stimulation. For example the at least one primary physiological sensor may repeatedly detect or monitor a selected parameter,

wherein only one or more of the detection is for detecting the physiological parameter in response to the brain stimulation. As it will be clear from the description and claims, the sensor system may in addition comprise one or more further sensors beyond the at least one primary sensor.

The brain stimulating system comprises a computer system comprising a controller configured for performing the following:

i. receiving stimulation data representing a set of stimulation parameters of a stimulation protocol, wherein the set of stimulation parameters comprises at least one modulation parameter and at least one spatial parameter,
ii. converting the received stimulation data to a set of current parameters according to a converting protocol and
iii. controlling the power arrangement, comprising supplying current to one or more of the conductor coils according to the set of current parameters for inducing the brain stimulation according to the stimulation protocol.

As explained, further below the computer system and/or the sensor system or a part thereof may form part of the headwear.

The computer system is in addition configured for

iv. detecting the physiological parameter using the primary physiological sensor, and
v. determining if the detected physiological parameter is indicative of a response to the induced brain stimulation,

and if not,

vi. adjusting the converting protocol, and
vii. optionally repeating the steps i-vi.

The inventors of the present invention have realized that by using a combination of a plurality of TMS coils, a power arrangement, a controller for controlling the power arrangement and at least one primary physiological sensor, a very effective brain stimulation may be provided, which in addition is adaptable to an individual user for performing a desired brain stimulation treatment. In addition, it has been found that the brain stimulation system is very reliable for reaching a desired treatment outcome.

The steps i-iv or i-iii provide a closed loop brain stimulation including a closed loop location adjustment comprising detecting by the at least one primary physiological sensor a physiological parameter which may be expected to indicate a response to an induced brain stimulation, determine if the detected parameter is indicative of such response to the induced brain stimulation, and thereby determine if the induced brain stimulation is in conformity with at least one stimulation parameter of the stimulation protocol.

According to the invention, it has been found that where the parameter detected by the at least one primary physiological sensor is not indicative of an expected or desired response to the induced brain stimulation, it may be caused by for example anatomical or functional differences in the brain from one user to another and/or differences in head shape resulting in difference in placements of the head wear as it relates to targeting the treatment scene. In addition, during use the headwear or a part thereof may be displaced such that one or more of the coils may shift location relative to the user's brain.

Therefor a standard converting protocol may often not be sufficient for obtaining a desired treatment. By the present invention, the converting protocol may in a closed loop be adjusted to the individual user and/or to the placement of the headwear on the user to thereby achieve a desired stimulation according to the stimulation protocol.

Thus, the computer system, e.g. the controller, is configured such that the converting protocol is subjected to a closed loop location adjustment when the parameter detected by the at least one primary physiological sensor is not indicative of an expected or desired response to the induced brain stimulation, such as at least one spatial parameter of the induced brain stimulation. The closed loop location adjustment comprises an adjustment of the converting protocol and thereby the resulting set of current parameters of the power arrangement, such as current amplitude, frequency, direction and selection of coils to which current is supplied.

The computer system is advantageously configured for repeating the closed loop location adjustment for at least a part of the time for a stimulation session, e.g. during the entire stimulation session.

In an embodiment, the closed loop brain stimulation further comprising adjusting the stimulation protocol if it is determined that a modulation parameter of the set of stimulation parameters is not correlated to affect the brain waves of the user. This will be described further below.

The modulation parameter may comprise a temporal parameter.

Advantageously, the modulation parameters comprises parameters for generating one or more stimulation sequences selected from a mono-phasic, a bi-phasic and a burst of pulses, a stimulus amplitude/intensity, a pulse frequency and number of pulses in a train, a burst frequency and a number of bursts in a train, a pulse frequency in a burst, a plurality of trains optionally comprising one or more inter-train interval(s). The spatial parameters are the parameters representing the respective location for the modulation.

In an embodiment, the closed loop brain stimulation comprises adjusting the stimulation protocol by a closed loop modulation adjustment if it is determined that a modulation parameter of the set of stimulation parameters based on the user's brain state, and the purpose of the treatment, such as to prolong a sleep brain state (supporting), to suppress a brain state (inhibitory modulations), to excite a brain state (excitatory) and etc.

The phrase "closed loop brain stimulation" is herein taken to mean a brain stimulation routine that adapts and if required adjusts by a "closed loop location adjustment" the converting protocol to provide that conversion of stimulation parameters to current parameters is in conformity with the user to be treated and the placement of the headwear on the user's head and/or a brain stimulation routine that adapts and if required adjusts by a "closed loop modulation adjustment" the stimulation protocol by updating one or more stimulation parameters of the set of brain stimulation parameters based on the user's brain state.

In an embodiment, the update and setting of the converting protocol may be performed offline, e.g. prior to starting a brain stimulation session. The update and setting of the converting protocol offline may for example be based on user characteristics, such as age, gender, or head size of the user; based on previous stimulation sessions of the user and/or based on the type of stimulation to be induced, such as the stimulation protocol.

The stimulation protocol advantageously comprises a plurality of sets of brain stimulation parameters, in the form of stimulation data readable by the computer system. In an embodiment, the update and selection of the set of brain stimulation parameters may be done offline, e.g. prior to starting a brain stimulation session.

In a preferred embodiment, the brain stimulating system is configured for performing the brain stimulation routine comprising updating one or more stimulation parameters of at least one set of brain stimulation parameters of

the stimulation protocol during the stimulation session, preferably in real time.

The terms "user" is herein meant to include "subject" and "patient" that is subjeced to the brain stimulation using the brain stimulating system. The user is advantageously, a mammal, such as a human being.

The terms "modify" and "adjust" are used interchangeable.

The computer system may be a single computer or a group of computers, including the controller, which are in data communication with each other e.g. by wire or wireless, such as Bluetooth. The computer system comprises a processor, such as a multi-core processor. The computer system may include a smartphone, a PC, a tablet etc. The computer system advantageously comprises a digital memory.

The treatment scene is the location of at least a portion of a user's cortex/brain within an operation distance from the coils when the user is carrying the headwear.

The term "brain" means the entire brain including both central and peripheral portions of the nervous system or any portions thereof, such as the prefrontal cortex or any portions thereof. In an embodiment, the brain stimulating system and/or the headwear is adapted for stimulation of at least one brain region, e.g. dorsolateral prefrontal cortex, which may have downstream effects on distant connected areas of the nervous system.

In an embodiment, the treatment scene comprises a location of a region of a user's brain network, that when stimulated using the brain stimulating system, modulates activity in the rest of the network. The region of the brain network may for example comprise a networkhub, i.e. a brain region comprising one or more network nodes that participate in multiple sub-networks of the brain.

The stimulation and/or modulation may be either excitatory or inhibitory, depending on the stimulation protocol used. Examples of different treatment scenes and associated stimulation protocols will be provided in later sections

A cooperation distance means herein a distance where the coils in cooperation distance may operate in synergy by supplying oppositely directed current through the coils thereby resulting in an increase in focality of the induced electric field. The set of brain stimulation parameters of a treatment may comprise a set of operational instructions, a recipe, on how to deliver the TMS treatment to the given user. The set of brain stimulation parameters

may for example comprise one or more series of one or more of pulses, bursts, trains, waveform, intensity, duration and/or location of coil(s) to be activated, that can be executed on a TMS device.

The stimulation protocol may comprise one or more sets of brain stimulation parameters that are predefined prior to a stimulation session. In an embodiment, the brain stimulating system is configured for updating the converting protocol and optionally the stimulation protocol during a treatment session to thereby optimize the treatment and increase treatment effectiveness.

The phrase "stimulation protocol" is herein used to mean the set of stimulation parameters, such as target location, stimulation waveform, and stimulation period, required for performing a stimulation session, wherein a stimulation session is the window wherein the user is treated with the one or more stimulation protocols, such as 10 minutes, such as 1 hour, such as a multiple hours during sleep.

A brain state may comprise a pattern of synchronous neural firing, metabolic markers, and other representations that reflect the activity of brain networks. Brain networks support a variety of brain states with different patterns of activity, as well as functional and dynamic connectivity.

The brain state may be a local brain state, such as a local brain state detected at a location in proximity to the dorsolateral prefrontal cortex, such as F7, F3, F4, F8; a location in proximity to the medial temporal lobe, such as P5, T3, T4, P6 and/or a location in proximity to the posterior parietal cortex such as CP1, P3, P4, CP2. A local brain state measurement may in an embodiment comprise multiphysiological measurements from distant sensors such as a peripheral heart rate sensor and frontal EEG, to infer downstream effects local stimulation, such as when stimulating a brain network hub, such as DLPFC.

In an embodiment, the brain state is provided in the form of a sensor-derived representation of the nervous system's underlying activity. It may include EEG signatures, metabolic biomarkers, and other physiological parameters, and representations thereof that are used to differentiate different states of nervous system activity.

In an embodiment, the brain state is derived from measurements obtained using physiological sensors, symptom scores, and performance on behavioral tasks.

Advantageously, the brain state is a computer-based state representation of the user's health.

Different temporal scales may be integrated to form part of a brain state representation, e.g. real time biometric data, biometric recordings and behavioral scores from past sessions, symptom scores from current and past sessions, as well as assessments and blood panels from past clinical visits.

In one embodiment, the device comprises a photodiode configured to synchronize with behavioral data.

The terms "coil" and "conductor coil" are used interchangeably.

It should be emphasized that the term "comprises/comprising" when used herein is to be interpreted as an open term, i.e. it should be taken to specify the presence of specifically stated feature(s), such as element(s), unit(s), integer(s), step(s) component(s) and combination(s) thereof, but does not preclude the presence or addition of one or more other features.

Throughout the description or claims, the singular encompasses the plural and the plural encompasses the singular unless otherwise specified or required by the context.

The "an embodiment" should be interpreted to include examples of the invention comprising the feature(s) of the mentioned embodiment.

The term "substantially" should herein be taken to mean that ordinary product variances and tolerances are comprised. All features of the invention and embodiments of the invention as described herein, including ranges and preferred ranges, may be combined in various ways within the scope of the invention, unless there are specific reasons not to combine such features.

All features of the invention and embodiments of the invention as described herein including ranges and preferred ranges may be combined in various ways within the scope of the invention, unless there are specific reasons not to combine such features.

In an embodiment, the step of determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, comprises determining if the induced brain stimulation is in compliance with or out of compliance with at least one spatial parameter of the stimulation protocol, such as the at least one spatial parameter of the set of stimulation parameters of the stimulation protocol. The computer system is configured for adjusting the converting protocol, if the induced brain stimulation is out of

compliance with the stimulation protocol, to provide that the system is adjusted to operate in compliance with the stimulation protocol.

In an embodiment, the computer system is configured for adjusting the converting protocol without changing the stimulation protocol.

In an embodiment, the computer system is configured for adjusting the stimulation protocol based on a parameter related to a user's brain state detected by a physiological sensor. The brainwave state e.g. at one or more brain locations e.g. EEG signatures, metabolic biomarkers, wave frequency and or intensity and other physiological parameters a one or more brain locations, such as at least one brain location that is target for the stimulation.

Advantageously, the computer system comprises a memory storing at least a portion of the stimulation protocol and/or is in data communication with an external memory storing a portion of or the entire stimulation protocol. The at least one portion of the stimulation protocol stored on the computer system is conveniently stored as at least one processed stimulation protocol portion of the stimulation protocol.

The computer system may be configured for receiving input data comprising at least a portion of the stimulation protocol or data for generating and/or selecting the stimulation protocol. The computer system is advantageously configured for processing the received data and storing the processed data as at least one processed stimulation protocol portion of the stimulation protocol.

In an embodiment, the computer system is configured for receiving, data representing the stimulation protocol or portions thereof and for storing the received stimulation protocol or portions thereof.

In an embodiment, the computer system stores at least one stimulation protocol, such as two or more stimulations protocols. Each stimulation protocol comprises data representing the sets of stimulation parameters.

The master protocol may advantageously comprise data for timely synchronizing of the respective nested protocols to operate according to the stimulation protocol and in dependence of detected brain states and/or local brain states.

Advantageously, the stimulation protocol and/or the at least one processed stimulation protocol portion comprises two or more nested protocols

In an embodiment, the master protocol is configured for monitoring the brain determine a brain state or local brain state in real time and classify the brain

state or local brain state comprising that the master protocol comprises data for instructing the computer system for activating one or more of the physiological sensors and optionally additional sensors at selected points of time during a stimulation session and determine and classify the brain state or a local brain state based on at least the physiological parameters determined by said activated physiological sensor(s).

The selected point in time, may advantageously be with a selected frequency, which may be equal or different for the respective sensors. For example the EEG sensor(s) HR sensor(s) and may operate with a first relative high frequency, the fNIRS sensor(s) may operate with a second frequency that may be different from the first frequency and the EDA sensor(s) may operate with a relative slow frequency.

In an embodiment, the master protocol comprises data for instructing the computer system to determine if the detected brain state or local brain state comprises an indication of a target event for stimulation of the brain.

Advantageously, the master protocol is configured to select if a nested protocol should be in active state and to select such active nested protocol

In an embodiment, the master protocol comprise data for instructing the computer system to continue a pause where the brain stimulating system is in a pause and none of the nested protocols are active.

In an embodiment, the master protocol comprise data for instructing the computer system to stop any ongoing processing of a nested protocol if the computer determines that the detected brain state or local brain state does not comprise an indication of a target event for stimulation of the brain.

In an embodiment, wherein if the computer determines that the detected brain state or local brain state do comprise an indication of a target event for stimulation the brain, the master protocol is configured to instruct the computer system to select a nested protocol in dependence of the target event indicated and to instruct the computer system to start or to continue the selected nested protocol.

The master protocol advantageously comprises data for instructing the computer system to perform a continuous routine comprising monitoring the brain, determine a brain state, classify the brain state, determining if the detected brain state or local brain state do comprise an indication of a target event for stimulation the brain, if no, continuing a pause or terminate stop operation of any active nested protocol; if yes, select a nested protocol in dependence of the classification of the brain state or local brain state and

start/activate the selected nested protocol or continue the selected nested protocol if already in activation.

Thereby the master protocol dynamically ensures a desired stimulation in dependence on the brain state without any required supervision or adjustment by a clinical person, such as a doctor or nurse.

In an embodiment, the one or more nested protocols advantageously comprises at least one nested static protocol, and/or at least one nested dynamic protocol.

The nested protocol is advantageously associated with and may be configured for stimulating at least one brain state or local brain state, by targeting one or more brain locations, such as one or more hubs in a brain network

The at least one nested static protocol comprises at least one sequence of one or more sets of stimulation parameters comprising a modulation parameter and a spatial parameter, wherein the at least one sequence remains unchanged. Where the nested protocols comprises of or consists of nested static protocols, the stimulation protocol advantageously comprises a relative high number of nested protocol, since a minor change of the brain state may require that a new nested protocol is to be activated.

Advantageously, the nested protocols comprises at least one and preferably several nested dynamic protocols. Each nested dynamic protocol comprises at least one start sequence as the initial operative sequence or is configured for acquire such at least one start sequence as the initial operative sequence e.g. from a look-up table of a database. The operative sequence comprises one or more sets of stimulation parameters comprising a modulation parameter and a spatial parameter, wherein the nested dynamic protocol is configured for dynamically modifying the operative sequence in dependence of the brain state determined in real time. The nested dynamic protocol may be configured for acquire data from a look-up table of a database and apply such data in the dynamically modifying of the operative sequence.

The brain state may advantageously be acquird or received from the master protocol, which continuously monitors the user's brain activity and determines their brain state in realtime.

The real time dynamic brain state may advantageously be obtained from the master protocol, which continuously monitor the brain and determine the real time brain state.

The master protocol may preferably comprise data for selecting and activating a nested protocol associated to the determined brain state or local brain state and/or wherein the master protocol comprises data for deselecting and deactivating an active nested protocol not-associated to said determined brain state or local brain state.

In an embodiment, the master protocol comprises data for selecting and activating selected nested protocols based on parameters related to a user's brain state detected by one or more physiological sensors. In an embodiment, the computer system e.g. based on instructions of the master protocol may be configured for activating one or more of the physiological sensors at selected points of time during a stimulation session and determine a brain state or a local brain state based on the physiological parameters determined by the activated physiological sensor(s).

Advantageously, the master protocol comprises data for selecting and activating a nested protocol associated to the determined brain state or local brain state and/or wherein the master protocol comprises data for deselecting and deactivating an active nested protocol not-associated to the determined brain state or local brain state.

The points of time for activating the one or more of the physiological sensors, may for example be points of time with a regular interval, such as with a selected frequency, such as a frequency of 0.01 – 100 Hz, preferably 0.1-10 Hz.

The master protocol advantageously comprises data for dynamically selecting and activating selected nested protocols based on a parameter related to a user's brain state detected by a physiological sensor.

Thereby the brain stimulation system does not require manual clinical adjustment during use or even prior to use.

Thus, where the brain state or a local brain state changes the brain stimulation system may dynamically modify the brain stimulation in dependence on the new brain state or local brain state.

The user may therefore perform brain stimulation sessions without requiring supervision or adjustment by a clinical person, such as a doctor or nurse.

The approximate location(s) of cortex is often provided in the form of map of scalp locations and optionally a depth indication. Well-recognized maps of scalp locations include the 10–20 system, the 10-10 system and the 10-5 system developed for placement of EEG electrodes. The system is based on the relationship between the location of an electrode and the underlying area

of the brain, specifically the cerebral cortex. The 10-10 system map is shown in figure 3.

In an embodiment, the spatial parameter of the set of stimulation parameters of the stimulation protocol is indicative of a target location of the cortex, preferably selected from the frontal, temporal, and parietal cortex. Advantageously, the step of determining if the detected physiological parameter is indicative of a response to the induced brain stimulation comprises determining if a spatial location of the induced brain stimulation is in conformity with the at least one spatial parameter of the set of stimulation parameters stimulation protocol.

The at least one primary physiological sensor may for example detect a response to an induced stimulation in the form of a change, such as a change in brain waves; a change in electrical conductance of the skin; a change in heart rate, such as acceleration or deceleration of the heart, or change in heart rate variability; a change in breathing pattern, such as breathing rate, depth of breathing or blood oxygenation; a change of muscle activity, such as a change in muscle tone, etc.

In an embodiment, the set of stimulation parameters of the stimulation protocol comprises one or more of a pulse, a burst, a pulse train, a combination and/or series of the before mentioned optionally forming one or more stimulation sequences, wherein the stimulation parameters preferably have selected frequencies and/or varying intensities, and wherein the stimulation parameters may be configured to induce inhibitory and/or excitatory stimulation and any combinations comprising one or more of these.

For example, theta burst stimulation (TBS) is a frequently used type of stimulation mode, which may be used either as inhibitory stimulation or as excitatory stimulation. TBS refers to a stimulation setting in which a fixed-frequency pulse is nested in another pulse mode with fixed-frequency. Theta burst pulse stimulation is a commonly used TBS mode in psychiatric diseases, which refers to embedding three continuous 50 Hz pulse stimulation into a 5 Hz pulse stimulation. It is believed that intermittent theta burst pulse stimulation (iTBS) plays an excitatory role, while continuous theta burst pulse stimulation (cTBS) have an inhibitory effect.

In an embodiment, the computer system is configured for controlling the activity of the primary physiological sensor and for detecting the physiological parameter using the primary physiological sensor.

In an embodiment, the computer system is configured for detecting the physiological parameter in real time relative to the inducement of the brain stimulation according to the stimulation protocol. Preferably, the computer is configured for monitoring the physiological parameter during the inducement of the brain stimulation and wherein the detection of the physiological parameter comprises the detection of potential changes of the physiological parameter.

The phrase "real time" is herein used to mean the time it requires without unrequired delay for the computer to detect the physiological parameter and process the obtained data to determine if the detected physiological parameter is indicative of a response to the induced brain stimulation to thereby determine if the induced brain stimulation is in conformity with at least one stimulation parameter of the stimulation protocol. Advantageously, real time means up to 5 seconds, up to 1 second, more preferably up to 0.1 second of providing the stimulation.

The headwear is conveniently adapted for being in contact with a user's head, preferably comprising at least a portion of a user's forehead. The headwear may for example be selected from a headband, a helmet, a cap, a hat and/or a swim cap.

The headwear may advantageously be adjustable for fitting to a user's head shape, e.g. by comprising adjustable straps. The headwear may conveniently comprise a flexible and/or stretchable foundation to which the electrical elements, such as coils, wiring etc. are attached and/or embedded.

To ensure a desired penetration of the TMS, it is desired that the portion(s) of the headwear carrying the conductor coils is/are adapted for being in short distance to a user's head, such as with a distance of up to 1 cm, such as up to 5 mm or for being in physical contact with a user's head.

Advantageously, the headwear comprises a headband comprising an annular band adapted for encircling a head of a user and having a width of from 1-6 cm, such as from 2-5 cm, preferably at least two, such as at least 4 of the plurality of coils are located at the annular band.

By providing the headwear in the form of a headband, the headwear offers prolonged comfort for a user. Thereby the headwear may be used for a prolonged period enabling a stimulation session to extend for a relatively long time, such as for an hour or more or even several hours. During the stimulation session, the user may simultaneously engage in other everyday tasks, such as working, eating and social activities.

In an embodiment, the stimulation session may even be performed while the user is sleeping. The stimulation session may for example comprise a sleep therapy as described below.

The headband may advantageously comprise at least one cross band extending from a first location of the annular band to a second location of the annular band. The first location and the second location may be located with a distance along the annular band of at least 5 cm, for example from a front location to a rear location relative to the front and rear location of the head of a user.

The cross band may conveniently be adapted for extending over and in contact with at least a portion of the top and/or the crown of the head of the user, preferably one or more, such as at least two of the plurality of coils are located at the cross band.

The headwear may in principle comprise any number of coils, such as at least 2 conductor coils, such as from 3 to 12 conductor coils, such as from 4 to 8 conductor coils, wherein the conductor coils preferably located at one or more portions of the headwear adapted to be in contact with a user's forehead in use.

The coils may be equal or they may be different from each other. In an embodiment, one or more coils comprise two or more sub-coils, which are located on top of each other to form stacked coils.

Each of the respective coils has an inner perimeter defining an inner dimension, such as an inner diameter, an outer perimeter, defining an outer parameter, e.g. an outer diameter and at least one winding which may form a closed loop or a spiral.

Where a coil has several windings, e.g. forming a spiral, such as an archimedean spiral, the inner dimension is determined as the innermost dimension and the outer diameter is determined as the outermost dimension.

The shape of the at least winding may for example be circular, oval or angular, such as rectangular. For example, the conductor coils have rectangular, round and/or rounded shapes, e.g. elliptical or circular.

Advantageously, the selected locations of the plurality of conductor coils comprises spatially distinct locations relative to the head-facing surface. Thereby, the respective coils may be applied to stimulate spatially distinct locations of a user's brain.

For example, the selected locations of the plurality of conductor coils may comprise locations selected to generate two or more magnetic fields at the treatment scene e.g. at different locations of the treatment scene.

In an embodiment at least two, such as all of the coils are circular coils.

The conductor coils may advantageously, independently of each other have a maximal outer perimeter dimension (if circular an external diameter), such as of up to 8 cm, such as up to 5 cm, such as up to 3.5 cm.

In an embodiment, the respective conductor coils independently of each other comprise one winding or a plurality of windings, such as 10 windings or more, such as from 50 to 100 windings or more.

In a preferred embodiment, the coils are round coils and independently of each other from 3 to 5 cm in outer diameter and preferably comprise up to 100 turns, such as from 50-100 turns of copper wire.

The respective coils may conveniently have an inductance of at least 100 μH, such as 125-300 μH, such as from 150 to 200 μH and/or a resistance of from 0.1 to 50 Ω, such as less than 2 Ω.

The coils may be of any conducting material having a desired conductivity, such as metal, advantageously metal selected from Copper, Gold, Silver or alloys comprising any of these. In an embodiment, the coils are of or comprise an electrically conductive polymer.

In an embodiment, the respective conductor coils each have an outer surface defining an outer perimeter. The coils are advantageously located in a configuration comprising that at least two conductor coils are located within cooperation distance.

The at least two conductor coils are advantageously located within cooperation distance comprising that at least two conductor coils are located with a distance between a section of the outer surfaces of the respective conductor walls of the at least two conductor coils which is up to a maximal cooperation distance and/or up to 3 cm, such as up to 2 cm.

By providing two or more coils to be located within cooperation distance the coils may operate in synergy by supplying oppositely directed current through the coils thereby resulting in an increase in the focality of the induced electric field.

In an embodiment, the respective conductor coils have an outer surface defining an outer perimeter and wherein the coils are located in a

configuration comprising that at least two of the conductor coils are located with a distance larger than the cooperation distance.

The brain stimulating system is advantageously adapted for feeding conductor coils within cooperation distance with current in opposite direction (clockwise and contra clockwise), to optimize the compliance with the stimulation parameter(s) with respect to depth and focality of the induced electric field. By feeding the current in opposite directions to conductor coils within cooperation distance the resulting induced electrical field may have a very high focality. However, at the expense of penetration depth. Thereby the selection of current direction in conductor coils within cooperation distance presents a trade-off between depth and focality.

Bringing the coils close to each other and supplying oppositely directed current through the coils increases the focality of the TMS, but reduces the penetration depth.

Selecting conductor coils that are located further from each other and/or supplying current directed in a common direction through the coils may decrease the focality, but increase the penetration depth.

In an embodiment, the conductor coils are mounted to the headwear to provide that the location of one or more of the conductor coils may be adjusted, e.g. by a click adjustment mechanism providing that a coil may be click adjusted between two or more locations. Thereby the location of one or more of the conductor coils may be selectable to provide a desired conductor coils location configuration for conducting a selected stimulation protocol and/or for adapting to a user's head shape/size.

Each of the respective conductor coils has a center axis and each respective conductor coil may be located relative to an adjacent conductor coil such that the center axis of the conductor coil has an angle to the center axis of the adjacent conductor coils which is zero (parallel center axis') or up to 60°, such as up to 40°, such as up to 20°.

In an embodiment, the center axes of the conductor coils are fixed in the headwear. Depending on the application, a preferred angle of the respective conductor coils may be determined.

In an embodiment, the controller is configured to control power arrangement to supply oppositely directed current through conductor coils within cooperation distance to adjust the depth and focality of the induced brain stimulation. The oppositely directed current through coils within cooperation

distance may be set to be equal or to differ from each other to direct the brain stimulation to a selected location of the cortex, preferably in compliance with at least one stimulation parameter of the stimulation protocol.

It has been found that by selecting the amount of current directed through coils within cooperation distance the TMS may be directed to stimulate a location of cortex, which is directly below the conductor coils within cooperation distance or which is laterally displaced relative to the conductor coils within cooperation distance. Thereby a very high accuracy in respect of the location of the stimuli may be provided.

By applying the regulation of current supply in combination with the detection of the physiological parameter simultaneously or in immediate connection inducing the brain stimulation, and in real time determining if or if not the detected physiological parameter is indicative of a response to the induced brain stimulation, and thereby determine if the induced brain stimulation is in conformity with at least one stimulation parameter of the stimulation protocol, a highly effective, precise and fast-acting brain stimulation system may be been provided.

Advantageously, the power arrangement comprises a wiring to each of the conductor coils (and optional sub-coils) for supplying current e.g. in the form of a pattern of current through the respective coils to induce the brain stimulation. Preferably the power arrangement comprises a wiring to each of the individual conductor coils for supplying the current e.g. in the form of a pattern of current through the respective coils independently of each other, preferably in concordance with the set of current parameters.

Advantageously, the wiring to each of the conductor coils for supplying current through the respective coils comprises a wiring with respect to a power source, which enables supplying current to one or more of the coils in a first direction or in a second opposite direction in dependence of the set of current parameters and in dependence of a desired penetration depth and/or focality.

The power arrangement conveniently comprises at least one pulse generator adapted for generating pulses of current in concordance with the set of current parameters.

In addition, it is desired that the power arrangement comprises a coil selector adapted for selecting one or more of the conductor coils to be activated and to activate the selected coils in concordance with the set of current

parameters by generating pulses of current and inducing a magnetic field in the selected coils according to the stimulation protocol.

The master protocol may advantageously comprise data for operating the coil selector, wherein the data for operating the coil selector comprises spatial parameters of respective sets of stimulation parameters. Based on the at least one spatial parameter that is target for a stimulation to be induced according to a nested protocol, the coil selector may select the coils to be activated and a direction of current to be supplied to the coil.

The amount of current to be supplied to the selected conductor coils may advantageously be based on data of the nested protocol.

In an embodiment, the respective nested protocols comprise data for instructing the power arrangement for supplying current to respective of the conductor coils.

The master protocol and/or the nested protocol(s) may comprise data for synchronizing the supply of current to the conductor coils.

Therefore, where one or more activated coils have shifted location during use, the computer system may optional based on data from the stimulation protocol, relatively fast determine if one or more detected physiological parameters are indicative of a response to the induced brain stimulation and if not the computer system will adjust the converting protocol providing the coil selector to perform a reselection of coil(s) to be activated for running a nested protocol in question.

Thereby no clinical assistance is required.

The controller is preferably configured to synchronize the supply of current and pattern of current to respective conductor coils to provide a synchronized stimulation pattern in concordance with the stimulation protocol.

In an embodiment, the controller is configured for controlling the set of current parameters by controlling the supply of current through the respective coils independently according to the stimulation protocol.

The stimulation protocol advantageously comprises stimulation data representing the plurality of sets of brain stimulation parameters for generating one or more stimulation sequences selected from a mono-phasic, a bi-phasic and a burst of pulses, a stimulus amplitude/intensity, a pulse frequency and number of pulses in a train, a burst frequency and a number of bursts in a train, a pulse frequency in a burst, a plurality of trains optionally comprising one or more inter-train interval(s).

Preferably the controller, optionally based on data from the stimulation protocol, is configured for controlling the supply of current through the respective coils to generate one or more stimulation sequences according to the stimulation protocol and preferably selected from a mono-phasic, a bi-phasic and a burst of pulses, a stimulus amplitude/intensity, a pulse frequency and number of pulses in a train, a burst frequency and a number of bursts in a train, a pulse frequency in a burst, a plurality of trains optionally comprising one or more inter-train interval(s).

In an embodiment, the one or more stimulation sequences comprises repetitive transcranial magnetic stimulation (rTMS).

Advantageously, the controller is configured for controlling the set of parameters of the TMS by controlling the supply of current through the respective coils to generate a magnetic field strength at a distance of 1 cm from the conductor coil of from 0.25 mT to 30 mT. Advantageously, the magnetic field strength is adjustable.

In an embodiment, the controller is configured for controlling the set of parameters of the TMS by controlling the supply of current through the respective coils to generate a magnetic field strength resulting in generation of an electric field of about 0.1-10 V/m^2 at the cortical surface, which is located about 5.9 +/- 1.5 mm from the scalp.

In an embodiment, the controller is configured for controlling the set of current parameters by controlling the supplying of current through the respective coils independently of each other, comprising controlling at least one of the current supply parameters selected from coils to which current is supplied, the direction of current and current pattern to thereby generate the brain stimulation according to the stimulation protocol.

The set of current supply parameters may in an embodiment be configured to correspond to the set of brain stimulation parameters that comprise

- at least one frequency of from 1 Hz to 1 kHz, preferably comprising frequencies sets below 250 Hz, such as below 100 Hz;
- at least one pulse having a pulse width of up to 100 ms, such as in increments of 10 µs (depending on the frequency),
- at least one pulse interval between single pulses or repetitive pulses of from 1 0s up to 30 minutes of a treatment session, and/or
- at least one current amplitude of at least 1 mA, such as at least 5 mA.

The strength of the magnetic field may be tied to the amount of current supplied. Thus, by adjusting the amount of supplied current, the strength of the magnetic field generated may likewise be adjusted.

The controller may advantageously be located on the headwear. The power arrangement may conveniently include a power supply comprising one or more batteries, such as a rechargeable battery or batteries. The power supply may advantageously be located on the headwear, enabling the headwear to be portable and untethered.

In an embodiment, the computer system comprises at least one portable computer unit, preferably configured for wireless communication. The computer unit advantageously comprises a smartphone, a PC, a tablet or a wearable computer, such as a smartwatch, optionally the at least one portable computer unit is located on the headwear.

The at least one primary physiological sensor of the sensor system may be any kind of sensor capable of sensing a physiological parameter that is affectable by brain stimulation. In an embodiment, the at least one primary physiological sensor comprises at least one sensor selected from the group comprising an electroencephalogram (EEG) sensor, a functional ultrasound imaging (fUS) sensor, an electrooculography (EOG) sensor, an electromyography (EMG) sensor, a heart rate sensor (pulse oximetry sensor, PPG, ECG, etc.), a functional near-infrared spectroscopy sensor (fNIRS), an electrodermal activity (EDA) sensor or a magnetoencephalogram (MEG) sensor.

It has been found to be preferred that the at least one primary physiological sensor comprises at least one of a heart rate sensor and a cerebral blood flow sensor, preferably the heart rate sensor and/or the cerebral blood flow sensor are located on the headwear.

It has been found that brain stimulation may have an effect on the heart rate and/or the cerebral blood flow when applied at certain locations of the cortex e.g. at locations of the prefrontal cortex.

For example, it has been found that stimulation at the dorsolateral prefrontal cortex (DLPFC) may affect the heart rate

The heart is one of the end organs of the DLPFC, and this mood regulatory center, therefore, has a strong parasympathetic connection. It has been found that excitatory stimulation to the left DLPFC results in a transient Heart

Rate Deceleration (HRD).In an embodiment the brain stimulating system is configured for using HR monitoring to confirm target engagement of DLPFC.

In an embodiment, the headwear comprises optical sensors (fNIRS/PPG) that can measure HR and HRV. The brain stimulating system is adapted to continuously measure the HR of the user when undergoing stimulation, and adapts the stimulation parameters to engage the stimulation target (DLPFC), as measured by HRD.

In an embodiment, the computer system of the brain stimulating system is adapted for timely synchronizing the at least one primary physiological sensor with the inducement of the brain stimulation according to the set of stimulation parameters of the stimulation protocol. Preferably the brain stimulation and/or the stimulation protocol comprises a plurality of stimulation time blocks and the computer system is adapted for timely synchronizing the at least one primary physiological sensor with one or more of the stimulation blocks.

The plurality of stimulation (time) blocks may advantageously be timely located with respective time intervals of 1 sec. or longer.

A stimulation block may for example comprise one or more series of pulses, burst and trains, such as a cTBS or iTBS series, at different locations and with varying waveforms and intensities, including sham blocks meant to mimic the characteristics of active stimulation.

Advantageously, the stimulation protocol comprises stimulation data representing a plurality of stimulation parameters organized in consecutive order and comprising the at least one set of stimulation parameters, wherein the plurality of stimulation parameters comprises one or more stimulation sequences preferably selected from a mono-phasic, a bi-phasic and a burst of pulses, a stimulus amplitude/intensity, a pulse frequency and a number of pulses in a train, a burst frequency and a number of bursts in a train, a pulse frequency in a burst, a plurality of trains optionally comprising one or more inter-train interval(s).

In an embodiment, the plurality of stimulation parameters of the stimulation protocol comprises a plurality of stimulation blocks. Advantageously the computer system is adapted for timely synchronizing the at least one primary physiological sensor with one or more of the stimulation blocks to thereby obtain a synchronized determination if the induced stimulation, such as at least one spatial parameter and optionally at least one modulation parameter

of the induced stimulation is in compliance with the one or more of the stimulation blocks of the stimulation protocol.

In an embodiment, a set of stimulation parameters is a stimulation block or a portion of a stimulation block. In an embodiment, a set of stimulation parameters comprises two or more stimulation blocks.

The computer system is advantageously configured for receiving input data comprising at least a portion of the stimulation protocol or data for generating and/or selecting the stimulation protocol. In an embodiment, the computer system comprises a memory storing at least a portion of the stimulation protocol and/or data for generating and/or selecting the stimulation protocol.

The stimulation protocol and/or data for generating the stimulation protocol map for example be obtained from known databases, such as from Centers for Medicare & Medicaid Services

www.cms.gov/medicare-coverage-database.

In an embodiment, the headwear comprises a plurality of EEG (electroencephalogram) sensors, preferably comprising one or more EEG sensors preferably located at a portion of the headwear adapted to be in contact with a user's head, such as a user's forehead.

The EEG sensors are advantageously configured for obtaining an electroencephalogram and for communicating the electroencephalogram to the computer system, wherein the computer system is in communication with a database comprising recordings of EEG brainwave data sets correlated to respective brain states and to respective treatment protocols for such brain states, and wherein the computer system is configured for fitting the electroencephalogram of the user to the EEG brainwave data sets of the database and selecting the treatment protocol for treating the user,

wherein the recordings of EEG brainwave data sets of the database, preferably are correlated to respective brain states selected from

- task-negative recordings, e.g. during resting-state studies from various user populations and healthy users.
- task-positive recordings, e.g. during cognitive-behavioral studies, such as task-elicited event-related potentials (ERPs), from various user populations and healthy users.

The database comprising recordings of EEG brainwave data sets correlated to respective brain states and to respective treatment protocols for such brain states may be an electrophysiology database.

The electrophysiology database may conveniently be a normative electroencephalogram (EEG) database. Such databases have been in existence for several years and are for example described in the articles *Quantitative Electroencephalogram Standardization: A Sex- and Age-Differentiated Normative Database*, Juhee Ko et al. Frontiers in Neuroscience. 17 December 2021 | Volume 15 | Article 766781. *Normative EEG databases and EEG biofeedback*. Robert W. Thatcher. Journal of Neurotherapy. March 1998 DOI: 10.1300/J184v02n04_02 and *HISTORY OF THE SCIENTIFIC STANDARDS OF QEEG NORMATIVE DATABASES*. Introduction to QEEG and Neurofeedback: Advanced Theory and Applications. Thomas Budzinsky, H. Budzinski, J. Evans and A. Abarbanel editors, Academic Press, San Diego, CA, 2008.

In an embodiment, the brain stimulating system is configured to determine a brain state based on one or more electroencephalograms obtained by the EEG sensor. The determination of a brain state is well known in the art.

Advantageously, the at least one physiological primary sensor comprises an optical heart rate monitor, such as a photoplethysmograph (PPG).

Advantageously, the at least one primary physiological sensor comprises an optical cortical hemodynamic activity sensor, such as an fNIRS. Optionally the at least one primary physiological sensor comprises both comprises an optical heart rate monitor and an optical cortical hemodynamic activity sensor.

The headwear preferably also includes an fNIRS sensor e.g. in the form of the at least one primary physiological sensor. In an embodiment, the brain stimulating system is configured to determine a brain state based on one or more electroencephalograms obtained by the EEG sensor in combination with cortical hemodynamic activity data determined by the fNIRS sensor.

In an embodiment, the computer system is adapted for receiving a set of input data and based on the input data and to generate and/or select the stimulation protocol using the input data. The generation and/or selection of the stimulation protocol advantageously further involves at least one of data determined on the user, the determined electroencephalogram, the determined brain state and/or a target EEG brainwave dataset, optionally obtained from a database of brain states correlated to EEG data.

The determined electroencephalogram may preferably comprise the user's real-time EEG.

The target EEG brainwave dataset may conveniently be based on data derived from a large EEG database. Data derived from the database may include data from a single EEG file and/or data derived from one or more groups of statistics derived from a subset of the EEG data in that database that is most relevant for that user. Input may be collected from these different sources, and the computer system may be configured for generating and/or selecting a best-fit stimulation protocol.

The input data may advantageously comprise user data such as age, gender, ethnicity, disorder, treatment history, current or past illness, genetic data, etc.

Examples of stimulation protocols or parts of stimulation protocols may include the following modulation parameters.

- inhibitory 1 Hz rTMS
- Continuous Theta-burst (cTBS)
- Intermittent Theta-burst (iTBS)
- excitatory 5 Hz rTMS
- 10-20Hz stimulation over left DLPFC

In an embodiment, the stimulation parameters of the stimulation protocol comprise one or more pulses, bursts, trains, and cycles, a pulse intensity, frequency, and waveform, and any combination comprising one or more of these.

It has been found that certain stimulation protocols produce an inhibitory effect in neural tissue, whereas other protocols produce an excitatory effect. The underlying mechanism of action is not fully understood but seems to involve modulation of plasticity in neurons, neurovascular changes, and other changes that effect the underlying neuronal function.

Examples of stimulation protocols include theta burst stimulation, which is derived from the firing patterns of neurons in the hippocampus. Theta burst stimulation (TBS) is a frequently used method that includes protocols for inhibitory and excitatory modulation and an FDA-approved treatment of Major Depressive Disorder (MDD).

Intermittent TBS (iTBS) is a short high-frequency excitatory protocol with trains containing patterned 5Hz bursts with 3 pulses at 50Hz and an 8 seconds pause between trains. Continuous TBS (cTBS) is a short 20-second

inhibitory protocol, also delivered in patterned 5Hz bursts with pulses at 50Hz but without pauses between trains.

Other stimulation protocols include 10Hz excitatory stimulation over DLPFC for the treatment of depression, and 50 Hz over the posterior parietal cortex for the treatment of Alzheimer's Disease. These protocols are usually performed using high-intensity TMS devices but can be adapted for low-intensity devices.

Other stimulation protocols are designed specifically for low-intensity applications, modulating activity with high-frequency fields. These include high-frequency low-intensity patterned TMS protocols with varying focality for the treatment of depression and other brain disorders. Such as 1000 Hz pulses on for 3 seconds and off for 1 second (The electric current passes 100 to 1000 times per second through the coil and the flux is interrupted every 3 seconds for 1 second).

Such stimulation protocols and methods of generating standard stimulations protocols are known in the art.

Preferably, the at least one primary physiological sensor of the sensor system comprises an optical heart rate sensor, such as a photoplethysmograph (PPG) (a pulse oximetry sensor). By using optical heart rate sensor e.g. configured for monitoring, the heart rate sensor may conveniently form part of the headwear.

In an embodiment, the heart rate sensor comprises an ECG (electrical) sensor.

In one embodiment the brain-stimulation system and/or the headwear is designed to have multiple sensor and stimulation modules placed in a headwear located in proximity to frontal, temporal and parietal areas of the cortex. This allows the system to be easily programmed for various protocols targeting different brain regions with different parameters. But also enabling multisite stimulation protocols for targeting different networks simultaneously.

As the brain is organized into parallel networks and functions, more advanced protocols are proposed to potentially improve treatment effects and individualization. Many mental disorders are heterogeneous and involve compensatory mechanisms that manifest in different network pathologies, which leads to complex and comorbid symptoms.

Unlike prior art brain stimulation systems, which are primarily designed for waking state neuromodulation, The brain stimulation system of the invention in an embodiment can be targeted for treatment during sleep and thereby may leverage sleep as a therapeutic window to improve brain health.

In an embodiment, the brain stimulation system is adapted for treatment of a user during sleep. During the sleep, the headwear may be moved such that one or more of the coils becomes displaced. However, as described above, this will be determined and corrected for by adjusting the converting protocol.

Sleep is composed of different stages and cycles that are crucial for various physiological and cognitive processes, such as synaptic plasticity and memory functions, emotional processing, metabolic functions, energy balance, clearance of neurotoxic waste, and cellular maintenance e.g. as described in the article "Sleep, recovery, and metaregulation: explaining the benefits of sleep" by Vladyslav V Vyazovskiy. Nat Sci Sleep 2015 Dec 17:7:171-84. doi: 10.2147/NSS.S54036. eCollection 2015.

The macro-architecture of sleep refers to the overall structure and organization of sleep stages across a sleep period, typically depicted in a hypnogram (see Figure 13a). Sleep consists of two main types: Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep, which cycle throughout the night.

NREM Sleep is normally divided into three stages:

- N1 (Stage 1): Light sleep, transition from wakefulness to sleep.
- N2 (Stage 2): Intermediate sleep, characterized by sleep spindles and K-complexes.
- N3 (Stage 3): Deep sleep, also known as slow-wave sleep (SWS), critical for restorative processes and memory consolidation.

REM sleep is generally characterized by rapid eye movements, vivid dreams, and increased brain activity similar to wakefulness. It is known that REM sleep is essential for emotional regulation and memory processing.

Table 1. Typically sleep stages

Stage	Duration	Characteristics
N1: Light non-REM Sleep	A few minutes	Transition from wakefulness to sleep. Muscle activity slows down, and there may be occasional

		muscle twitching. The person can be easily awakened.
N2: Intermediate non-REM Sleep	10-25 minutes in the first cycle, shorter in later cycles	Heart rate slows, body temperature drops. This stage constitutes about 50% of the total sleep cycle. Brain wave activity slows with occasional bursts of rapid waves called sleep spindles.
N3: Deep non-REM Sleep	20-40 minutes in the first cycle, shorter in later cycles	This is the most restorative stage of sleep. Breathing slows down, muscles are completely relaxed, and it is difficult to wake the person. Brain produces slow delta waves. This stage is crucial for physical repair and growth, immune system function, and overall health.
REM sleep	Initially a few minutes, increasing to about an hour in later cycles	This stage is marked by rapid movement of the eyes, increased brain activity, and vivid dreams. The body experiences temporary paralysis of the muscles to prevent acting out dreams. Heart rate and breathing become irregular. REM sleep is important for cognitive functions such as memory consolidation, learning, and mood regulation.

The proportion of REM sleep increases in the latter half of the night, while deep NREM sleep is more prevalent in the first half.

Disruptions in these cycles, such as waking up frequently or not getting enough sleep, may impact the restorative processes and lead to feelings of tiredness and cognitive impairments.

A typical night's sleep includes 4-6 cycles, each lasting approximately 90-120 minutes, transitioning through different sleep stages.

The micro-architecture of sleep involves finer details of sleep physiology, including specific EEG, EOG, and HR signatures, related to different brain processes and occurring at different cycles during the night. These include

- Slow Oscillations (SOs) that occur during NREM sleep, particularly in SWS. These oscillations (<1 Hz) are crucial for memory consolidation

by coordinating the timing of hippocampal sharp-wave ripples and cortical sleep spindles.

- Sleep Spindles: Bursts of oscillatory brain activity (12-16 Hz) during N2 sleep, associated with memory consolidation and neural plasticity.

Sleep disturbances are widely observed in psychiatric and neurological disorders, and are increasingly recognized as a critical factor in brain health, particularly in relation to Alzheimer's disease (AD). Recent research suggests that sleep macrostructure dynamics and specific sleep-related EEG features can serve as biomarkers for the accumulation of tau and beta-amyloid (Aβ), two of the primary pathological features of AD. As described in this paper: "Sleep as a Potential Biomarker of Tau and β-Amyloid Burden in the Human Brain" by Winer et al. J Neurosci, 2019 Aug 7;39(32):6315-6324. doi: 10.1523/JNEUROSCI.0503-19.2019. Epub 2019 Jun 17.

It has been found that there is a relationship between Sleep and AD

- Tau Accumulation: Impaired slow oscillation-sleep spindle coupling predicts a greater burden of tau in the medial temporal lobe (MTL). Tau forms tangles inside neurons, leading to cell damage and death, and its accumulation in the MTL is a hallmark of early AD. Weaker SO-spindle coupling is associated with increased tau deposition, highlighting its potential as a predictive biomarker.
- Beta-Amyloid (Aβ) Accumulation: The amplitude of <1 Hz slow-wave activity (SWA) during NREM sleep is inversely related to Aβ burden. Aβ forms plaques outside neurons, disrupting communication and leading to neuroinflammation. Reduced SWA, a key feature of deep sleep, correlates with higher levels of Aβ, suggesting that disruptions in deep sleep may facilitate Aβ accumulation.

In accordance with the present invention, it has been found that the brain stimulating system may be configured such that it enables the use ofsleep as a therapeutic window.

Given the intricate relationship between sleep disturbances and AD pathology, sleep represents a critical therapeutic window for neuromodulation. Stimulating the underlying brain networks responsible for producing critical sleep states, such as slow-wave sleep, may mitigate the progression of AD by reducing tau and Aβ accumulation. This therapeutic approach leverages the natural restorative functions of sleep to support brain health.

In an embodiment, the brain stimulation system is adapted to monitor sleep-related brain states, and to augment those brain states through targeted neuromodulation. The brain stimulating system, such as the headband may comprise a plurality of sensors, preferably comprising EEG, PPG, and IMU (Inertial Measurement Unit), or other subsets of sensors used in PSG for sleep monitoring. In an embodiment the brain stimulation system is equipped with on-device methods for decoding sleep-related dynamics, such as sleep stages, cycles, and microstructures in real-time,

enabling the application of personalized stimulation protocols during sleep to optimize therapeutic outcomes.

In an embodiment, the brain stimulating system is adapted for performing stimulation to improve specific sleep processes during different phases of sleep such as slow-wave sleep (SWS) and rapid eye movement (REM) sleep. Thereby the brain stimulating system may improve memory, emotional, glymphatic, and other processes during sleep and improve treatment outcomes.

The closed loop brain stimulation mechanism allows for dynamic adjustment of stimulation parameters based on physiological responses, ensuring personalized and effective treatment. The closed loop brain stimulation may advantageously comprise both closed loop location adjustments and closed loop modulation adjustments.

In an embodiment, the computer system, such as the controller stores a sleep stimulation protocol. Adapted for sleep monitoring and neuromodulation before and during sleep. The stimulation protocol enables applying the sleep session as a therapeutic window with the possibility for multiple interventions.

In an embodiment, the brain stimulation system is adapted for operating throughout the night, continuously monitoring sleep by repeatedly determining one or more physiological parameters using one or more of the physiological sensors optionally including the primary physiological sensor e.g. as described above.

The start and end time of a stimulation protocol may be preselected, selected based on previous treatment-response maps for that user, and/or be dynamically selected during runtime using event-detection methods.

In the case of dynamic selection based on event detection, the stimulation may be started, stopped or adjusted when detecting a sleep-related event, such as a change of brain state, such as the onset of slow-wave sleep

(SWS). The stimulation may run until a predefined stop point or until a pause/stop event or different sleep-related event has been detected.

The stimulation protocol advantageously includes data representing these events to be detected, such that the computer system with the stimulation program is adapted for receiving data from the plurality of sensors representing the detected brain state comparing the detected brain state to the event data and determining if there is an event detection.

In an embodiment, the stimulation protocol includes data representing slow wave sleep (SWS) and REM sleep.

It has event detection capabilities for slow wave sleep (SWS) and REM sleep. When these sleep stages are detected, the system activates the stimulation device, ensuring the therapy is timed to the relevant sleep phase and cycle (macro scale). The device measures relevant signatures within that specific period and optimizes the stimulation (micro-scale). This could be to optimize parameters to induce particular SWS by using a resonant frequency to increase SWS coupling in the brain through brain entrainment.

In an embodiment, the stimulation protocol comprises a master protocol and nested protocols that target different phases of sleep. The brain stimulation system may operate throughout the night, continuously monitoring sleep and other relevant metrics in order to orchestrate the stimulation protocols during the night (See e.g. Figure 13b).

The stimulation protocol conveniently comprises a master protocol and a plurality of nested protocols as described above, wherein each of the respective nested protocols comprises stimulation data representing (coding for) sets of stimulation parameters, each set comprising at least one modulation parameter and at least one spatial parameter.

To ensure a desired sleep stimulation therapy, each of the respective nested protocols is associated with a brain state or a local brain state wherein the stimulation data of the each nested protocol are adapted for stimulating a user's brain at the associated brain state or local brain state.

The nested protocols advantageously differ from each other, preferably the sets of stimulation parameters of the nested protocols differ from each other.

The nested protocols preferably comprise at least one nested protocol associated with a pre-sleep brain state or local brain state, at least one nested protocol associated with a slow wave sleep brain state and/or at least one nested protocol associated with a rapid eye movement (REM)sleep brain state.

The nested protocols may for example comprises two or more nested protocol associated to a pre sleep brain state, wherein one of the nested protocol associated to the pre sleep brain state, is associated to a pre sleep brain state of one activity level and wherein another one of the nested protocol associated to the pre sleep brain state, is associated to a pre sleep brain state of another activity level. Thus may in particular be desired where the nested protocols ate nested static protocols.

Where the nested protocol associated with a pre-sleep brain state is a nested dynamic protocol, a single nested dynamic protocol associated with the pre sleep brain state may be sufficient.

In the same way the nested protocols may comprises two or more nested static protocol associated to respective slow wave sleep brain states of different activity level and/or two or more nested static protocol associated to respective REM sleep brain states of different activity level

In an embodiment, the nested protocols may comprises one nested dynamic protocol associated to the slow wave sleep brain state and/or one nested dynamic protocol associated to the REM sleep brain state.

The computer system is advantageously, based on data of the master protocol, configured for activating one or more of the physiological sensors at selected points of time during a sleep stimulation session and determine a brain state or a local brain state based on the physiological parameters determined by the activated physiological sensor(s), e.g. as described above e.g. with a selected frequency of from 1-10 Hz.

The master protocol advantageously comprises data for selecting and activating a nested protocol associated to the determined brain state or local brain state and/or wherein the master protocol comprises data for deselecting and deactivating an active nested protocol not-associated to the determined brain state or local brain state.

Where the stimulation protocol comprises two or more nested static protocols associated to a mutual brain state or local brain state, each of the two or more nested protocols associated to a mutual brain state or mutual local brain state advantageously comprises a treatment attribute representing the intended treatment purpose, such as to prolong the duration of a REM sleep brain state, to calm down during a REM sleep brain state, to modify a slow wave sleep brain state of a relatively high activity to a slow wave sleep brain state of a lower activity etc. The master protocol may comprise data for selecting the nested protocols based on both the real time determined brain state/local brain state and the stimulation attribute.

For ensuring a desired positioning of the headwear on a user's head, the headwear advantageously comprises one or more markings, which is/are adapted to be positioned at a selected location of the user. In an embodiment, the headwear comprises a right side and a left side and a marking for a user to locate the right side of the headwear in contact with the right side of the user's scalp and to locate the left side of the headwear in contact with the left side of the user's scalp. The marking, may e.g. be located between the right side and the left side of the headwear and at a location adapted to be positioned above a user's nasal bridge.

In an embodiment, the headwear is adapted to be positioned on a user's head using a camera and/or augmented reality technology combined with a computer element of the computer system trained via machine learning or artificial intelligence.

In an embodiment, the headwear comprises a head band comprising at least four coils located in a line, such as a line of coils located with their center located a position adapted to be in contact with a user's head at locations according the International 10–10 EEG positioning system, preferably comprising locations in proximity to the dorsolateral prefrontal cortex such as F7, F3, F4, F8, locations in proximity to the medial temporal lobe such as P5, T3, T4, P6 and/or locations in proximity to the posterior parietal cortex such as CP1, P3, P4, CP2.

In an embodiment, the headwear comprises a headband comprising one or more EEG sensors located at position(s) adapted to be in contact with a user's head at locations according to the International 10–10 EEG positioning system preferably comprising locations in proximity to the dorsolateral prefrontal cortex such as F7, F3, F4, F8, locations in proximity to the medial temporal lobe such as P5, T3, T4, P6 and/or locations in proximity to the posterior parietal cortex such as CP1, P3, P4, CP2.

Advantageously, the step of determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, comprises determining if the modulation parameter of the set of stimulation parameters is or is not correlated to affect brain waves of the user.

The brain state and related biometric profiles for each user changes moment by moment. The computer system tries to classify past and current brain states and predict future brain states by modelling these dynamic changes. By determining if the modulation parameters of the set stimulation parameters is or is not correlated with the changing brain state of the user in

the closed loop brain stimulation process, the stimulation may be optimized in real time.

In an embodiment, determining if the modulation parameters of the stimulation protocol correlates with changes in brain waves of the user comprises obtaining at least a portion of an EEG of the user, preferably comprising obtaining EEG data using one or more EEG sensors, wherein the EEG sensor optionally is the primary physiological sensor.

In an embodiment, the stimulation system is configured for adjusting the stimulation protocol if it is determined that the modulation parameter of the set of stimulation parameters is not correlated to affect the brain waves of the user.

It has been found that the brain stimulating system of the invention is very suitable for personalized brain-stimulation.

In personalized brain-stimulation, the treatment is tailored to the individual user based on their specific symptoms, medical history, and neurophysiological profile. This approach takes into account individual differences in brain structure and function, as well as the underlying causes of neurological or psychiatric disorders, in order to maximize the therapeutic benefits of brain stimulation while minimizing side effects and optimizing the user's quality of life.

Frequency-tuning for working memory enhancement

One example where personalized brain stimulation has been investigated is in the application of working memory, where research has found that changes in EEG peak frequency are associated with working memory performance.

A peak frequency refers to the frequency of the brain waves that are most prominent in a given EEG recording. The peak frequency can vary depending on the state of the brain, such as during a cognitive task, and is often used as a measure of cortical excitability and cognitive processing.

Research has shown that tasks that require working memory, such as remembering and manipulating information are associated with changes in different peak frequencies. Usually, a change in the theta (4-8Hz) and alpha (8-12Hz) frequency bands has been associated with better working memory performance. There are intra- and inter-individual differences in peak frequencies and by frequency tuning the stimulation protocol to the individual peak frequencies more effective treatments can be delivered.

With current technologies on the market, that don't enable concurrent monitoring and stimulation, stimulation is often tuned offline, meaning before or after the stimulation session, either during a resting-state or task-positive EEG task. Thanks to the present invention, this problem has now been overcome. This invention enables the stimulation to be tuned during the stimulation session and adapted to the changing peak frequencies across tasks.

It has been found that the brain stimulation system of this invention is very suitable for Neurofeedback training, e.g. for use in meditation, executive functioning, concentration, and calming exercises.

Neurofeedback training is a type of brain training that involves measuring and analyzing brain activity for example using EEG and providing feedback to the user, usually in the form of visual or auditory cues to help them learn to self-regulate their brain activity. The goal of EEG neurofeedback training is to improve brain function and alleviate symptoms associated with various neurological and psychiatric disorders, including ADHD, anxiety, depression, and migraines.

Over time, through repeated neurofeedback sessions, the user learns to self-regulate their brain activity, which can lead to improvements in their cognitive and emotional functioning, as well as reductions in symptoms associated with their condition.

This invention allows for augmentation and further improvement of neurofeedback training, by assisting the user in regulating brain activity by applying stimulation to areas of the brain at specific frequencies related to the activity the user is trying to regulate.

An example is neurofeedback training for meditation, where several frequency bands of EEG are of interest. The specific bands that are targeted may vary depending on the specific goals and type of meditation, but some mutually targeted bands include

- alpha band (8-12Hz), which is associated with a relaxed and calm state of mind, where increasing alpha power may be beneficial for enhancing meditation practices.
- theta band (4-8Hz), which is associated with a state of deep relaxation, where increasing theta power may help individuals achieve deeper levels of meditation.

- beta band (12-30Hz), which is associated with a more active state of mind and may interfere with meditation, therefor reducing beta power may be beneficial for enhancing meditation.
- gamma band (30-50Hz), which is associated with high levels of focus and attention and may be targeted in neurofeedback training to enhance concentration during meditation.

In one embodiment, the brain-stimulation system is set up to monitor frequencies of interest to neurofeedback training and stimulate areas of the brain with specific frequencies to enhance the effects of neurofeedback training.

The invention also comprises a headwear for transcranial magnetic stimulation (TMS) of the brain.

The headwear comprises a head facing surface configured for being in contact with a user's head and defining a treatment scene, the headwear comprises

- a plurality of conductor coils, wherein the conductor coils are located at selected locations, wherein each of the coils are orientated to generate a magnetic field at the treatment scene adapted for inducing an electric field at the cortex of a user,
- a power arrangement for supplying current to the respective plurality of coils,
- a computer in the form of a controller, and
- a sensor system comprising at least one primary physiological sensor adapted for detecting a physiological parameter in response to a brain stimulation,

wherein the controller configured for

i. receiving stimulation data representing a set of stimulation parameters of a stimulation protocol, wherein the set of stimulation parameters comprises at least one modulation parameter and at least one spatial parameter,
ii. converting the received stimulation data to a set of current parameters according to a converting protocol and
iii. controlling the power arrangement, comprising supplying current to one or more of the conductor coils according to the set of current parameters for inducing the brain stimulation according to the stimulation protocol,

iv. detecting the physiological parameter using the physiological primary sensor, and
v. determining if the detected physiological parameter is indicative of a response to the induced brain stimulation,

and if not,

vi. adjusting the converting protocol, and
vii. optionally repeating the steps i-vi.

The determination if the detected physiological parameter is indicative of a response to the induced brain stimulation, thereby comprises determine if the induced brain stimulation is out of compliance (no indication of a response to the induced brain stimulation) with at least one stimulation parameter of the stimulation protocol.

The headwear may advantageously be as described above and as illustrated in the examples and figures below.

BRIEF DESCRIPTIONS OF EMBODIMENTS AND EXAMPLES

In the following, the invention will be further illustrated by the description of a number of illustrative and non-limiting embodiments and examples of the present invention, with reference to the appended drawings and examples given below.

The figures are schematic and are not drawn to scale and may be simplified for clarity. Throughout, the same reference numerals are used for identical or corresponding parts.

Figure 1 is a schematic illustration of an embodiment of a brain stimulating system in use.

Figure 2 is a schematic illustration of a computer system of an embodiment of a brain stimulation system of the invention.

Figure 3 is an illustration of the International 10-10 EEG positioning system.

Figure 4a is a side view of an embodiment of a headwear of the invention on a users head.

Figure 4b is a side view of an embodiment of another headwear of the invention on a users head.

Figures 5a-5f are illustrations of examples of conductor coils of embodiments of brain stimulation systems of the invention.

Figure 6 illustrates conductor coils located within cooperation distance.

Figure 7 illustrates a portion of a Stimulation Protocol suitable for use in the stimulation system of the invention.

Figure 8a is a side view of an embodiment of a headwear of the invention on a users head.

Figure 8b is a schematic top view of the headwear of figure 8a.

Figure 9 is a schematic illustration of a closed loop brain stimulation.

Figure 10 is a schematic illustration of an example of an adaptive stimulation.

Figure 11 is a schematic illustration of an example of concurrent stimulation and sensing.

Figure 12 is a schematic illustration of an example of Neuromodulation-aided Neurofeedback.

Figure 13a illustrates an example of sleep stages and cycles across a sleep session.

Figure 13b is a schematic illustration of illustrates of the sleep cycles of figure 13a

Figure 14a schematically illustrates a master protocol of a stimulation protocol suitable for performing a sleep therapy session using a stimulation system of an embodiment of the invention.
Figure 14b schematically illustrates a nested dynamic protocol of a stimulation protocol suitable for performing a sleep therapy session using a stimulation system of an embodiment of the invention.

Figure 14c schematically illustrates a nested static protocol of a stimulation protocol suitable for performing a sleep therapy session using a stimulation system of an embodiment of the invention.

The brain stimulating shown in figure 1 comprises a headwear 1 system in use.

Shows a brain stimulation system comprising a headwear 1 in the form of a headband and a computer system comprising a smartphone 3.

In this embodiment, the headwear 1 is in the form of a headband designed to surround the head 2 of a user, such that a portion of the headwear 1 is in contact with the user's forehead 1a. The computer system comprises the smartphone 3 and a not shown controller located in the headwear. The not shown controller and the smartphone 3, are adapted for wireless communication as indicated by reference 4 in the figure. Wireless communication may be provided as described above e.g. by using Bluetooth or Wifi

In a variation, the smartphone is omitted and the entire computer system is integrated in the headwear 1. In another variation the computes system comprises a PC or other portable or non-portable elements comprising a processor, e.g. as described above.

The computer system in figure 2 is schematically illustrated to have three computer blocks a controller block 11, a stimulating block 12 and a sensor block 13.

The controller block 11 is advantageously integrated into the headwear 1. In an embodiment, the stimulating block 12 and/or the sensor block 13 or parts thereof are also integrated into the headwear 1: In a variation the stimulating block 12 and/or the sensor block 13 or parts thereof are external computer elements that are not integrated in the headwear, but are or are adapted to be in data communication with the controller block 11 as illustrated with the dotted lines L. The communication between the computer blocks or may be by wire or wireless as described above.

The controller block 11 comprises a processor system 11a e.g. comprises one or more microprocessors; a memory system 11b, e.g. integrated with the processor system 11a: a communication system 11c and a power system 11d.

The power system 11d may comprise a power receiver and a power converter for converting the power to a desired voltage. This is often desired if the power is fully or partly supplied from an external power source, such as an external power source to correctly power the electronics circuits and components of the system. In a preferred embodiment the power system 11

the power system 11 comprises a power source. The power source may advantageously comprise a lithium-ion battery.

The communication system 11c may comprise wired connections between internal components, e.g. using protocols such as I2C and SPI. In an embodiment, the communication system 11c is configured for wireless communication to and from external systems e.g. using Bluetooth and wifi. This allows the internal components of the communication system 11c to communicate effectively and the controller block 11 to communicate with external devices, e.g. the stimulating block 12 and/or the sensor block 13 or parts thereof, such as a smartphone or remote server.

The memory system 11b, may for example comprise fast and temporary memory units such as RAM for onboard processing, and stable storage, e.g. such as an SSD to store recordings and results locally on the device.

The stimulating block 12 may comprise a pulse generator 12a to generate and shape the current pulses delivered to the magnetic conductor coils and optionally a voltage booster to change the amplitude of the pulses. The stimulating block 12 may further comprise a coil selector 12b with a set of multiplexers to select one or more conductor coils 12c to deliver currents to the respective coils. The coil selector and conductor coils are wired as indicated by the dotted lines L to the conductor coils 12c of the headwear in a way such that the coil selector has control of individually supplying current to the selected conductor coil(s). Optionally the stimulation system contains an LED to indicate the state of stimulation.

The sensor block 13 comprises a processor 13a that conveniently may comprise an analog-to-digital converter, signal amplifiers, analog and digital filters, and a multiprocessing unit to control the sensing processes of the one or more sensors 13b.

The conductor coil 12c and the sensors 13b are not forming part of the computer system, but the computer system is controlling the activity of the conductor coils 12b and preferably the activity of one or more of the sensors 13, preferably comprising the at least one primary physiological sensor.

The International 10-10 EEG positioning system shown in figure 3 is a standardized system and method for placing electrodes on the scalp to obtain electroencephalography (EEG) recordings. It provides a standardized system and method for recording EEG signals that are widely used in both clinical and research settings. It allows for accurate and consistent electrode placement across different users and across different studies.

In figure 4a, the headwear 21a is in the form of a headband, which is shown when applied to surround a user's head 22a. A number of modules 23a comprising one or more not shown coils and/or one or more not shown sensors are strategically located in proximity to the treatment scenes of interest. In some embodiments, the modul(es) 23a are located in areas of the forehead in order to measure and stimulate areas of the DLPFC, on the side, above the ear to engage with areas of the temporal lobe and at the top back of the head to engage with areas of the parietal cortex.

In figure 4b the headwear 21b is in the form of a headband which is shown when applied to surround a user's head 22b and with a cross band 21b'. A number of modules 23b comprising one or more not shown coils and/or one or more not shown sensors are strategically located in proximity to the treatment scenes of interest. In some embodiments, the modul(es) 23b are located at the cross band 21b'.

Figures 5a-5f show various examples of coils with different geometries, and shapes, layers, dimensions, windings, and properties, such as conductivity and inductance. The different coil designs along with stimulation parameters produce differential effects on the treatment scene.

Figure 5a show an example of an angular conductor coil wit 4 edges. In an example, the conductor coil is substantially square. Figure 5b is a perspective view of a conductor coil where an edge portion of the coil is cut away. The conductor coil is angular and comprises two layers. In figure 5c is illustrated a conductor coil similar to the conductor coil shown in figure 5 b, but here with a single layer. Figure 5b is a perspective view of a conductor coil where an edge portion of the coil is cut away. Figure 5d is a perspective view of a conductor coil where a portion of the coil is cut away. The conductor coil is round, has a rounded cross sectional shape and comprises a single layer. The conductor coil shown in figure 5e is similar to the conductor coil of figure 5b, but here with 3 layers and with a square cross sectional shape. The conductor coil shown in figure 5f is similar to the conductor coil of figure 5e, but here with a single layer and a larger diameter.

The two conductor coils 31 shown in figure 6 are located within cooperation distance. When current at supplied in opposite directions through the coils as illustrated with the arrows 32 the coils 32 are producing a magnetic field with associated magnetic field vectors 34 and magnetic field lines 35, inducing eddy currents 33 at the treatment scene 37 through the surface of the scalp 36 of a user.

Figure 7 shows various examples of stimulation sequences that may be included in a stimulation protocol including iTBS and cTBS stimulation sequences, that vary the number of pulses, bursts, and pulse trains in a given session to produce either inhibitory or excitatory effects, respectively.

The atomic unit of a stimulation protocol is a pulse, with a given frequency and intensity, determined by the current running through the coil. Pulses can be grouped into bursts of pulses, optionally with a pause between bursts, together defining a train of bursts. The trains of bursts can furthermore be combined into cycles, with optional pauses between trains. A session consists of cycles of stimulation that are either predetermined, meaning based on a static protocol, or adaptive, meaning adapted over time, according to some parameter.

The headwear 44 shown in figure 8a and 48b comprises system modules at frontal and parietal regions. The modules include conductor coils 41, EEG sensors 42, and fNIRS sensors 43 embedded in the headwear 44

Figure 9 illustrates a closed-loop brain stimulation system that takes feedback 51 via the sensor system, e.g. in the form of biometric sensors, processes the data, e.g. via digital signal processing and machine learning algorithms in the computer system 53, in order to determine a set of parameters for the stimulation protocol, that are then fed to the stimulation system 53 all embedded in the headwear 54.

Figure 10 shows an example of a decision-making process (flow chart) for adapting the stimulation parameters based on a given feedback.

The system starts by initializing and doing a baseline recording in order to determine the user's initial brain state prior to stimulation, which is used for the selection of stimulation protocol.

The parameters of the stimulation protocol are then selected, e.g. based on “standard” stimulation protocols known in the art, based on previous protocols used by the user or other users conditioned on the baseline recording of the user. The stimulation cycle is then activated with the selected stimulation parameters.

While the stimulation is running, the system retrieves data from the sensor system comprising at least one primary physiological sensor and optionally other sources relevant to optimizing the next stimulation cycle. This could be live data from sensors, sensor data from previous sessions, and auxiliary data, e.g. from MADRS symptom scores. The data is processed by algorithms running on the computer systems optionally comprising remote

computer unit(s) in order to classify the user's current brain state and select the stimulation parameters that will move the user closer to the desired brain state. If the current stimulation parameters are predicted to induce the desired brain state, the system continues, otherwise, a different set of parameters is selected that increases the likelihood of guiding the user's brain to the desired state. If the session is complete, the system stops stimulation and optionally sensing.

The system may repeat the steps i-vi in a plurality of loops

i. receiving stimulation data representing a set of stimulation parameters of a stimulation protocol, wherein the set of stimulation parameters comprises at least one modulation parameter and at least one spatial parameter,
ii. converting the received stimulation data to a set of current parameters according to a converting protocol and
iii. controlling the power arrangement, comprising supplying current to one or more of the conductor coils according to the set of current parameters for inducing the brain stimulation according to the stimulation protocol,

wherein the computer system further is configured for

iv. detecting the physiological parameter using the primary physiological sensor, and
v. determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, and thereby determine if the induced brain stimulation is out of compliance with at least one stimulation parameter of the stimulation protocol,

and if not,

vi. adjusting the converting protocol, and

Figure 11 is a schematic illustration of an example of concurrent stimulation and sensing.

An illustration of a session running concurrent physiological measurements stimulation during consecutive blocks of stimulation parameters. Being able to measure brain state while stimulating in parallel creates a tight feedback loop, that enables effective treatment-response detection, safety monitoring, and response prediction, which allows the system to adjust stimulation parameters live during the session. The stimulation parameters in each block are adapted

based on physiological measurements from the previous blocks, which are processed and used to select the optimal stimulation parameters.

Figure 12 shows an example of Neuromodulation-aided Neurofeedback process. The Neuromodulation-aided Neurofeedback process is similar to the process illustrated in figure 10, but with an additional reward/penalty feedback, which may advantageously be applied in Neurofeedback training e.g. as described above.

The system starts by initializing and doing a baseline recording in order to determine the user's initial brain state prior to stimulation, which is used for the selection of stimulation protocol as in the system of figure 10. The analysis in the Brain State Classifier may involve identifying specific patterns of brainwave activity that are associated with desired or undesired brain states or behaviors. For instance, certain patterns might be linked to calm and focused attention, while others might be linked to distractibility or anxiety. Once the desired and undesired brain states have been identified, the system may provide feedback to the user based on their current brain state. If their brain state is in the desired range, they may receive rewarding feedback, e.g. in the form of an auditory signal, in order to enforce that activity. If the brain state is in an undesired range, the user may receive a penalty feedback, to guide the user towards the desired brain state. Over time, the user learns to associate the reward feedback with the desired brain state and the penalty feedback with the undesired brain state. The goal is for them to learn how to consciously and unconsciously steer their brain state towards the desired state and away from the undesired state. The neurofeedback training typically involves multiple sessions over a period of weeks or months, with the user's progress being monitored and the feedback parameters being adjusted as necessary. With neuromodulation-aided neurofeedback training, the training period can be reduced significantly and the process optimized for better results.

As described above the brain stimulation system may in an embodiment be adapted for performing augmented sleeptherapy, comprising performing brain stimulation on a user's brain while the user is sleeping. The stimulation session may advantageously cover the entire sleep period, e.g. a full night's sleep comprising several sleep cycles, such as 4-6 sleep cycles or the treatment session may be performed during a portion of the entire sleep period of the user.

Figure 13a shows a hypnogram of a stereotypical night's sleep, representing the sleep macro-architecture. Throughout the night, the user transitions through different cycles with varying stages of sleep.

As seen in figure 13a, a full night of sleep consists of multiple cycles, where the brain transitions through different stages of sleep. The distribution and time spent in each stage changes throughout each cycle, representing the changing brain processes that occur throughout the night. As illustrated in the figure, the first 2 cycles are dominated by deep sleep (N3), with little REM sleep, whereas after the third cycle this distribution shifts, REM periods lengthen while the deep sleep periods shorten as the night progresses.

Advantageously the stimulation protocol of the brain stimulation system adapted for performing brain therapy also comprises nested protocols for performing stimulation during one or both of the pre sleep stage and the post sleep stage.

Figure 14a schematically illustrates a master protocol of a stimulation protocol suitable for performing a sleep therapy session using a stimulation system of an embodiment of the invention.
The master protocol may advantageously be configured to perform a continuous routine, for example in that the master protocol comprises data for instructing the computer system to perform the continuous routine.

As illustrated in figure 14a the routine of the master protocol comprises in step 51 performing a brain monitoring. The brain monitoring may advantageously be a real time monitoring of key physiological signals, as described above. In step 52, the master protocol determines the brain state or local brain state based on data from the brain monitoring and optionally other data, such as data representing gender, age, and optionally data representing a disease or potential disease if the user has not been fully diagnosed. The disease may for example be Alzheimer. In addition, the master protocol classifies the determined brain state or local brain state according to a classification system related to the nested protocols, preferably such that the classification comprises at least classes associated to the respective nested protocols and at least one class associated to "no simulation" also referred to as "pause/stop" or "stimulation pause or stop".

In step 53, the master protocol determines if the detected brain state or local brain state do comprise an indication of a target event for stimulation the brain,

If no, the master protocol in step 54 continues an ongoing pause or stop the operation of any active nested protocol to ensure that the brain stimulating system is at least temporarily stopped.

If yes, the master protocol, in step 55, selects a nested protocol in dependence of the classification of the brain state or local brain state and start/activate the selected nested protocol or continue the selected nested protocol if already in activation.

The master protocol may stop the operation of a nested protocol at any time, when the real time determined brain state or local brain state reveal that the operating nested protocol is no longer in association to the real time determined brain state.

Figure 14b schematically illustrates a nested dynamic protocol of a stimulation protocol suitable for performing a sleep therapy session using a stimulation system of an embodiment of the invention.

The nested dynamic protocol may advantageously be configured for performing a stimulation routine, such as a continuous repeated stimulation routine, such as the routine illustrated in figure 7, for example in that the nested dynamic protocol comprises data for instructing the computer system to perform the stimulation routine.

As illustrated in figure 14b the stimulation routine starts in step 56, where the nested dynamic protocol measures the brain state or local brain state or receives data representing the real time brain state or real time local brain state. Preferably, the nested dynamic protocol receives the measurement of the brain state as determined directly from the master protocol.

In step 57, the nested dynamic protocol generates, modifies or confirms at least one stimulation sequence of the nested stimulation protocol.

The nested dynamic protocol may advantageously comprise at least one start stimulation sequence as the initial operative stimulation sequence(s) of the nested dynamic protocol. Advantageously, the nested dynamic protocol comprises or is configured for receive an initial converting protocol. The computer system may advantageously store one of more initial converting protocols, which may be acquired by the nested dynamic protocol. The initial converting protocol is deemed to be the operative converting protocol.

In the first run, the nested dynamic protocol may maintain the operative stimulation sequence(s) or modify the operative stimulation sequence(s) and

deem the modified operative stimulation sequence(s) to be the operative stimulation sequence(s).

In step 58, the nested dynamic protocol converts the stimulation parameters of the stimulation sequence preferably according to the operative converting protocol.

In step 59, the nested dynamic protocol runs the at least one stimulation sequence. In step 60 the nested dynamic protocol measure the at least one physiological parameter or receives real time data representing the least one physiological parameter from the computer system and/or the master protocol and in step 61, the nested dynamic protocol determines if the detected physiological parameter is indicative of a response to the induced brain stimulation and thereby in compliance with at least one set of stimulation parameters of the stimulation sequence.

If yes, the nested dynamic protocol continues to step 56 for a next circle of the routine.

If no, the nested dynamic protocol may adjust the converting protocol, and deem the adjusted converting protocol to be the operative converting protocol and return to step 58 for converting the stimulation parameters of the stimulation sequence in accordance with the operative converting protocol and so on.

Alternatively, if no, the nested dynamic protocol may optionally adjust the converting protocol, and deem the adjusted converting protocol to be the operative converting protocol and return to step 57. Wherein in step 57 the nested dynamic protocol may modify the operative stimulation sequence(s) and deem the modified operative stimulation sequence(s) to be the operative stimulation sequence(s). From there the nested dynamic protocol may continue to step 58.

In that way the nested dynamic protocol may dynamically be adjusted, co continuously ensure a desired stimulation in a very flexible way.

Figure 14c schematically illustrates a nested static protocol of a stimulation protocol suitable for performing a sleep therapy session using a stimulation system of an embodiment of the invention.

The nested static protocol may advantageously be configured for performing at least one static stimulation sequence, which may be repeated as long as the nested static protocol is active. The nested static protocol illustrated in figure 14c may be configured for continuously repeat a stimulation routine,

for example in that the nested static protocol comprises data for instructing the computer system to perform the stimulation routine.

As illustrated in figure 14c the stimulation routine starts in step 57.

The nested static protocol may advantageously comprise the at least one static stimulation sequence the nested dynamic protocol comprises or the at least one static stimulation sequence may be acquired e.g. from a database e.g. as described above. The nested static protocol differs from the nested dynamic protocol in that the nested static protocol maintain the at least one static stimulation sequence until the nested static protocol is terminated by the master protocol and/or optionally the master protocol selects and activates another nested protocol

In step 58, the nested static protocol converts the stimulation parameters of the stimulation sequence preferably according to the operative converting protocol.

In step 59, the nested static protocol runs the at least one stimulation sequence. In step 60 the nested static protocol measure the at least one physiological parameter or receives real time data representing the least one physiological parameter from the computer system and/or the master protocol and in step 61. The nested static protocol determines if the detected physiological parameter is indicative of a response to the induced brain stimulation and thereby in compliance with at least the spatial parameter of at least one set of stimulation parameters of the stimulation sequence.

If yes, the nested dynamic protocol continues to step 56 for a next circle of the routine.

If no, the nested dynamic protocol may adjust the converting protocol, and deem the adjusted converting protocol to be the operative converting protocol and return to step 58 for converting the stimulation parameters of the stimulation sequence in accordance with the operative converting protocol and so on.

The master protocol cooperating with one or more nested static protocols may advantageously be configured to classify data of the brain monitoring in a higher number of classes of brain states or local brain states than where the nested protocols are dynamic protocols, such that the master protocol so that the master protocol may very fast, such as in real time determine if the at least one static stimulation sequence of a nested static protocol is no longer suitable for treatment and thereby the master protocol may stop the

operating nested static protocol and activate a new nested protocole or pause the stimulation

In that way the nested static protocol may together with the master protoco continuously ensure a desired location of stimulation in a very flexible way.

Example 1:

Sleep of a user with Alzheimer's

In this example, the brain stimulating system is arranged for monitoring the user for the entire night, continuously analyzing sleep macro and microstructure. The stimulation protocol may advantageously comprise a master protocol and a plurality of different nested protocols designed to improve various aspects of one or more sleep stages related to a, such as a specific user. In this example, the master is configured for monitoring the brain and classify the sleep according to the brain state or local brain state determined by the monitoring.

In this example the stimulation protocol comprises a master protocol and three nested dynamic protocols, comprising a protocol to assist in falling asleep (pre-sleep nested protocol) protocols for inducing slow-wave sleep (slow wave (SWS) nested protocol), and protocols to modulate REM sleep (REM sleep nested protocol).

Pre-Sleep nested Protocol

The user puts on the headband before sleeping, initiating the pre-sleep stimulation protocol. The headband performs a baseline recording of the user's brain data to determine the peak frequencies for theta and alpha waves. Afterward, the headband stimulates the user's brain with these determined peak frequencies to assist the user in falling asleep. This pre-sleep protocol may automatically stop once the user falls asleep or it may be manually stopped.

SWS nested Protocol

The device continuously monitors the user's brain activity and sleep patterns throughout the night. As the user transitions into deep sleep during the first sleep cycle, slow-wave sleep (SWS) patterns increase. When the system detects specific signatures as target event indicative of SWS, the SWS stimulation protocol is activated to enhance memory consolidation. This protocol targets the prefrontal cortex (Fz) and medial temporal lobe (T7) with

frequency-coupled delta waves (1-4 Hz), which are tuned to optimize SWS and promote restorative sleep.

REM nested Protocol

Later in the night, as the user enters REM sleep, the system detects REM sleep signatures as target event and activates the REM stimulation protocol. This protocol targets frontal brain areas, such as Fp1 and Fp2, with theta, beta, or gamma frequencies to optimize the timing and distribution of REM sleep, which is crucial for emotional processing. The stimulation is precisely timed to align with REM sleep phases, ensuring maximum therapeutic benefit.

Throughout the night, the system continuously analyzes the user's brain activity and adjusts the stimulation parameters in real time. This dynamic adjustment ensures that the stimulation protocols are personalized and effective, catering to the specific sleep needs of the user. If the system detects the end of a slow-wave or REM cycle, it pauses the stimulation and prepares for the next relevant sleep phase.

By leveraging continuous brain monitoring and adaptive neuromodulation, this system aims to enhance sleep quality and support brain health for example in users with Alzheimer's disease. Integrating various nested protocols within the master protocol ensures a comprehensive approach to sleep therapy, addressing different aspects of sleep and optimizing therapeutic outcomes.

Example 2:

Master and Nested Stimulation Protocols

Master protocol (or stimulation program)

A master protocol governs the overall sleep session, encompassing a set of nested stimulation protocols with varying parameters tailored to different stages and cycles of sleep. These parameters can be predefined or dynamically set by the system using real-time data and advanced algorithms. The master protocol ensures a comprehensive and adaptive approach to neuromodulation throughout the entire sleep period.

Key Elements of the Master Protocol:

In this example, the following are key elements of the master protocol

- **Overall Governance:** The master protocol oversees the entire sleep session, integrating various nested protocols.

- **Dynamic Adjustment:** Parameters can be adjusted in real time based on physiological data.
- **Sleep Cycle Integration:** Protocols are spread out and synchronized with different sleep cycles (e.g., NREM, REM).

Nested Protocol

The nested stimulation protocol may comprise a set of neuromodulation instructions designed to target specific brain areas during specific sleep stages.

Each nested protocol may comprise one or more stimulation sequences forming at least a part of a stimulation protocol, where the parameters may be preselected or dynamically tuned to the underlying sleep process to optimize therapeutic outcomes.

Target & Coil selection

The target brain area or network where the protocol aims to modulate.

Target locations may be preselected, selected based on previous treatment-response maps for that user, or dynamically selected during runtime using target engagement and source localization methods e.g. as explained above.

In the case of dynamic target selection based on treatment-response methods, a set of primary sensors may be selected to measure treatment-response monitoring, to select conductor coils that best target the brain area, based on target-engagement measures.

Waveform

The shape and frequency of the stimulation signal may conveniently be applied to the target brain area.

Stimulation waveforms can be preselected, selected based on previous treatment-response maps for that user, or dynamically selected during runtime using frequency-tuning methods.

In the case of dynamic selection of waveform based on frequency-tuning, endogenous brain activity characteristics, such as slow-wave sleep (SWS) coupling, may be analyzed to derive the waveform characteristics used in the stimulation protocol.

Stimulation Period

The duration and timing of the stimulation session.

The start and end time of the stimulation protocol may be preselected, selected based on previous treatment-response maps for that user, or dynamically selected during runtime using event-detection methods.

In the case of dynamic selection based on event detection, the stimulation may be started when detecting a sleep-related event (target event), such as the onset of slow-wave sleep (SWS), the stimulation runs until a predefined stop point or until a pause/stop event has been detected.

Example 3:

Pre-Sleep protocol

Objective: Assist in falling asleep

A desired stimulation e.g. forming part of a pre-sleep nested dynamic protocol may comprise one or more stimulation sequences that targets frontal areas (Fp1, Fp2) with brain stimulation at frequency-tuned theta (4-6Hz) and alpha (9-11Hz) frequencies to assist in falling asleep.

The peak frequencies may be recorded during the pre-sleep phase (live) or from past resting-state recordings from the user, in order to optimize the one or more stimulation sequences.

It has been found that the pre-sleep stimulation provided by embodiments of the invention may improve sleep quantity by 22 min, reduce sleep onset by 28%, and increase sleep duration by 33 min.

The pre-sleep stimulation may for example be performed according to the stimulation process shown in figure 10.

Example 4:

SWS Protocol

In this example, the stimulation protocol comprises a master protocol as illustrated in figure 14a and nested protocols as illustrated in figure 14b.

Brain Monitoring Triggering Nested Protocol

The master protocol monitors the user's brain from the sensors in the headband. These sensors provide real-time data that AI algorithms analyze to classify different sleep phases and cycles. When the sleep classifier detects that the user has entered a target sleep phase, such as slow-wave sleep (SWS), the system initializes the nested stimulation protocol.

Protocol Initialization

During initialization, the system performs a baseline recording using a select set of sensors, such as EEG-Fz, to measure SO spindle coupling and SWA signature characteristics. The system then runs a stimulation protocol by applying a preset protocol through a conversion process or conducting a dry run before determining the stimulation parameters.

Adjust Parameters

The system continuously adjusts the stimulation parameters during the stimulation session in real-time. This may comprise modifying the target brain areas and respective coils, adjusting the stimulation waveform, and the stimulation period based on ongoing analysis of SWS signatures and related sleep events.

Run Stimulation

Once the stimulation parameters are set and the stimulation period has been detected, the actual stimulation process begins. For example, during a slow wave sleep period, conductor coils are selected to target Fz, with frequency-coupled delta waves (1-4Hz). The purpose of the simulation is to increase measured NREM-SO spindle coupling and NREM-SWA activity in the prefrontal and temporal regions of the brain and improve overall N3 sleep cycles to regulate Tau and Beta-Amyloid (Aβ) accumulation.

Continuous Monitoring and Adjustment

Throughout the stimulation, the system continues to monitor the brain state and process data to ensure the effectiveness of the intervention. This includes measuring treatment-response biomarkers and detecting relevant brain events. If the system detects changes in the brain state that indicate a need for adjustment, it updates the stimulation parameters accordingly.

The system may be designed to pause or stop stimulation based on specific criteria. The stimulation is temporarily halted if the end of a slow-wave cycle is detected. The system may also pause stimulation if a predefined stop point is reached or if a significant change in the brain state is detected.

Treatment-Response Monitoring:

The system records detailed data on brain states and responses to stimulation protocols during the stimulation session. This treatment-response

monitoring, evaluates the effectiveness of the intervention during runtime and is used to optimize future protocols. By analyzing perturbation biomarkers, the system can provide therapeutic and diagnostic insights, ensuring that the treatment is effective and safe and can be used to early diagnostic and prognostic use cases.

Example 5:

REM Protocol

The REM protocol may similar to SWS protocol, but with different start stimulation sequences

Depending on the converting/closed-loop protocol configuration, the stimulation device may optimize the stimulation waveform, target, and period to improve the quantity and quality of REM signatures. For example, it may stimulate frontal areas (F3) with frequencies tuned to theta (4-8Hz), beta (16-32Hz), or gamma (>32Hz) while measuring treatment response and target engagement, using heart rate deceleration measures to determine the stimulation period.

In other words, the start and end time may be determined by detecting relevant target events. The waveform may be determined by peak-frequency estimation of X. The appropriate conductor coils may be selected based on target engagement with HR/HRV, as well as EEG signatures.

Desired sleep treatment for embodiments of the invention may comprise

- Emotional processing (REM)
- Avoid early awakenings (arousal)
- Treatment, adjunct treatment

The monitoring may advantageously comprise

EEG

Signatures for DLPFC

HR/HRV

Target Engagement

Arousal

PATENT CLAIMS

1. A brain stimulating system for transcranial magnetic stimulation (TMS), comprising a headwear,

wherein the headwear comprises a head facing surface configured for being in contact with a subject's head and defining a treatment scene, the headwear comprises

- a plurality of conductor coils, wherein the conductor coils are located at selected locations, wherein each of the conductor coils are orientated to generate a magnetic field at the treatment scene adapted for inducing an electric field at the cortex of a subject
- a power arrangement for supplying current to the respective plurality of conductor coils,

wherein the brain stimulating system comprises a sensor system comprising at least one primary physiological sensor adapted for detecting a physiological parameter in response to a brain stimulation,

wherein the brain stimulating system comprises a computer system comprising a controller configured for

i. receiving stimulation data representing a set of stimulation parameters of a stimulation protocol, wherein the set of stimulation parameters comprises at least one modulation parameter and at least one spatial parameter,
ii. converting the received stimulation data to a set of current parameters according to a converting protocol and
iii. controlling the power arrangement, comprising supplying current to one or more of said conductor coils according to the set of current parameters for inducing the brain stimulation according to the stimulation protocol,

wherein the computer system further is configured for

iv. detecting the physiological parameter using the primary physiological sensor, and
v. determining if the detected physiological parameter is indicative of a response to the induced brain stimulation,

and if not,

vi. adjusting the converting protocol, and
vii. optionally repeating the steps i-vi.

2. The brain stimulating system of claim 1, wherein the determining if the detected physiological parameter is indicative of a response to the induced brain stimulation comprises determine if the induced brain stimulation is in compliance with or out of compliance with at least one stimulation parameter of the stimulation protocol, wherein if the induced brain stimulation is out of compliance with the stimulation protocol, adjusting the converting protocol.

3 The brain stimulating system of claim 1 or claim 2, wherein the computer system is configured for adjusting the converting protocol without changing the stimulation protocol.

4. The brain stimulating system of any one of the preceding claims, wherein the computer system comprises a memory storing at least a portion of the stimulation protocol and/or is in data communication with an external memory storing a portion of or the entire stimulation protocol, wherein the at least one portion of the stimulation protocol stored on the computer system is stored as at least one processed stimulation protocol portion.

5. The brain stimulating system of any one of the preceding claims, wherein the computer system is configured for receiving input data comprising at least a portion of the stimulation protocol or data for generating and/or selecting the stimulation protocol and wherein the computer system is configured for processing the received data and storing the processed data as at least one processed stimulation protocol portion of the stimulation protocol.

6. The brain stimulating system of claim 5, wherein the computer system comprises a memory storing at least one stimulation protocol, wherein each stimulation protocol comprises the sets of stimulation parameters for a stimulation session.

7. The brain stimulating system of any one of claims 4-6, wherein the stimulation protocol and/or the at least one processed stimulation protocol portion of the stimulation protocol comprises a master protocol and one or more nested protocols, wherein the nested protocols are protocols associated to respective brain states and/or local brain states of a subject and comprises stimulation data to be activated in response to detection of said respective associated detected brain states and/or local brain states.

8. The brain stimulating system claim 7, wherein the master protocol comprises data for timely synchronizing the respective nested protocols operate according to the stimulation protocol and in dependence of detected brain states and/or local brain states.

9. The brain stimulating system of claim 7 or claim 8, wherein the stimulation protocol and/or the at least one processed stimulation protocol portion of the stimulation protocol comprises two or more nested protocols.

10. The brain stimulating system of any one of claims 7-9, wherein the master protocol is configured for monitoring the brain and determine a brain state or local brain state and classify the brain state or local brain state comprising that the master protocol comprises data for instructing the computer system for activating one or more of the physiological sensors and optionally additional sensors at selected points of time during a stimulation session and determine and classify the brain state or a local brain state based on at least the physiological parameters determined by said activated physiological sensor(s).

11. The brain stimulating system of claim 10, wherein the master protocol comprises data for instructing the computer system to determine if the detected brain state or local brain state comprises an indication of a target event for stimulation the brain.

12. The brain stimulating system of claim 11, wherein the master protocol is configured to instruct the computer system to continuing a pause or to stop any ongoing processing of a nested protocol if the computer determines that the detected brain state or local brain state does not comprise an indication of a target event for stimulation the brain.

13. The brain stimulating system of claim 11 or claim 12, wherein if the computer determines that the detected brain state or local brain state do comprise an indication of a target event for stimulation the brain, the master protocol is configured to instruct the computer system to select a nested protocol in dependence of the target event indicated and to instruct the computer system to start or to continue the selected nested protocol.

14. The brain stimulating system of any one of the preceding claims, wherein the one or more nested protocols comprises at least one nested static protocol, and/or at least one nested dynamic protocol, wherein the nested protocol is configured for stimulate at least one brain state and for targeting one or more brain locations, with one or more stimulation target.

15. The brain stimulating system of claim 14, wherein the at least one nested static protocol comprises at least one sequence of one or more sets of stimulation parameters comprising a modulation parameter and a spatial parameter, wherein the at least one sequence remains unchanged.

16. The brain stimulating system of claim 14 or claim 15, wherein the at least one nested dynamic protocol comprises at least one start sequence as

the operative sequence comprising one or more sets of stimulation parameters comprising a modulation parameter and a spatial parameter, wherein the nested protocol dynamic is configured for dynamically modifying the operative sequence in dependence of a real time determined brain state.

17. The brain stimulating system of any one of claims 7-9, wherein the master protocol comprises data for selecting and activating a nested protocol associated to said determined brain state or local brain state and/or wherein the master protocol comprises data for deselecting and deactivating an active nested protocol not-associated to said determined brain state or local brain state.

18. The brain stimulating system of any one of the preceding claims, wherein the step of determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, comprises determining if the induced brain stimulation is out of compliance with at least one spatial parameter of the stimulation protocol.

19. The brain stimulating system of any one of the preceding claims, wherein the spatial parameter of the set of stimulation parameters of the stimulation protocol is indicative of a target location of the cortex, preferably selected from the frontal, temporal, and parietal cortex, and wherein the step of determining if the detected physiological parameter is indicative of a response to the induced brain stimulation comprises determining if a location of the induced brain stimulation is in conformity with the spatial parameter of the set of stimulation parameters stimulation protocol.

20. The brain stimulating system of any one of the preceding claims, wherein the set of stimulation parameters of the stimulation protocol comprises one or more of a pulse, a burst, a pulse train, a combination and/or series of the before mentioned optionally forming one or more stimulation sequences, wherein the stimulation parameters preferably have selected frequencies and/or varying intensities, and wherein the stimulation parameters may be configured to induce inhibitory and/or excitatory stimulation and any combinations comprising one or more of these.

21. The brain stimulating system of any one of the preceding claims, wherein the computer system is configured for detecting the physiological parameter in real time relative to the inducement of the brain stimulation according to the stimulation protocol, preferably the computer is configured for monitoring the physiological parameter during the inducement of the brain stimulation and wherein the detection the physiological parameter comprises detection of potential changes of the physiological parameter.

22. The brain stimulating system of any one of the preceding claims, wherein the computer system is configured controlling the at least one primary physiological sensor, comprising activating and deactivating the primary physiological sensor and wherein the computer system is configured for simultaneously supplying current to one or more of said conductor coils and activating the primary physiological sensor or keeping the primary physiological sensor activated.

23. The brain stimulating system of any one of the preceding claims, wherein the headwear is adapted for being in contact with a subject's head, preferably comprising at least a portion of a subject's forehead, more preferably the headwear is selected from a headband, a helmet, a cap, a hat and/or a swim cap.

24. The brain stimulating system of any one of the preceding claims, wherein the headwear comprises a headband comprising an annular band adapted for encircling a head of a subject and having a width of from 1-6 cm, such as from 2-5 cm, preferably at least two, such as at least 4 of the plurality of coins are located at the annular band.

25. The brain stimulating system of claim 24, wherein the headband comprises at least one cross band extending from a first location of the annular band to a second location of the annular band, wherein the first location and the second location are located with a distance along the annular band of at least 5 cm, preferably the cross band is adapted for extending over and in contact with at least a portion of the top and/or the crown of the head of the subject, preferably one or more, such as at least two of the plurality of coins are located at the cross band.

26. The brain stimulating system of any one of the preceding claims, wherein the headwear comprises at least 2 conductor coils, such as from 3 to 12 conductor coils, such as from 4 to 8 conductor coils, wherein the conductor coils preferably is located at one or more portions of the headwear adapted to be in contact with the forehead of a subject in use.

27. The brain stimulating system of any one of the preceding claims, wherein the selected locations of the plurality of conductor coils comprises spatially distinct locations relative to the head facing surface.

28. The brain stimulating system of any one of the preceding claims, wherein the selected locations of the plurality of conductor coils comprises locations selected to generate two or more magnetic fields at the treatment scene.

29. The brain stimulating system of any one of the preceding claims, wherein the respective conductor coils have an inductance of at least 100 μH, such as 125-300 μH, such as from 150 to 200 μH and/or a resistance of from 0.1 to 50 Ω, such as less than 2 Ω.

30. The brain stimulating system of any one of the preceding claims, wherein the respective conductor coils have an outer surface defining an outer perimeter and wherein the conductor coils are located in a configuration comprising that at least two of the conductor coils are located within cooperation distance.

31. The brain stimulating system of claim 23, wherein at least two of the conductor coils are located within cooperation distance comprising that at least two conductor coils are located with a distance between a section of the outer surfaces of the respective conductor walls of the at least two conductor coils, which is up to a maximal cooperation distance and/or up to 3 cm, such as up to 2 cm.

32. The brain stimulating system of any one of the preceding claims, wherein the respective conductor coils have an outer surface defining an outer perimeter and wherein the conductor coils are located in a configuration comprising that at least two of the conductor coils are located with a distance larger than the cooperation distance.

33. The brain stimulating system of any one of the preceding claims, wherein the controller is configured to control the power arrangement to supply oppositely directed current through conductor coils within cooperation distance to adjust the depth and focality of the induced brain stimulation, wherein the oppositely directed current through conductor coils within cooperation distance preferably may be set to be equal or to differ from each other to direct the brain stimulation to a selected location of the cortex, preferably compliance with at least one stimulation parameter of the stimulation protocol.

34. The brain stimulating system of any one of the preceding claims, wherein the power arrangement comprises a wiring to each of the conductor coils for supplying current through the respective conductor coils to induce the brain stimulation, preferably the power arrangement comprises a wiring to each of the individual conductor coils for supplying the current through the respective conductor coils independently of each other, preferably in concordance with the set of current parameters.

35. The brain stimulating system of claim 34, wherein the wiring to each of the conductor coils for supplying current through the respective conductor coils comprises a wiring with respect to a power source, which enables

supplying current to one or more of the conductor coils in a first direction or in a second opposite direction in dependence of the set of current parameters.

36. The brain stimulating system of any one of the preceding claims, wherein the power arrangement comprises at least one pulse generator adapted for generating pulses of current in concordance with the set of current parameters of the protocol.

37. The brain stimulating system of any one of the preceding claims, wherein the power arrangement comprises a coil selector adapted for selecting one or more of the conductor coils to be activated and to activate said selected conductor coils in concordance with said set of current parameters by generating pulses of current and inducing a magnetic field in said selected conductor coils according to the stimulation protocol.

38. The brain stimulating system of claim 37, wherein the one or more nested protocols and/or the master protocol comprises data for instructing the computer system to operating said coil selector, wherein the data for operating the coil selector comprises spatial parameters of respective sets of stimulation parameters.

39. The brain stimulating system of any one of the preceding claims, wherein the controller is configured to synchronize the supply of current and pattern of current to respective conductor coils to provide a synchronized stimulation pattern in concordance with the stimulation protocol.

40. The brain stimulating system of claim 39, wherein the respective nested protocols comprises data for supplying current to respective of said conductor coils.

41. The brain stimulating system of any one of the preceding claims, wherein the stimulation protocol comprises one or more nested dynamic protocols and wherein the one or more nested dynamic protocols comprises instruction for the computer system for

i. detecting the physiological parameter using the primary physiological sensor, and
ii. determining if the detected physiological parameter is indicative of a response to the induced brain stimulation,

and if not,

iii. adjusting the converting protocol, and
iv. optionally repeating the steps i-vi.

42. The brain stimulating system of any one of the preceding claims, wherein the controller is configured for controlling the supply of current through the respective conductor coils independently according to the stimulation protocol and preferably the controller is configured for controlling the supply of current through the respective conductor coils to generate one or more stimulation sequences selected from a mono-phasic, a bi-phasic and a burst of pulses, a stimulus amplitude/intensity, a pulse frequency and number of pulses in a train, a burst frequency and a number of bursts in a train, a pulse frequency in a burst, a plurality of trains optionally comprising one or more inter-train interval(s).

43. The brain stimulating system of claim 42, wherein the respective nested protocols comprises data for instruction the computer system to supplying current to respective of said conductor coils independently.

44. The brain stimulating system of any one of the preceding claims, wherein the set of current supply parameters comprises at least one of

- at least one frequency of from 1 Hz to 1 kHz, preferably comprising frequencies sets below 250 Hz, such as below 100 Hz;
- at least one pulse having a pulse width of up to 100 ms, such as in increments of 10 µs (depending on the frequency),
- at least one pulse interval between single pulses or repetitive pulses of from 1 0s up to 30 minutes of a treatment session, and/or
- at least one current amplitude of at least 1 mA, such as at least 5 mA.

45. The brain stimulating system of any one of the preceding claims, wherein the controller is located on the headwear, optionally the power arrangement is adapted to include a battery, which may advantageously be located on the headwear.

46. The brain stimulating system of any one of the preceding claims, wherein the computer system comprises at least one portable computer unit, preferably configured for wireless communication, the computing unit advantageously comprises a smartphone, a PC, a tablet, or a wearable computer, such as a smartwatch, optionally the at least one portable computer unit is located on the headwear.

47. The brain stimulating system of any one of the preceding claims, wherein the at least one primary physiological sensor comprises at least one sensor selected from the group comprising an electroencephalogram (EEG) sensor, a functional ultrasound imaging (fUS) sensor, an electrooculography (EOG) sensor, an electromyography (EMG) sensor, a heart rate sensor (pulse oximetry sensor, PPG, ECG, etc.), a functional near-infrared

spectroscopy sensor (fNIRS) sensor, an electrodermal activity (EDA) sensor or a magnetoencephalogram (MEG) sensor.

48. The brain stimulating system of any one of the preceding claims, wherein the at least one primary physiological sensor comprises at least one of a heart rate sensor and a cerebral blood flow sensor, preferably the heart rate sensor and/or the cerebral blood flow sensor are located on the headwear.

49. The brain stimulating system of any one of the preceding claims, wherein the computer system is adapted for timely synchronizing the at least one primary physiological sensor with the inducement of the brain stimulation according to the set of stimulation parameters, preferably the brain stimulation and/or the stimulation protocol comprises a plurality of stimulation blocks, advantageously the computer system is adapted for timely synchronizing the at least one primary physiological sensor with one or more of the stimulation blocks.

50. The brain stimulating system of any one of the preceding claims wherein the stimulation protocol comprises a plurality of stimulation parameters organized in consecutive order and comprising the at least one set of stimulation parameters, wherein the plurality of stimulation parameters comprises one or more stimulation sequences selected from a mono-phasic, a bi-phasic and a burst of pulses, a stimulus amplitude/intensity, a pulse frequency and a number of pulses in a train, a burst frequency and a number of bursts in a train, a pulse frequency in a burst, a plurality of trains optionally comprising one or more inter-train interval(s).

51. The brain stimulating system of claim 50, wherein the plurality of stimulation parameters comprises a plurality of stimulation blocks, advantageously the computer system is adapted for timely synchronizing the at least one primary physiological sensor with one or more of the stimulation blocks.

52. The brain stimulating system of any one of the preceding claims wherein the brain stimulation system is adapted for treatment of a subject during sleep, wherein the stimulation protocol comprises a master protocol and a plurality of nested protocols, wherein each of the respective nested protocols comprises stimulation data representing (coding for) sets of stimulations parameters, each set comprising at least one modulation parameter and at least one spatial parameter.

53. The brain stimulating system of claim 52, wherein each of the respective nested protocols is associated to a brain state or a local brain state and wherein the stimulation data of said each nested protocol are data

adapted for stimulating a subjects brain at said associated brain state or local brain state.

54. The brain stimulating system of claim 52 or claim 53, wherein the nested protocols differs from each other, preferably the sets of stimulations parameters of the nested protocols differs from each other.

55. The brain stimulating system of any one of claims 52-54, wherein the nested protocols comprises at least one nested protocol associated to a pre sleep brain state or local brain stage, at least one nested protocol associated to a slow wave sleep brain state and/or at least one nested protocol associated to a rapid eye movement (REM) sleep brain state.

56. The brain stimulating system of any one of claims 52-55, wherein the master protocol comprises data for instructing the computer system for activating one or more of the physiological sensors at selected points of time during a sleep stimulation session and determine a brain state or a local brain state based on the physiological parameters determined by said activated physiological sensor(s) and wherein the master protocol comprises data for selecting and activating a nested protocol associated to said determined brain state or local brain state and/or wherein the master protocol comprises data for deselecting and deactivating an active nested protocol not-associated to said determined brain state or local brain state.

57. The brain stimulating system of any one of the preceding claims, wherein the computer system is configured for receiving input data comprising at least a portion of the stimulation protocol or data for generating and/or selecting the stimulation protocol and/or wherein the comprises a memory storing at least a portion of the stimulation protocol and/or data for generating and/or selecting the stimulation protocol.

58. The brain stimulating system of any one of the preceding claims, wherein the headwear comprises a plurality of EEG (electroencephalogram) sensors, preferably comprising one or more EEG sensors preferably located at a portion of the headwear adapted to be in contact with a subjects head, such as a forehead of the subject.

59. The brain stimulating system of claim 58, wherein the EEG sensors are configured for obtaining an electroencephalogram of a subject and for communicating the electroencephalogram to the computer system, wherein the computer system is in communication with a database comprising recordings of EEG brainwave data sets correlated to respective brain states and to respective treatment protocols for such brain states, and wherein the computer system is configured for fitting the electroencephalogram of the

subject to the EEG brainwave data sets of the database and selecting the treatment protocol for treating the subject,

wherein the recordings of EEG brainwave data sets of the database, preferably are correlated to respective brain states selected from

- task-negative recordings, e.g. during resting-state studies from various patient populations and healthy subjects.
- task-positive recordings, e.g. during cognitive-behavioral studies, such as task-elicited event-related potentials (ERPs), from various patient populations and healthy subjects.

60. The brain stimulating system of claim 58 or claim 59 wherein the brain stimulating system is configured to determine a brain state based on the subject based one or more electroencephalograms obtained by the EEG sensor, preferably the headwear also includes an fNIRS sensor and wherein the brain stimulating system is configured to determine a brain state based on one or more electroencephalograms obtained by the EEG sensor in combination with cortical hemodynamic activity data determined by the fNIRS sensor.

61. The brain stimulating system of any one of claims 59-60, wherein the computer system is adapted for receiving a set of input data and based on the input data and to generate and/or select the stimulation protocol using the input data, wherein the generation and/or selection of the stimulation protocol further involves at least one of data determined on the subject, the determined electroencephalogram, the determined brain state and/or a target EEG brainwave dataset, optionally obtained from a database of brain states correlated to EEG data.

62. The system of any one of the preceding claims, wherein the at least one physiological primary sensor comprises an optical heart rate monitor, such as a photoplethysmograph (PPG).

63. The system of any one of the preceding claims, wherein the at least one primary physiological sensor comprises an optical cortical hemodynamic activity sensor, such as an fNIRS.

64. The brain stimulating system of any one of the preceding claims, wherein the headwear comprises a right side and a left side and a marking for a subject to locate the right side of the headwear in contact with the right side of the subject's scalp and to locate the left side of the headwear in contact with the left side of the subject's scalp.

65. The brain stimulating system of any one of the preceding claims, wherein the headwear comprises a headband comprising at least four

conductor coils located in a line, such as a line of conductor coils located with their center located in a position adapted to be in contact with a subject's head at locations according to the International 10–10 EEG positioning system, preferably comprising locations in proximity to the dorsolateral prefrontal cortex such as F7, F3, F4, F8, locations in proximity to the medial temporal lobe such as P5, T3, T4, P6 and/or locations in proximity to the posterior parietal cortex such as CP1, P3, P4, CP2.

66. The brain stimulating system of any one of the preceding claims, wherein the headwear comprises a headband comprising one or more EEG sensors located at position(s) adapted to be in contact with a subject's head at locations according to the International 10–10 EEG positioning system preferably comprising locations in proximity to the dorsolateral prefrontal cortex such as F7, F3, F4, F8, locations in proximity to the medial temporal lobe such as P5, T3, T4, P6 and/or locations in proximity to the posterior parietal cortex such as CP1, P3, P4, CP2.

67. The brain stimulating system of any one of the preceding claims, wherein the step of determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, comprises determining if the modulation parameter of the set of stimulation parameters is or is not correlated to affect brain waves of the subject.

68. The brain stimulating system of claim 67, wherein the determining if the modulation parameter of the stimulation protocol computer is correlated to affect brain waves of the subject comprises obtaining at least a portion of an electroencephalogram of the subject, preferably comprising obtaining EEG data using an EEG sensor, wherein the EEG sensor optionally is the primary physiological sensor.

69. The brain stimulating system of claim 67 or claim 68, further comprising adjusting the stimulation protocol if it is determined that the temporal parameter of the set of stimulation parameters is not correlated to affect the brain waves of the subject.

70. A headwear for transcranial magnetic stimulation (TMS) of the brain, wherein the headwear comprises a head-facing surface configured for being in contact with a subject's head and defining a treatment scene, the headwear comprises

- a plurality of conductor coils, wherein the conductor coils are located at selected locations, wherein each of the conductor coils are orientated to generate a magnetic field at the treatment scene adapted for inducing an electric field at the cortex of a subject,

- a power arrangement for supplying current to the respective plurality of conductor coils,
- a computer system in the form of a controller, and
- a sensor system comprising at least one primary physiological sensor adapted for detecting a physiological parameter in response to a brain stimulation,

wherein the controller configured for

i. receiving stimulation data representing a set of stimulation parameters of a stimulation protocol, wherein the set of stimulation parameters comprises at least one modulation parameter and at least one spatial parameter,
ii. converting the received stimulation data to a set of current parameters according to a converting protocol and
iii. controlling the power arrangement, comprising supplying current to one or more of said conductor coils according to the set of current parameters for inducing the brain stimulation according to the stimulation protocol,
iv. detecting the physiological parameter using the physiological primary sensor, and
v. determining if the detected physiological parameter is indicative of a response to the induced brain stimulation, ,

and if not,

vi. adjusting the converting protocol, and
vii. optionally repeating the steps i-vi.

71. The headwear of claim 70, wherein the determining if the detected physiological parameter is indicative of a response to the induced brain stimulation comprises determine if the induced brain stimulation is in compliance with or out of compliance with at least one stimulation parameter of the stimulation protocol, wherein if the induced brain stimulation is out of compliance with the stimulation protocol, adjusting the converting protocol.

72. The headwear of claim 70 or claim 71, wherein the computer system is configured for operating in according to any one of claims 1-69.

73. The headwear of any one of claims 70-72, wherein the headwear is as defined in any one of claims 1-69.

Fig. 1

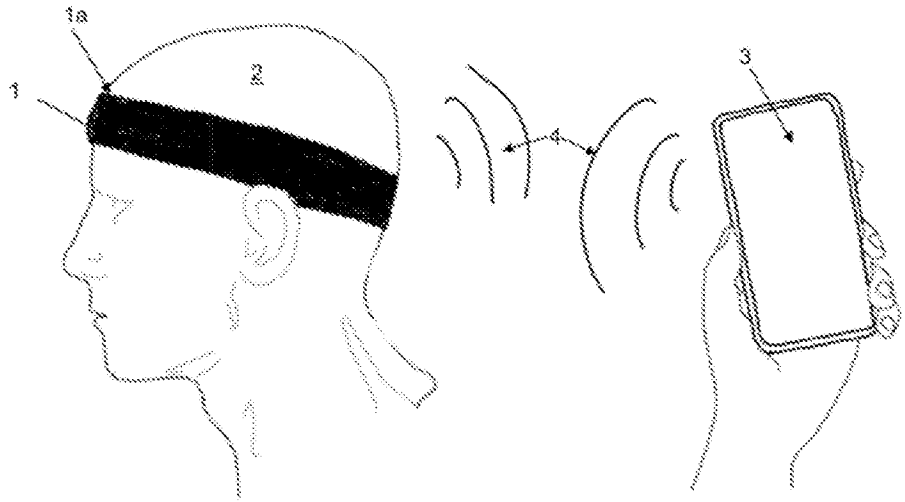

1a
1
2
3
4

Fig. 2

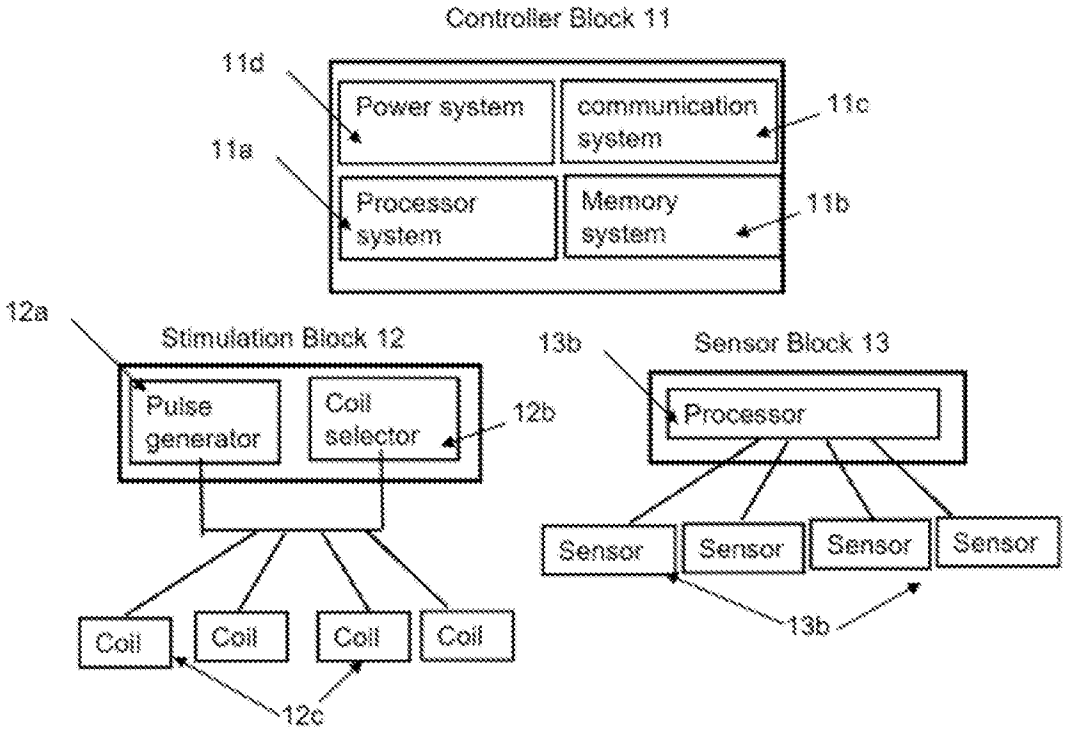

Controller Block 11
11d
Power system
communication system
11c
11a
Processor system
Memory system
11b
12a
Stimulation Block 12
Pulse generator
Coil selector
12b
13b
Sensor Block 13
Processor
Sensor
Sensor
Sensor
Sensor
Coil
Coil
Coil
Coil
12c
13b

Fig. 3

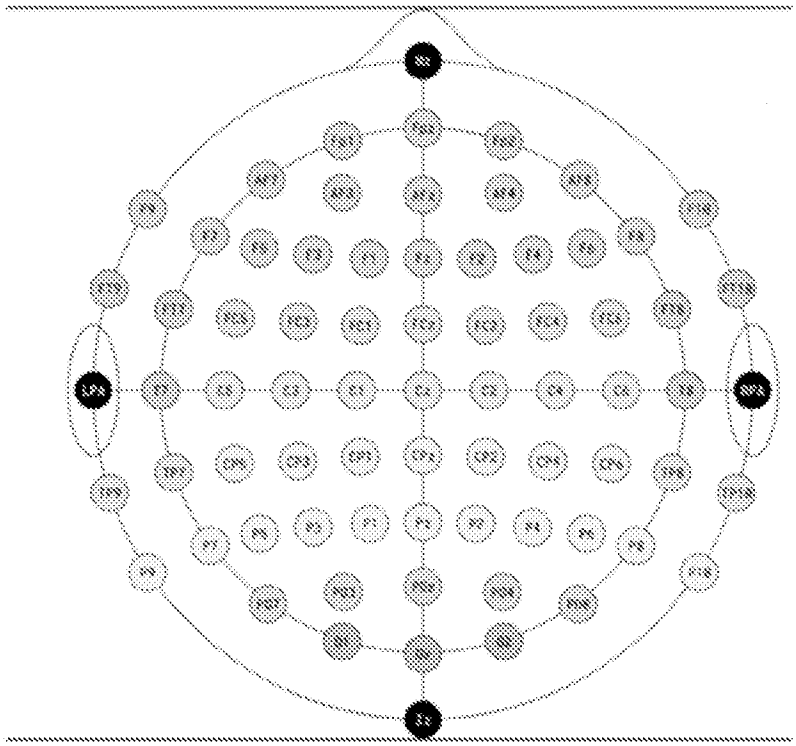


Fig. 4a

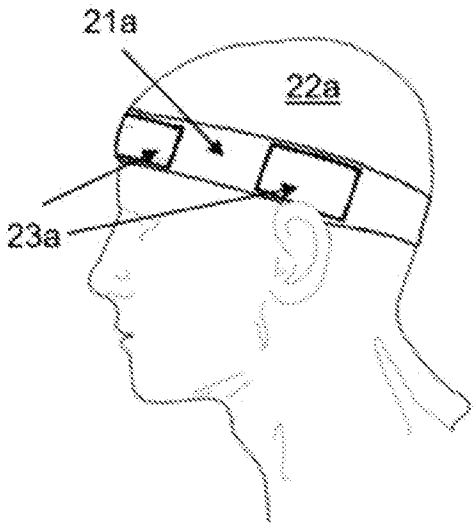


Fig. 4b

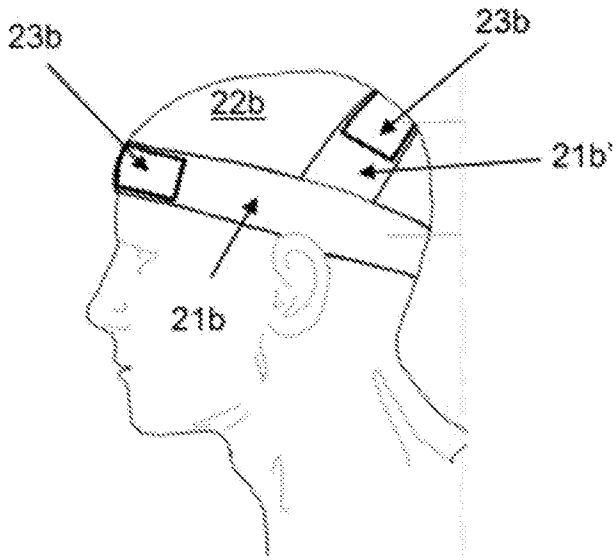


Fig. 5a

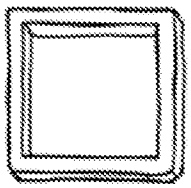
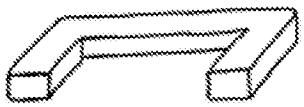


Fig. 5b

Fig. 5c



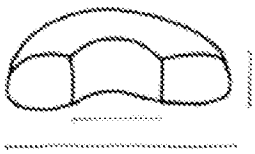


Fig. 5d

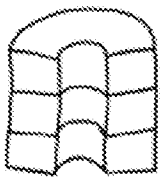


Fig. 5e

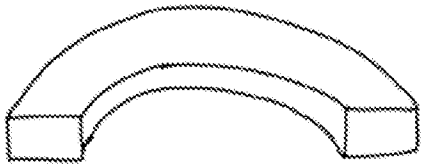


Fig. 5f

Fig. 6

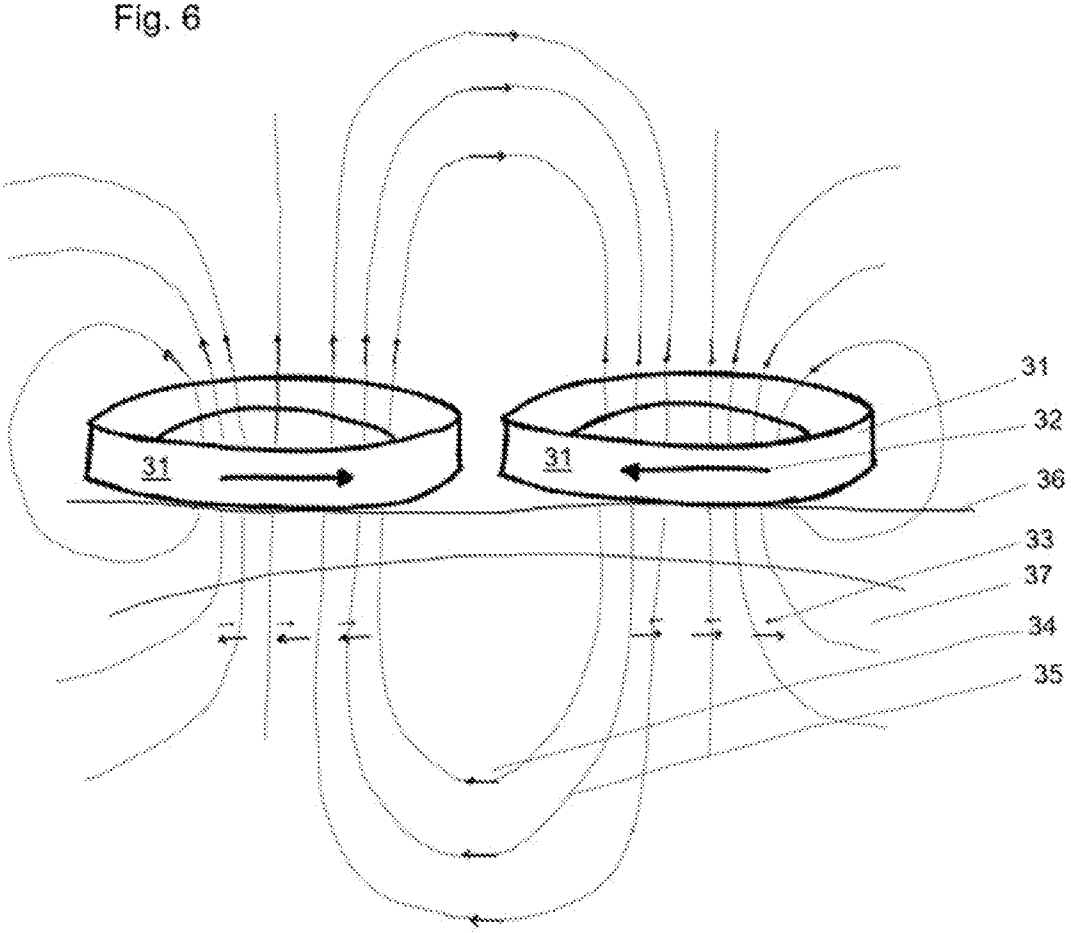


Fig. 7

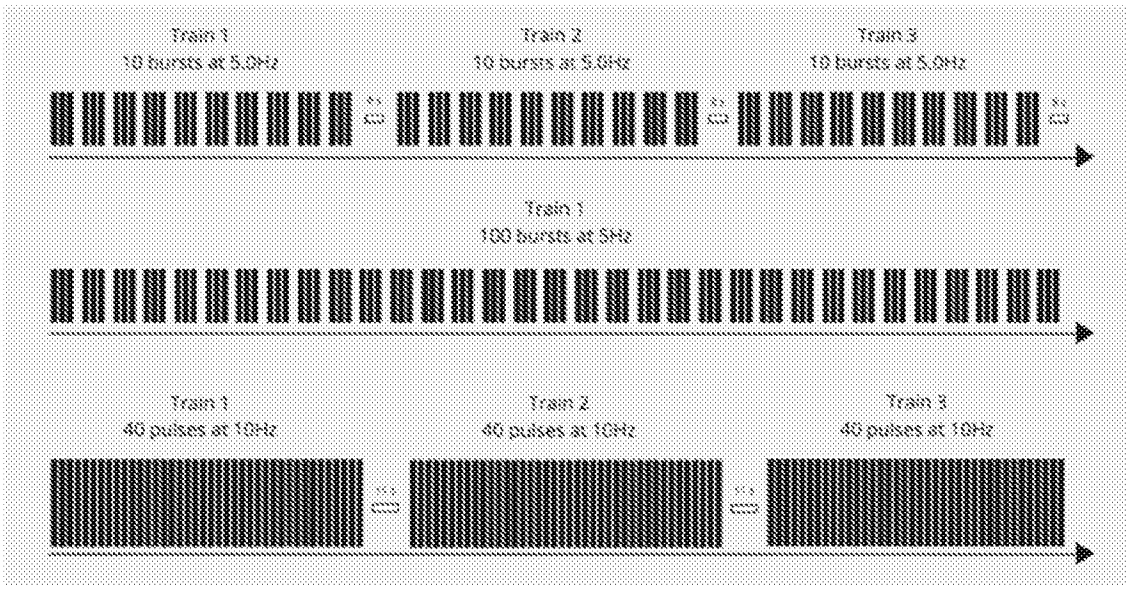

Train 1
10 bursts at 5.0Hz
Train 2
10 bursts at 5.0Hz
Train 3
10 bursts at 5.0Hz
Train 1
100 bursts at 5Hz
Train 1
40 pulses at 10Hz
Train 2
40 pulses at 10Hz
Train 3
40 pulses at 10Hz

Fig. 8a

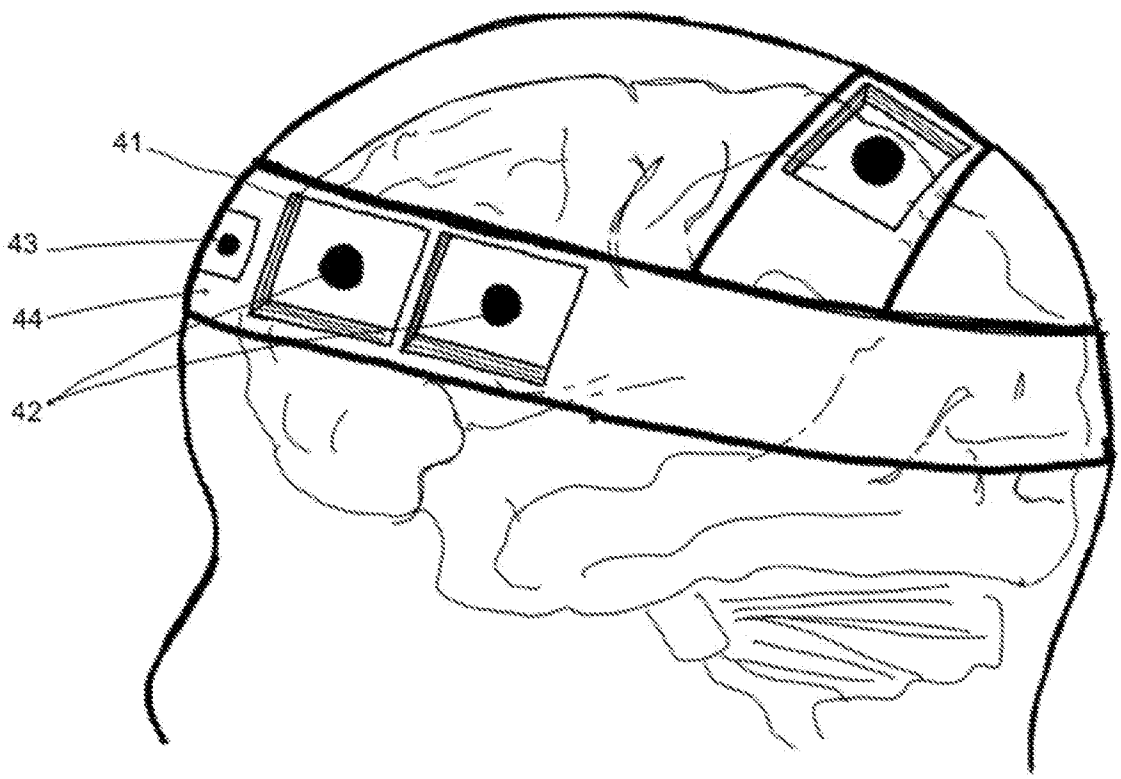

41
43
44
42

Fig. 8b

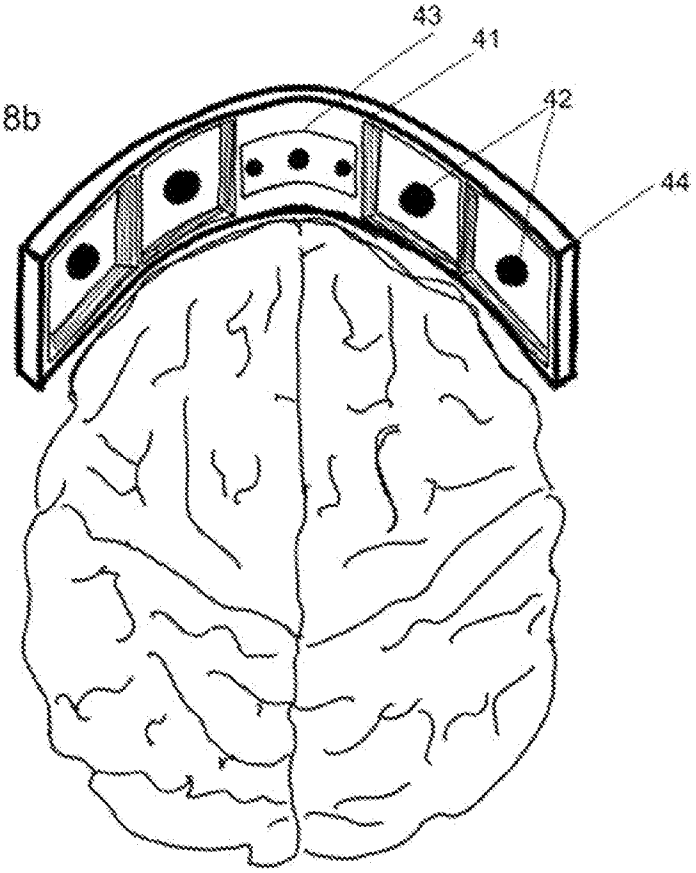
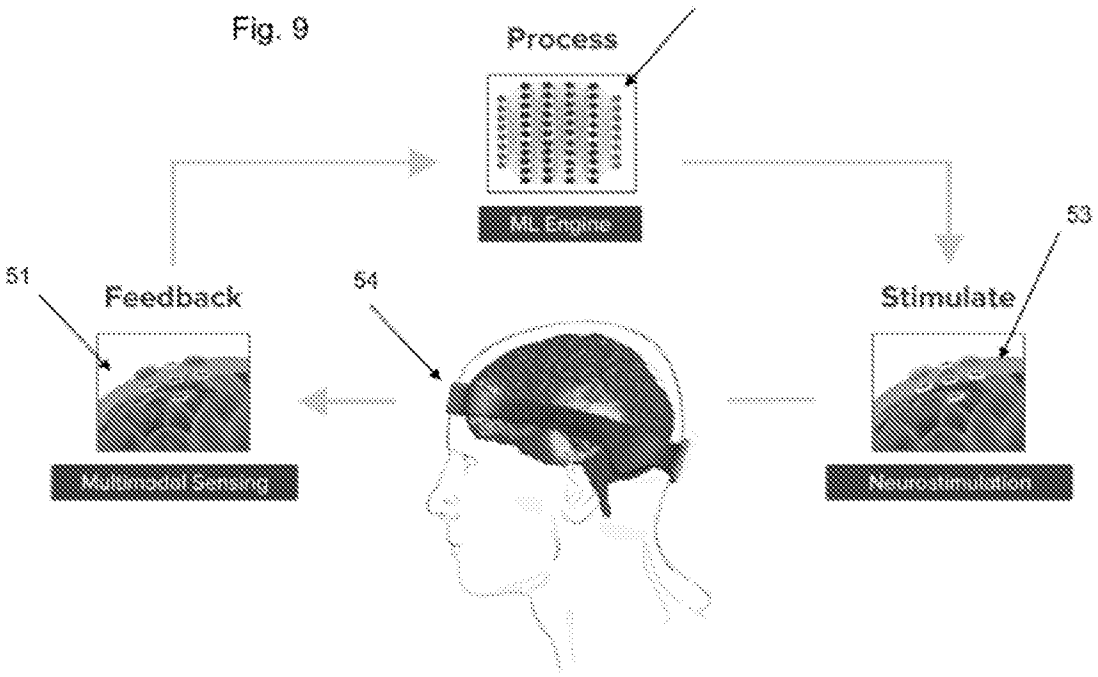

43
41
42
44

Fig. 9


Process
ML Engine
51
Feedback
Motion and Sensing
54
53
Stimulate
Neurostimulation

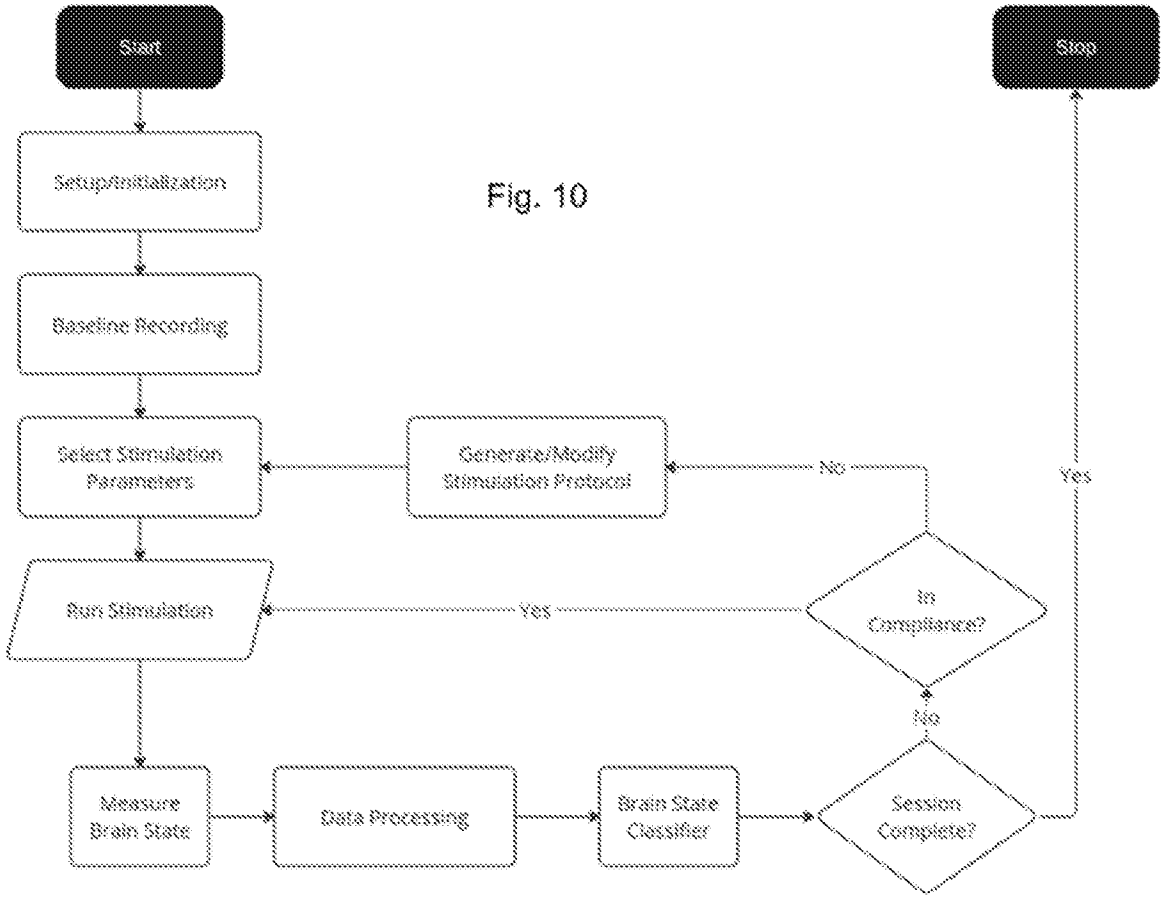
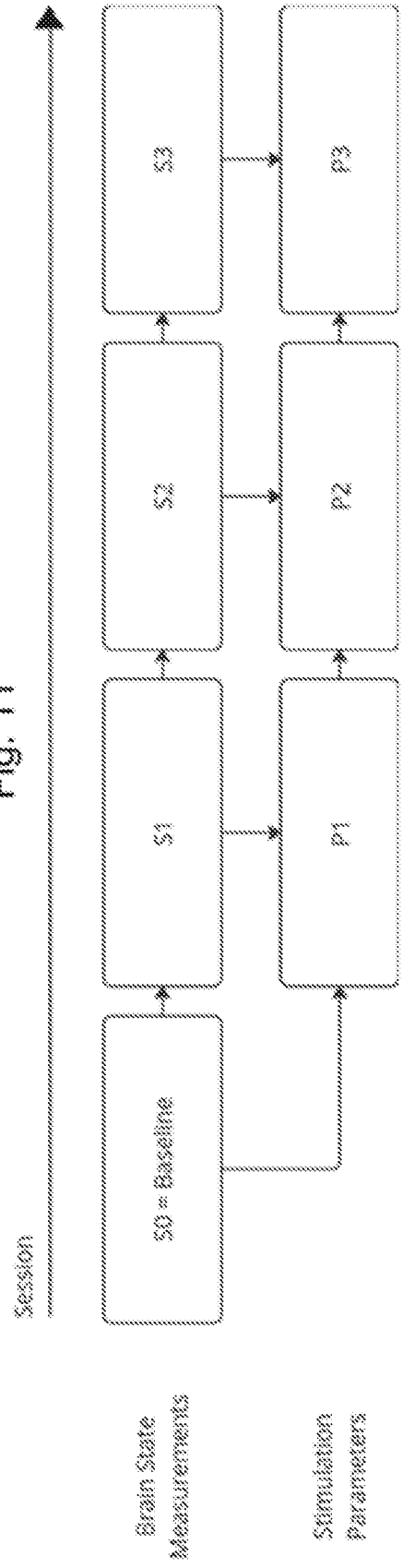

Start
Stop
Setup/Initialization
Baseline Recording
Select Stimulation Parameters
Generate/Modify Stimulation Protocol
No
Yes
Run Stimulation
Yes
In Compliance?
No
Measure Brain State
Data Processing
Brain State Classifier
Session Complete?
Yes

Fig. 10

Fig. 11


Session
S0 = Baseline
S1
S2
S3
P1
P2
P3
Brain State Measurements
Stimulation Parameters

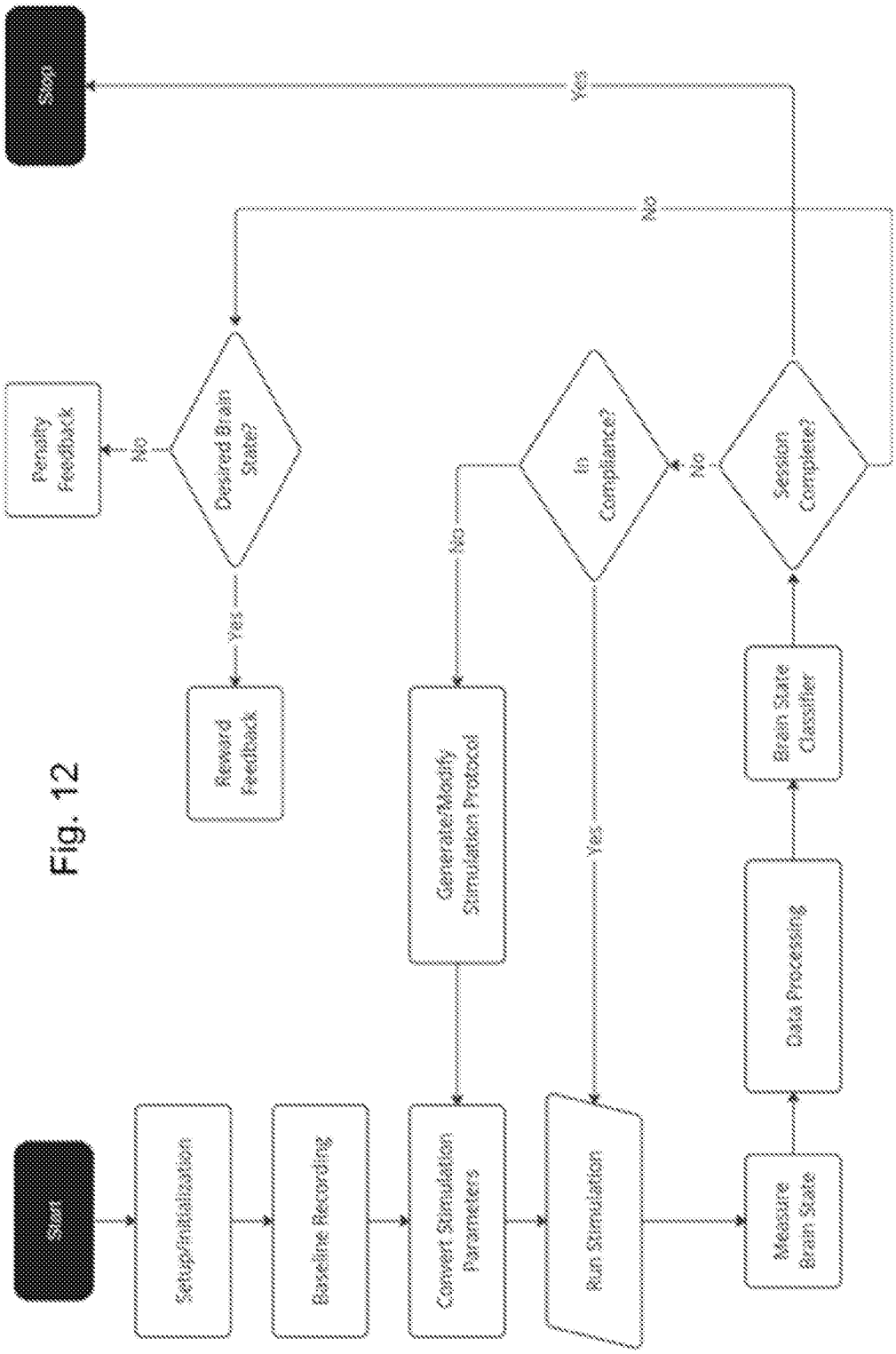
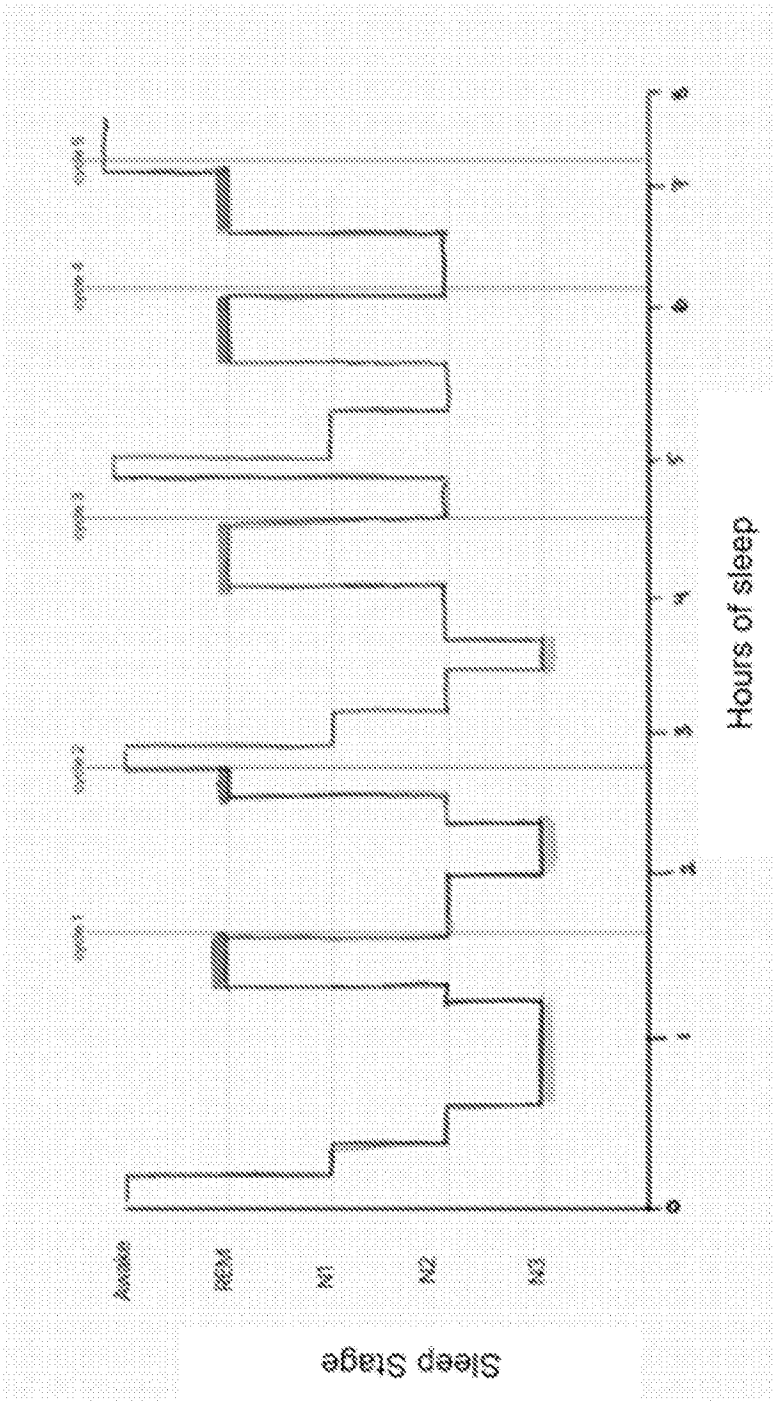

Start
Setup/Initialization
Baseline Recording
Convert Stimulation Parameters
Run Stimulation
Measure Brain State
Data Processing
Brain State Classifier
Session Complete?
In Compliance?
Generate/Modify Stimulation Protocol
Desired Brain State?
Reward Feedback
Penalty Feedback
Yes
No
Yes
No
Yes
No
Stop

Fig. 12

Fig. 13a



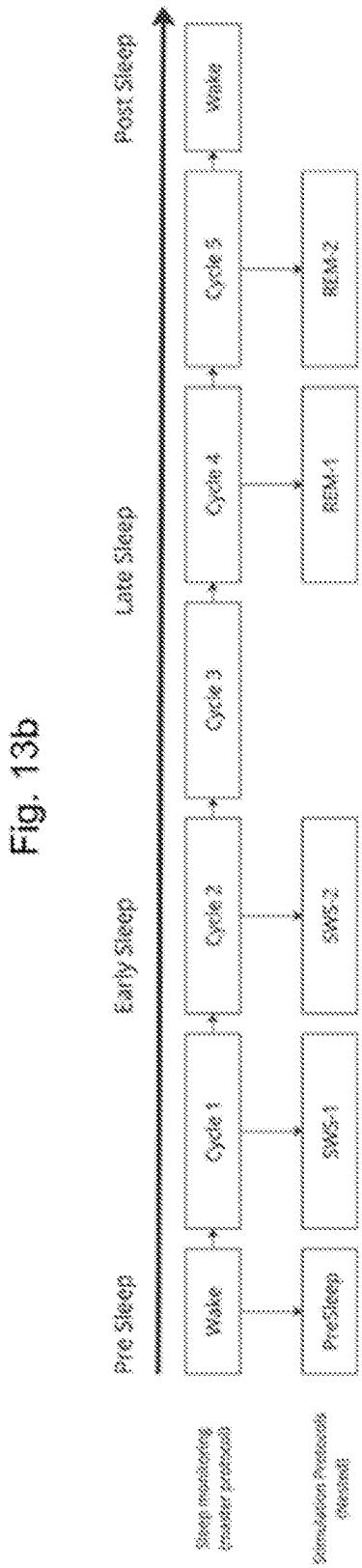

Pre Sleep
Early Sleep
Late Sleep
Post Sleep
Wake
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Wake
PreSleep
SWS-1
SWS-2
REM-1
REM-2
Sleep monitoring (sensor principle)
Stimulation (schematic design)

Fig. 13b

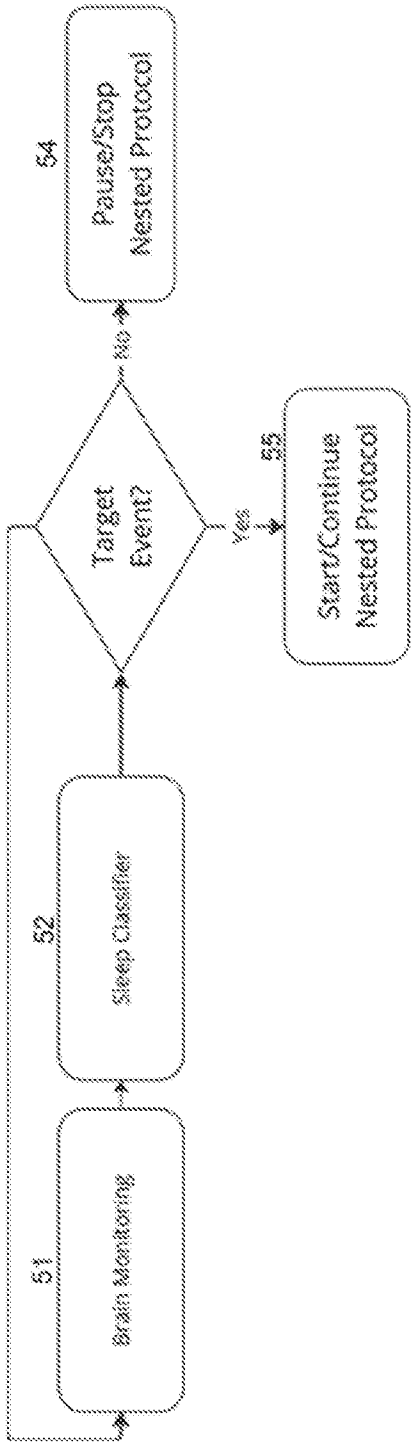


Fig 14a - master protocol

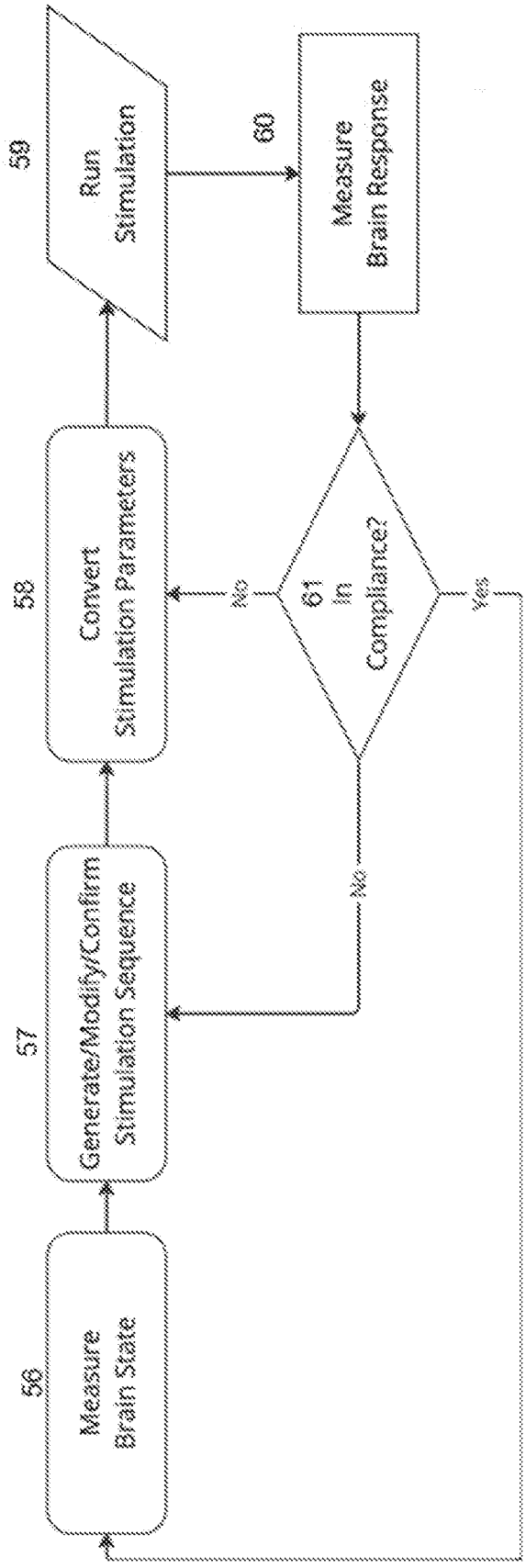


Fig 14b - Nested dynamic protocol

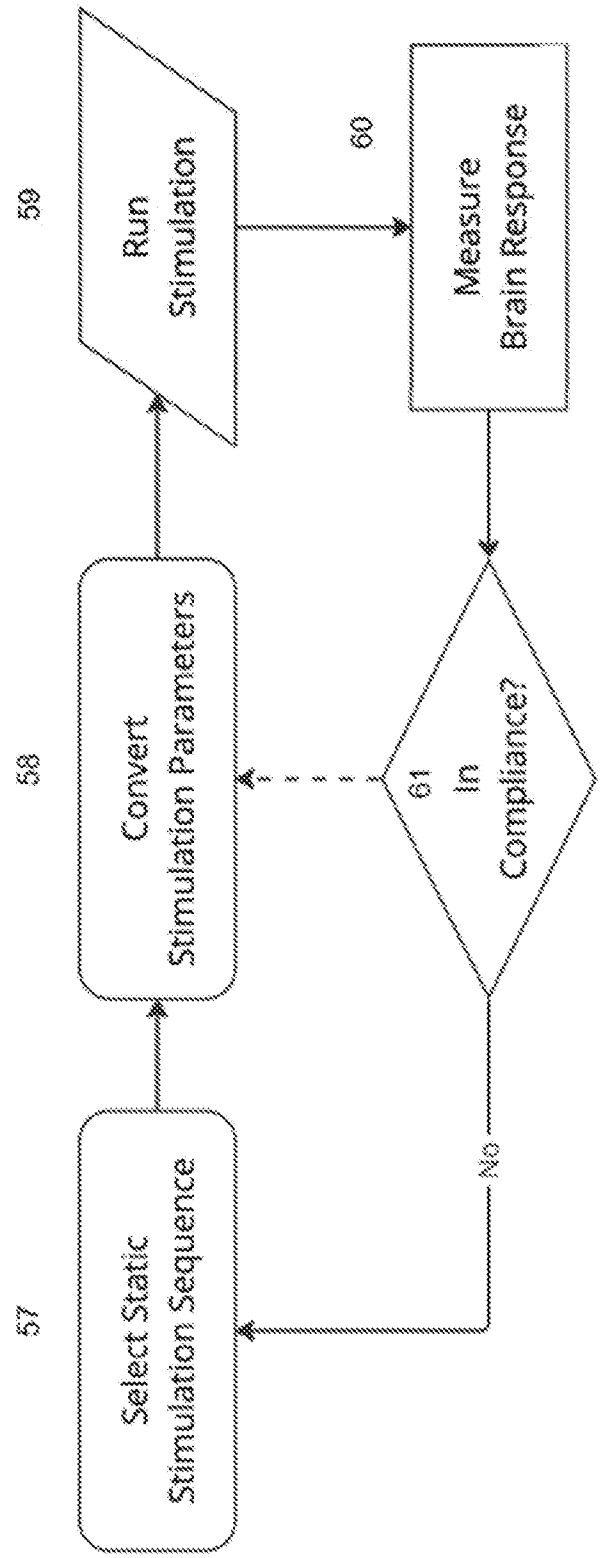


Fig 14c - Nested static protocol

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2024/050137

A. CLASSIFICATION OF SUBJECT MATTER

A61N 2/02(2006.01)i; **A61B 5/00**(2006.01)i

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)

A61N 2/02

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

DK, NO, SE, FI: Classes as above.

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

EPODOC, FULLTEXT: English.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/0008620 A1 A1 (STUBBEMAN WILLIAM F) 14 January 2016 (2016-01-14) par. 0036-0038, 0091, 0094-0096, 0098-0100-0101, 0103, 0107, 0112, 0119, 0125-0127, 0142, 0218, fig. 1 and 7.	1-73
X	US 2023/0104434 A1 (ANSARI KAMRAN et al.) 06 April 2023 (2023-04-06) Whole document	1-73
X	WO 2021/226197 A1 (ANSARI KAMRAN et al.) 11 November 2021 (2021-11-11) Whole document	1-73
X	US 2021/0346711 A1 (ANSARI KAMRAN et al.) 11 November 2021 (2021-11-11) Whole document	1-73
A	WO 2022/204726 A1 (WAVE NEUROSCIENCE INC) 29 September 2022 (2022-09-29) par. 0068.	52-56

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"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	Date of mailing of the international search report
20 August 2024	**21 August 2024**

Name and mailing address of the ISA/XN	Authorized officer
Nordic Patent Institute **Helgeshoj Allé 81,** **2630 Taastrup** **Denmark** Telephone No. **+45 43 50 85 00** Facsimile No. **+4543508008**	**Maria Markussen** Telephone No.