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(54) **DIAGNOSIS AND TREATMENT OF CHRONIC PAIN**

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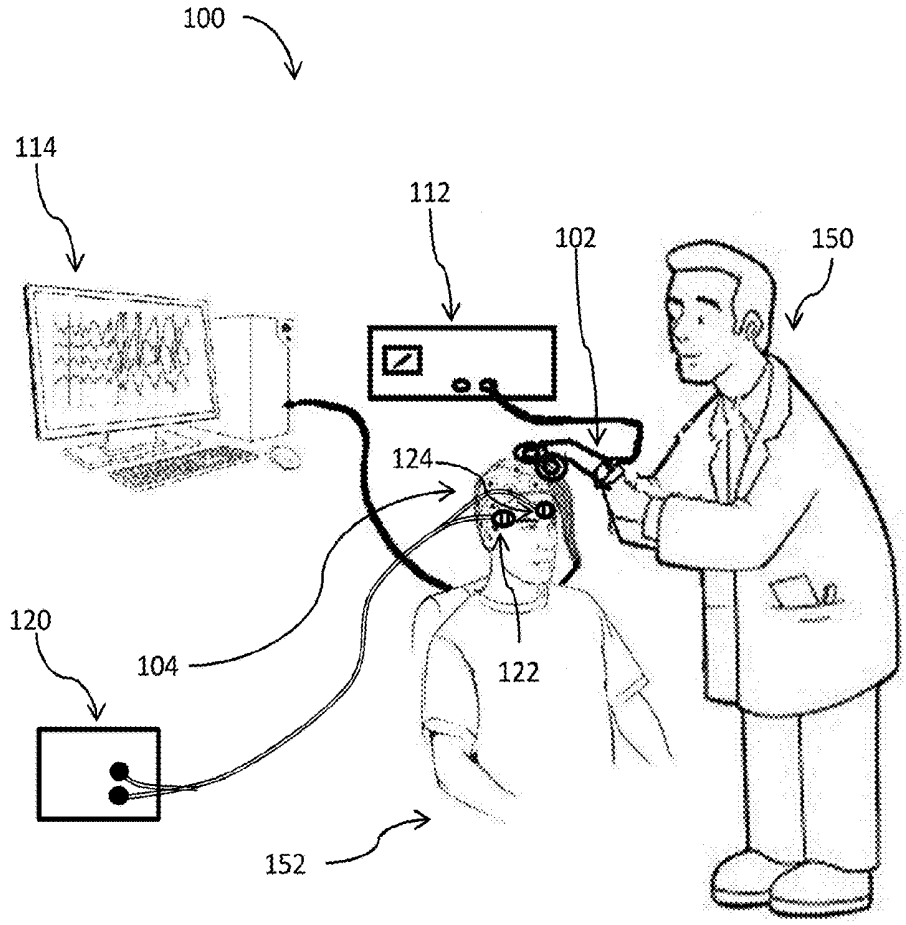
(57) **ABSTRACT**

Methods, systems and devices for treating chronic pain by inducing stimulation to a predetermined region of the brain and measuring neural activity response to the stimulation and evaluating a neuroplasticity and/or excitability of neural-structures in a predetermined brain region, then stimulating the predetermined brain region to treat the chronic pain.



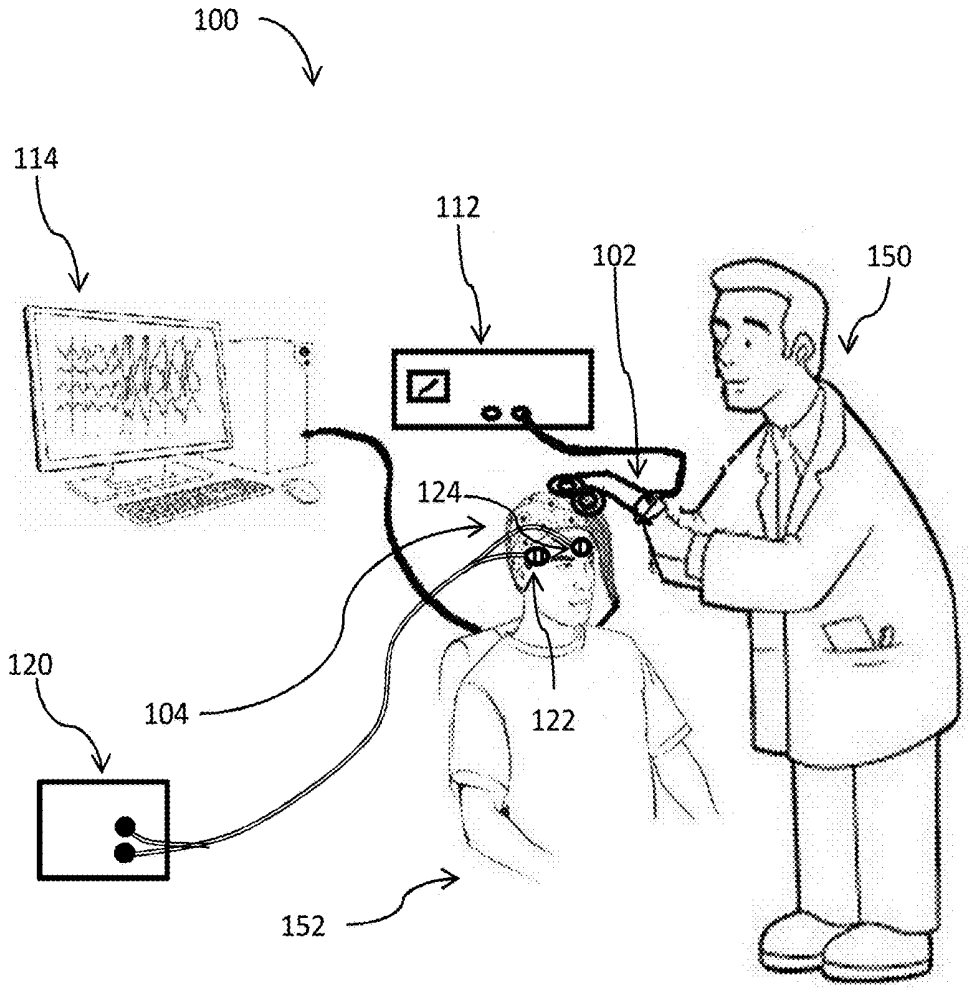


Fig. 1

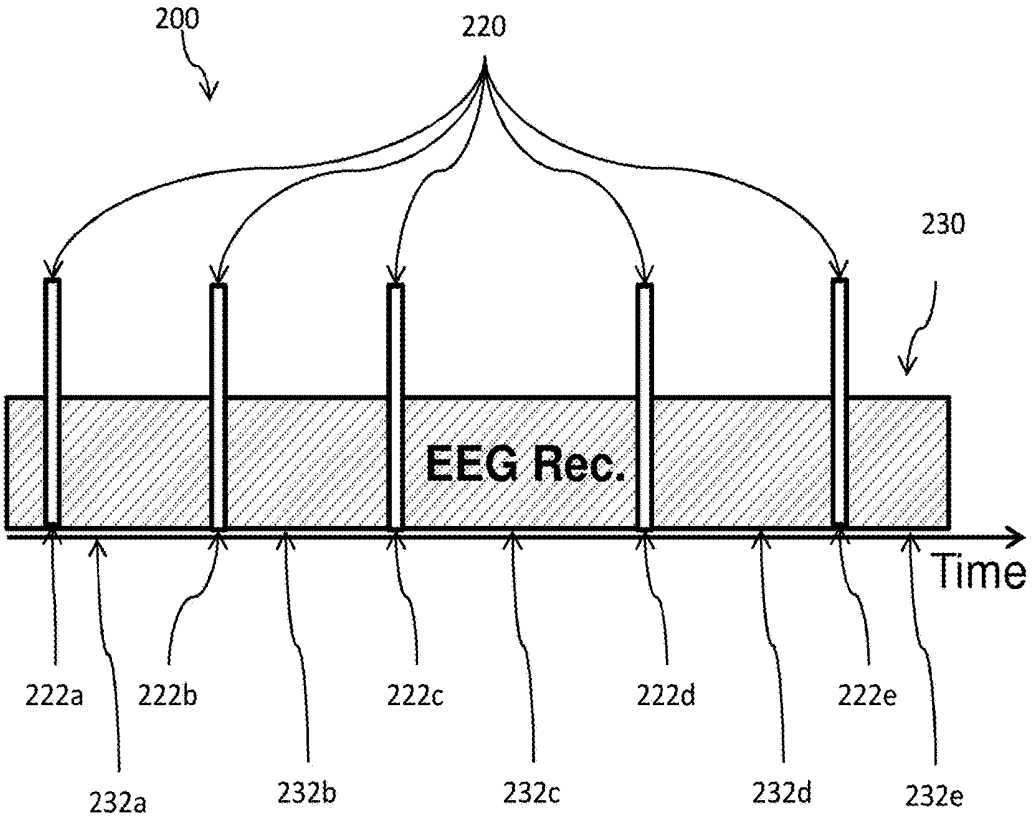

200
220
230
EEG Rec.
Time
222a
222b
222c
222d
222e
232a
232b
232c
232d
232e

Fig.2a

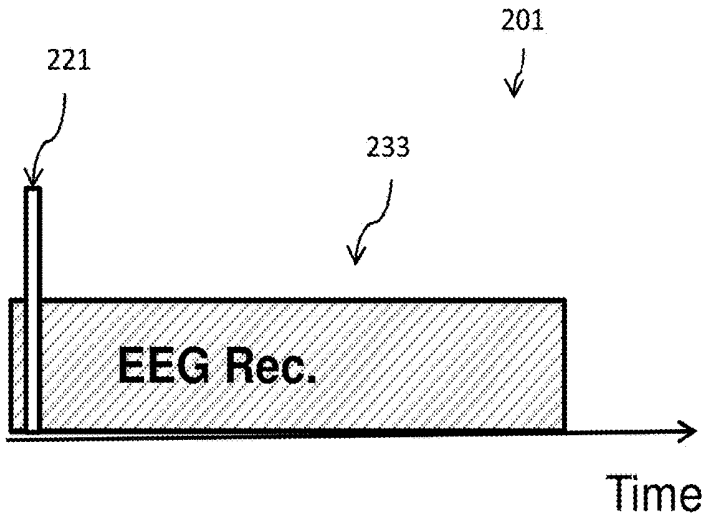

201
221
233
EEG Rec.
Time

Fig.2b

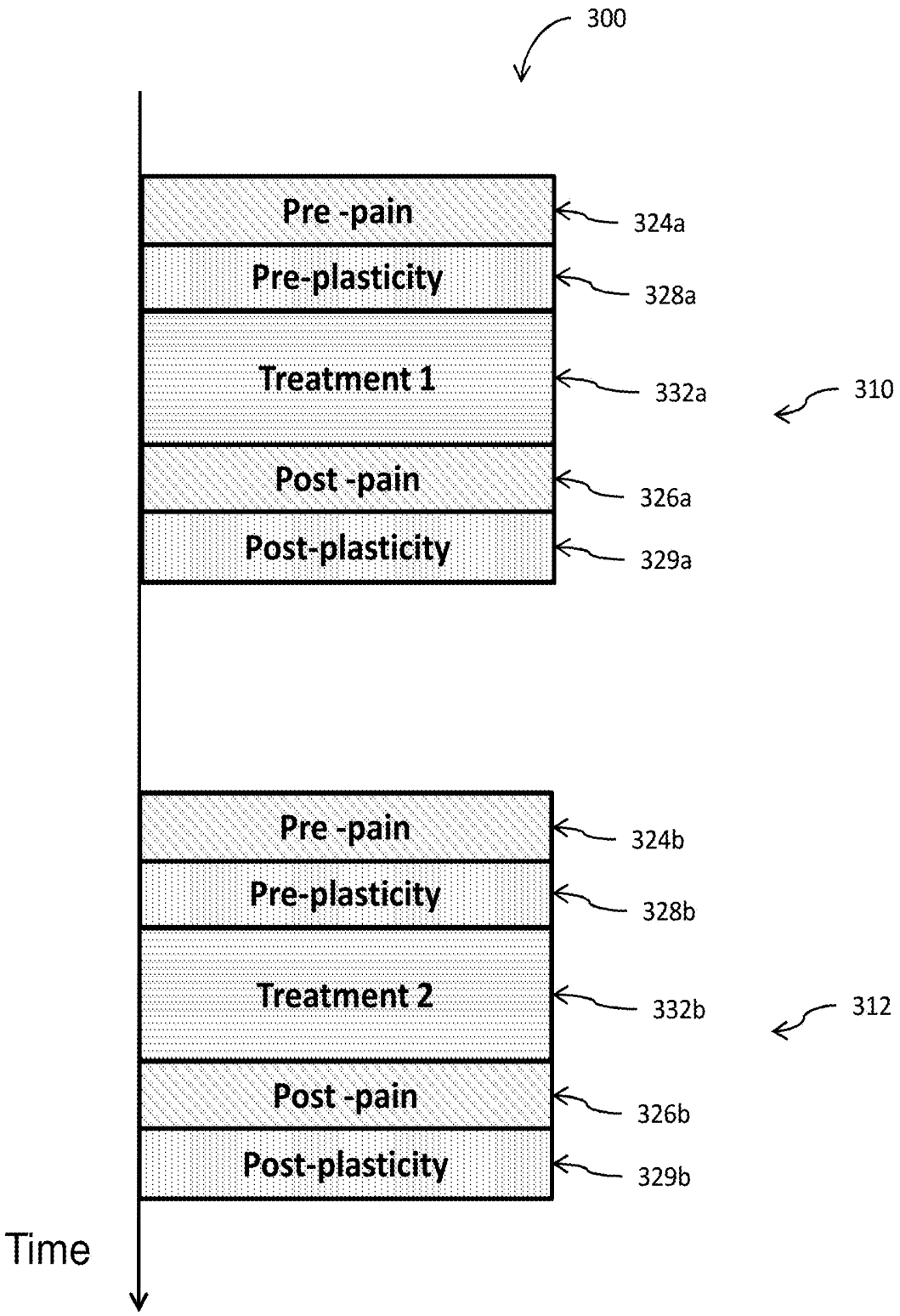

300
Pre -pain
324a
Pre-plasticity
328a
Treatment 1
332a
310
Post -pain
326a
Post-plasticity
329a
Pre -pain
324b
Pre-plasticity
328b
Treatment 2
332b
312
Post -pain
326b
Post-plasticity
329b
Time

Fig.3

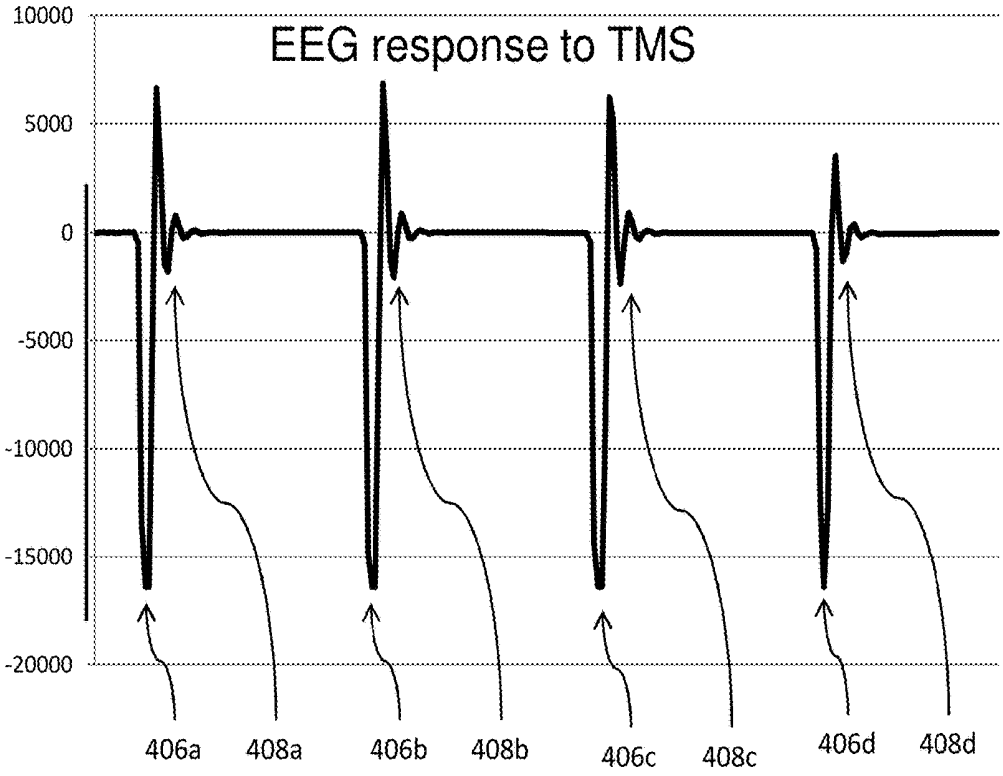

EEG response to TMS
10000
5000
0
-5000
-10000
-15000
-20000
406a
408a
406b
408b
406c
408c
406d
408d

Fig. 4

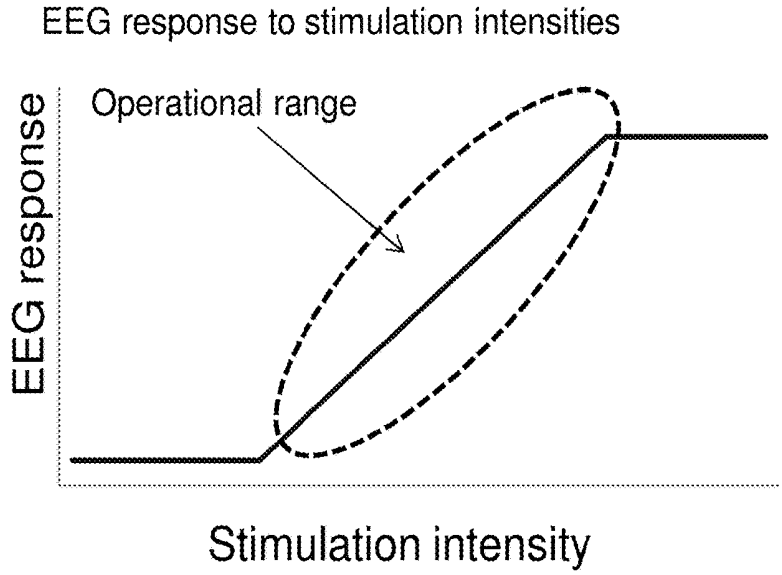

EEG response to stimulation intensities
Operational range
EEG response
Stimulation intensity

Fig. 5

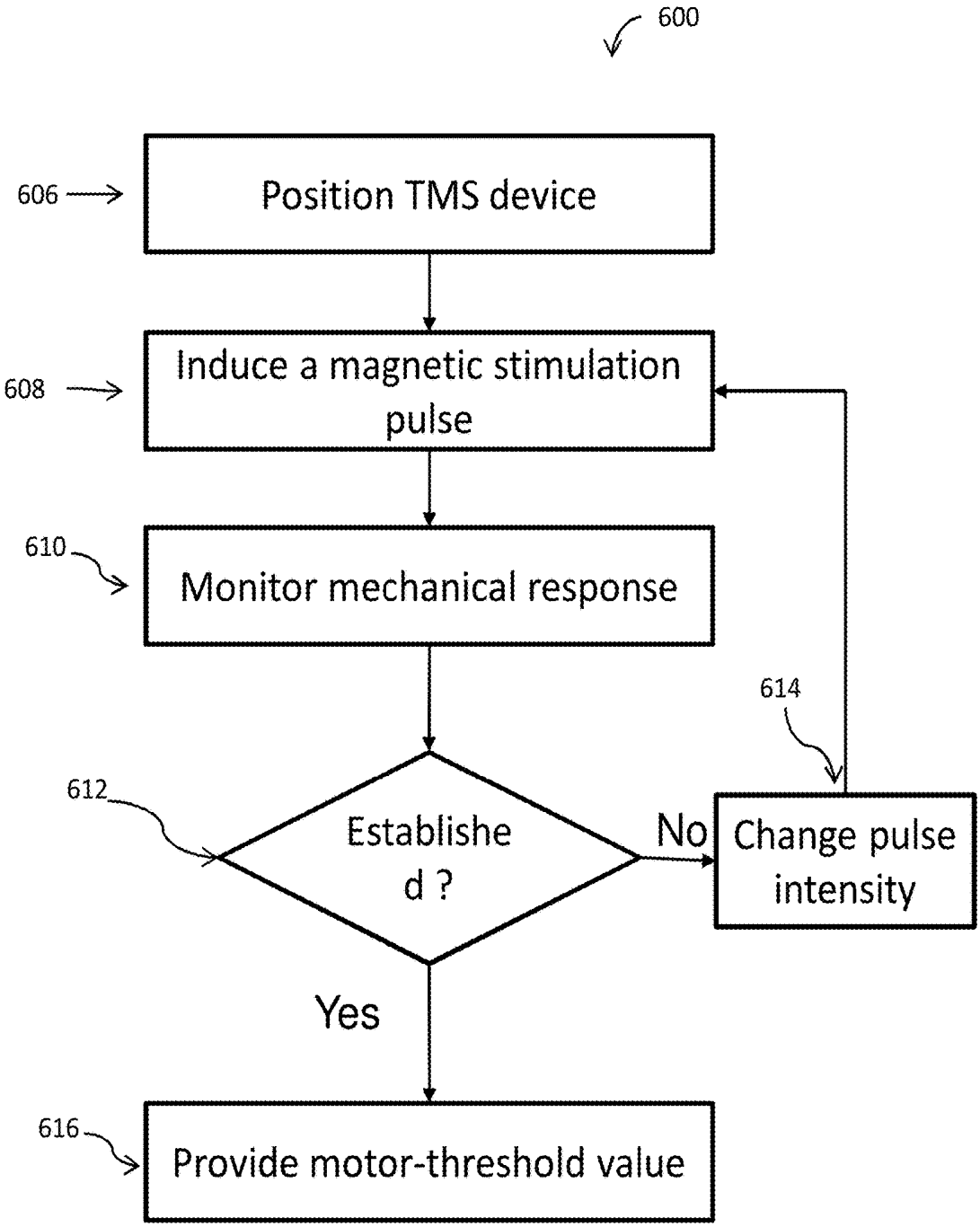

600
606
Position TMS device
608
Induce a magnetic stimulation pulse
610
Monitor mechanical response
614
612
Establishe d ?
No
Change pulse intensity
Yes
616
Provide motor-threshold value

Fig. 6

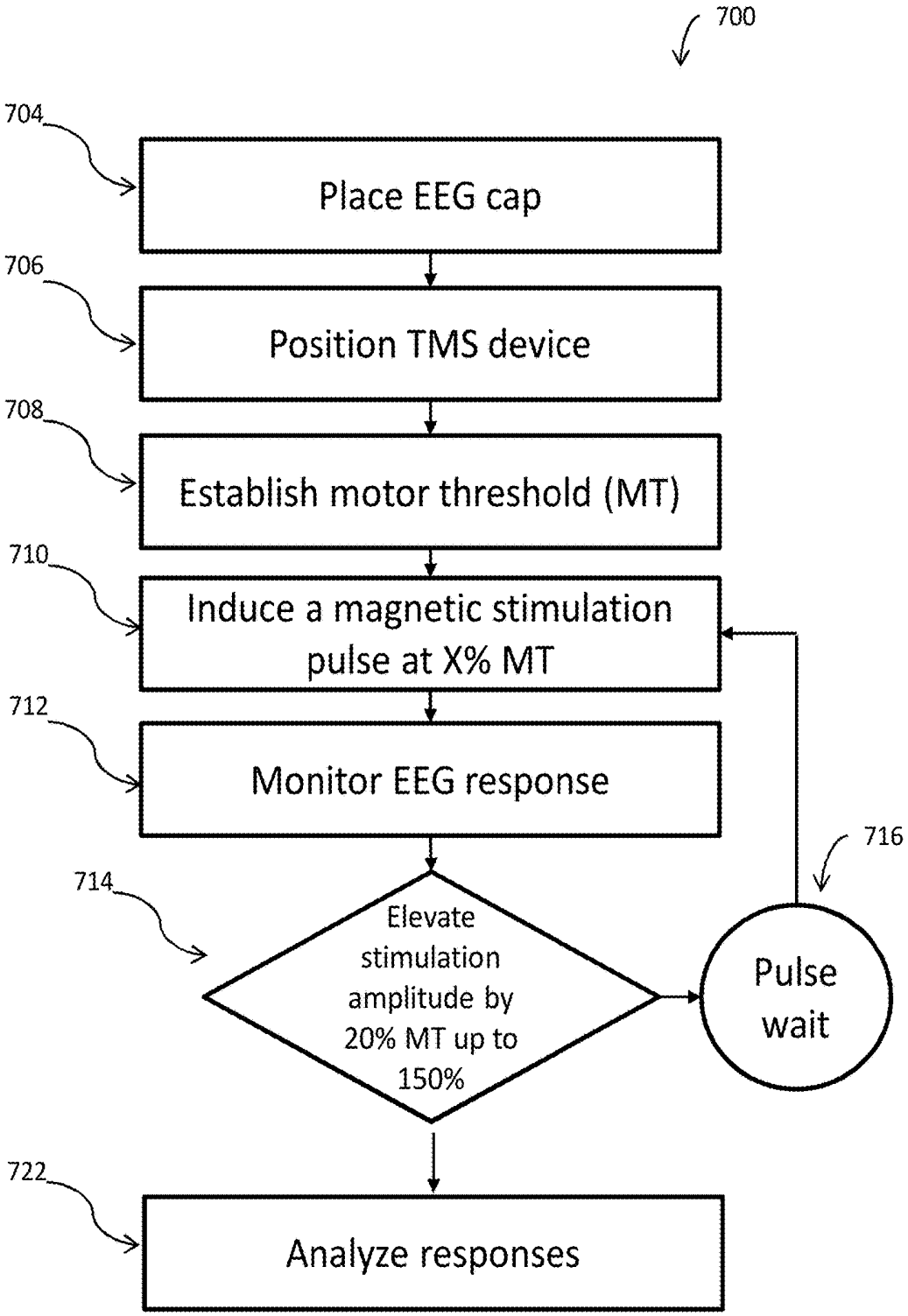

700
704
Place EEG cap
706
Position TMS device
708
Establish motor threshold (MT)
710
Induce a magnetic stimulation pulse at X% MT
712
Monitor EEG response
714
Elevate stimulation amplitude by 20% MT up to 150%
716
Pulse wait
722
Analyze responses

Fig. 7

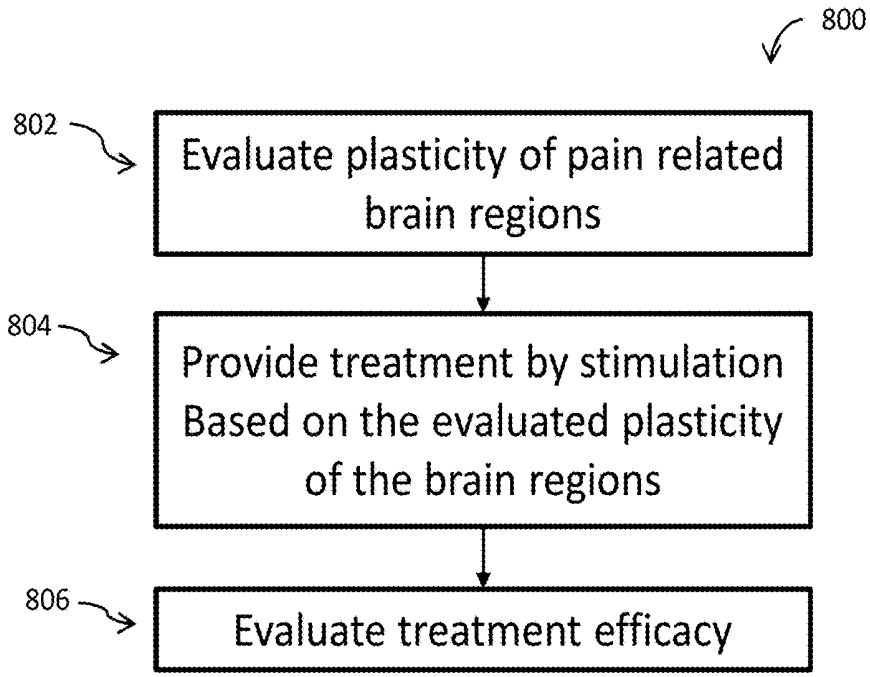

800
802
Evaluate plasticity of pain related brain regions
804
Provide treatment by stimulation Based on the evaluated plasticity of the brain regions
806
Evaluate treatment efficacy

Fig. 8

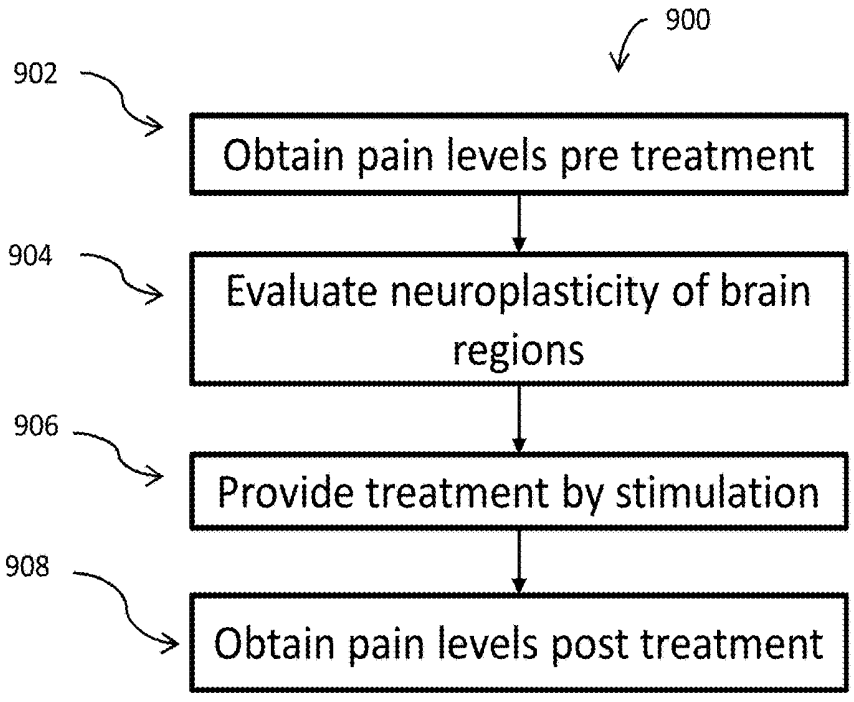

900
902
Obtain pain levels pre treatment
904
Evaluate neuroplasticity of brain regions
906
Provide treatment by stimulation
908
Obtain pain levels post treatment

Fig. 9

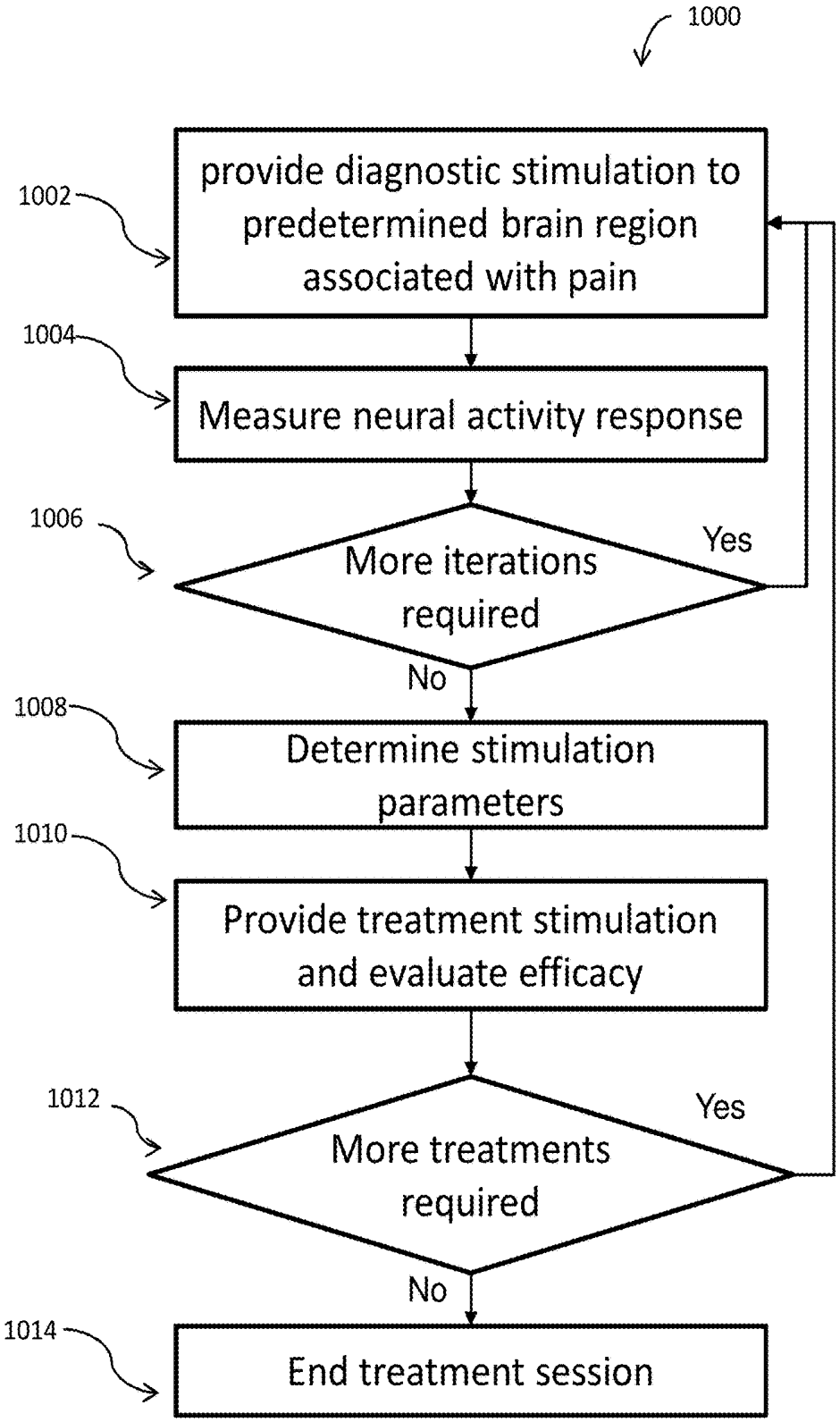

1000
1002
provide diagnostic stimulation to predetermined brain region associated with pain
1004
Measure neural activity response
1006
More iterations required
Yes
No
1008
Determine stimulation parameters
1010
Provide treatment stimulation and evaluate efficacy
1012
More treatments required
Yes
No
1014
End treatment session

Fig. 10

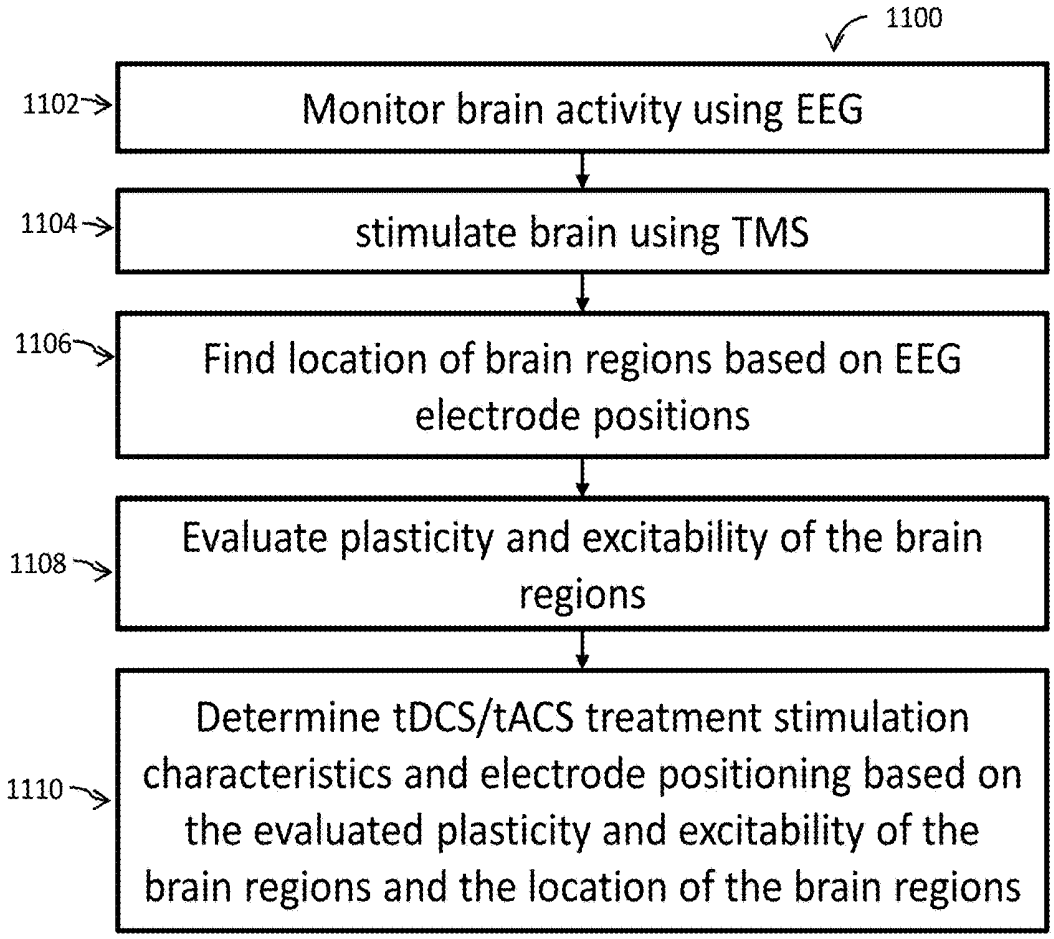

1100
1102
Monitor brain activity using EEG
1104
stimulate brain using TMS
1106
Find location of brain regions based on EEG electrode positions
1108
Evaluate plasticity and excitability of the brain regions
1110
Determine tDCS/tACS treatment stimulation characteristics and electrode positioning based on the evaluated plasticity and excitability of the brain regions and the location of the brain regions

Fig. 11

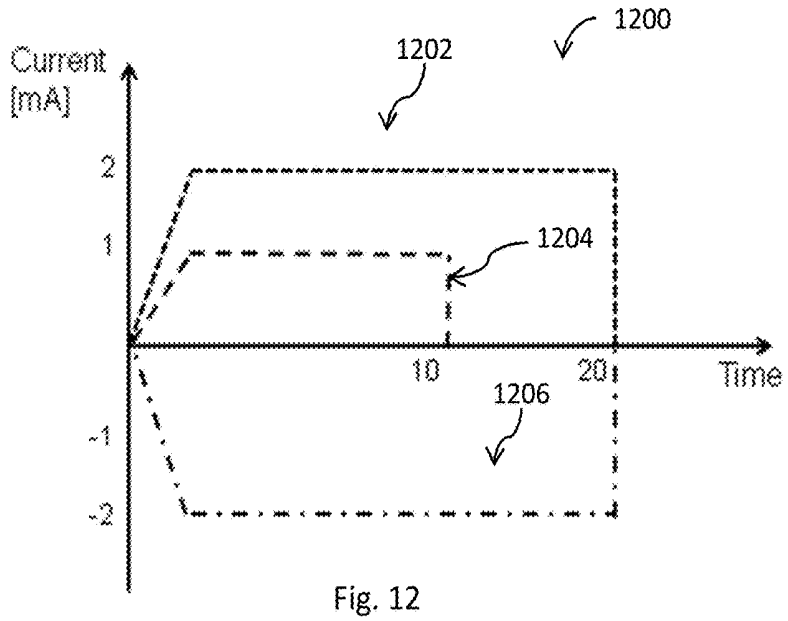

1200
1202
Current [mA]
2
1
1204
10
20
Time
1206
-1
-2

Fig. 12

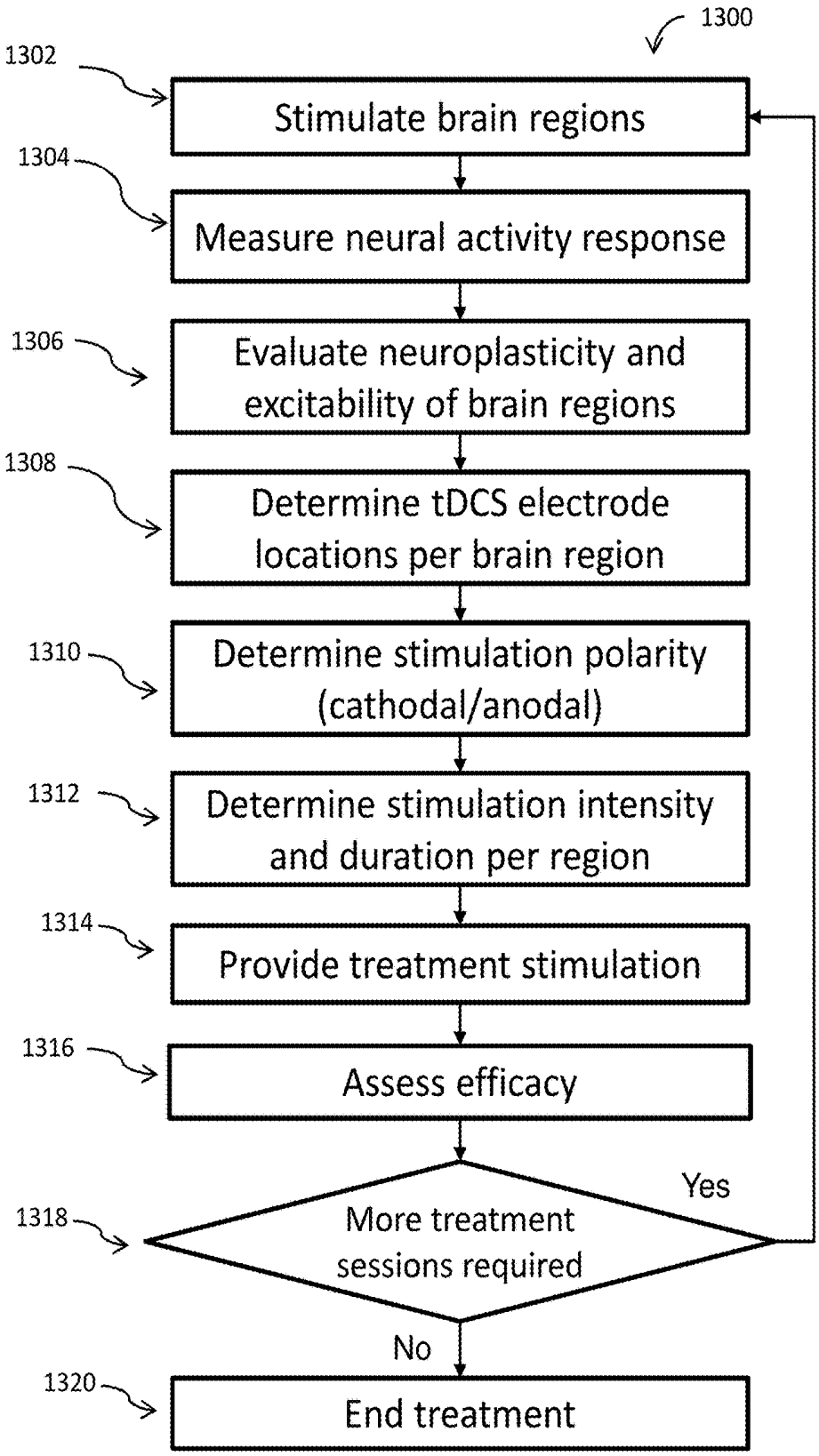

1300
1302
Stimulate brain regions
1304
Measure neural activity response
1306
Evaluate neuroplasticity and excitability of brain regions
1308
Determine tDCS electrode locations per brain region
1310
Determine stimulation polarity (cathodal/anodal)
1312
Determine stimulation intensity and duration per region
1314
Provide treatment stimulation
1316
Assess efficacy
1318
More treatment sessions required
Yes
No
1320
End treatment

Fig. 13

DIAGNOSIS AND TREATMENT OF CHRONIC PAIN

TECHNICAL FIELD

[0001] The present disclosure generally relates to the field of pain management.

BACKGROUND

[0002] Pain, when suffered over a long period of time can be categorized as chronic pain, generally, if the time since onset is more than 3-6 months. Chronic pain can originate from the body of a subject, the brain or the spinal cord, and is classified as either neuropathic pain, caused by a condition/malfunction of the nervous system, or nociceptive pain, caused by inflammation or damage to a tissue that activates pain sensory neurons called nociceptors.

[0003] Commonly, chronic pain is managed by pain relief drugs such as opioids (morphine, codeine and others), or non-opioid medications (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants and others). Evidently, the efficacy of the medications varies and may not always help in managing the pain suffered in some cases. Additionally, some medications are associated with harmful side effects including hypogonadism, infertility, impaired immune system, falls and fractures in older adults, neonatal abstinence syndrome, heart problems, sleep-disordered breathing, opioid-induced hyperalgesia, physical dependence, addiction, and overdose.

[0004] There is thus a need in the art for effective non-pharmaceutical solutions for chronic pain management.

SUMMARY

[0005] The following embodiments and aspects thereof are described and illustrated in conjunction with systems, tools and methods which are meant to be exemplary and illustrative, not limiting in scope. In various embodiments, one or more of the above-described problems have been reduced or eliminated, while other embodiments are directed to other advantages or improvements.

[0006] Chronic pain has been found associated with affecting the brain structure and function, which are expressed in abnormal anatomical and functional connectivity in various brain regions/areas related to the processing of pain, in addition to causing grey matter loss. These changes in the brain are explained by a neurological/neuro-structural property called neuroplasticity.

[0007] Neuroplasticity is manifested in two directions of neural behavior: potentiation, which is when a neural response is increased over time (training) by parts and strengthening of neuronal connection, or depression, which is when a neural response is decreased over time by parts and weakening of neuronal connections

[0008] According to some embodiments, there are provided herein devices, systems and methods for treatment/management of chronic pain conditions by stimulating predetermined brain regions of a subject associated with pain, measuring a neural activity response to the stimulation, and assessing the plasticity of the neurons/neural-networks (neuroplasticity) in the predetermined brain regions based on the characteristics of the neural activity response to the stimulation.

[0009] According to some embodiments, a treatment may be provided to the subject by providing electrical stimulation sessions targeting the predetermined brain regions, and assessing the effectiveness of the treatment by evaluating the plasticity of the neurons/neural-networks by measuring the neural activity response to neural stimulation.

[0010] According to some embodiments, characteristics and parameters of the electrical stimulation sessions may be changed and adapted based on the assessed effectiveness of previous treatment sessions.

[0011] According to some embodiments, there is provided a method for treating chronic pain of a subject, the method including inducing a diagnostic stimulation to a predetermined brain region of the subject, measuring a neural activity response to the diagnostic stimulation, evaluating a neuroplasticity and/or excitability of neural-structures in the predetermined brain regions based on the neural activity response to the diagnostic stimulation, and inducing a treatment stimulation to the predetermined brain region based on the evaluated neuroplasticity of the neural structures in the predetermined brain region.

[0012] According to some embodiments, the chronic pain is a neuropathic pain. According to some embodiments, the predetermined brain region is selected from a group including: primary motor cortex and primary somatosensory cortex, prefrontal cortex and insular cortex. According to some embodiments, inducing a diagnostic stimulation to a predetermined brain region of the subject includes utilizing transcranial magnetic stimulation (TMS).

[0013] According to some embodiments, measuring a neural activity response to the diagnostic stimulation includes obtaining electroencephalogram (EEG) measurements indicative of a neural activity of the brain of the user during and/or after inducing the diagnostic stimulation. According to some embodiments, inducing a treatment stimulation to the predetermined brain region includes electric brain stimulation. According to some embodiments, the inducing electric brain stimulation includes placing a first electrode and a second electrode on the subject, such that an electric signal passing through the user via the first electrode and the second electrode reaches a predetermined brain region.

[0014] According to some embodiments, the method further includes evaluating specific brain areas for plasticity changes by dipole fitting the EEG measurements and performing a source modeling for detecting the location (source localized areas) of the specific areas and providing treatment stimulation to the source localized areas.

[0015] According to some embodiments, the electric brain stimulation includes transcranial direct current stimulation (tDCS). According to some embodiments, the tDCS utilizes a current density of no more than 5 A/m^2, and has a duration of no more than 30 minutes. According to some embodiments, the tDCS stimulation is selected to be either Anodal stimulation or Cathodal stimulation for a brain region based on the evaluated neuroplasticity and/or excitability of neural-structures in the predetermined brain regions.

[0016] According to some embodiments, the electric brain stimulation includes transcranial alternating current stimulation (tACS). According to some embodiments, the tACS is performed by inducing an alternating current at a frequency in the range of 1-120 Hz at current density of 5 A/m^2 to be matched with a desired oscillatory behavior needed.

[0017] According to some embodiments, the method further includes evaluating a subjective pre-treatment-pain level of the subject before inducing a treatment stimulation,

a subjective post-treatment-pain level of the subject after inducing a treatment stimulation, and determining an efficacy of the treatment stimulation based on the difference between the pre-treatment-pain level and the post-treatment-pain level.

[0018] According to some embodiments, the method further includes inducing a post-treatment diagnostic stimulation to the predetermined brain region of the subject, measuring a neural activity response to the post-treatment diagnostic stimulation, evaluating a post-treatment neuroplasticity and/or excitability of neural-structures in the predetermined brain regions based on the neural activity response to the post-treatment diagnostic stimulation, and inducing a treatment stimulation to the predetermined brain region based on the evaluated post-treatment neuroplasticity of the neural structures in the predetermined brain region.

[0019] According to some embodiments, there is provided a system for treating chronic pain of a subject, the system including a directed inspective/diagnostic stimulation unit, configured to induce a diagnostic stimulation to a predetermined brain region of the subject. a brain activity sensor, configured to measure a neural activity response to the diagnostic stimulation induced by the directed brain stimulation unit, a processing circuitry in communication with the brain activity sensor, the processing circuitry is configured to evaluate a neuroplasticity and/or excitability of neural-structures in the predetermined brain region based on the neural activity response to the diagnostic stimulation, and an electric current stimulation unit including a first electrode and a second electrode, the electric current stimulation unit is configured to induce a treatment stimulation to the predetermined brain region based on the evaluated neuroplasticity of the neural structures in the predetermined brain region, by driving a current signal through the user via the first electrode and the second electrode such that the current reaches the predetermined brain region.

[0020] According to some embodiments, the directed inspective stimulation unit includes a transcranial magnetic stimulation (TMS) unit. According to some embodiments, the brain activity sensor includes an electroencephalography (EEG) device. According to some embodiments, the processing circuitry is configured to obtain an EEG signal from the EEG device and evaluate a neuroplasticity and/or excitability of neural-structures in the predetermined brain region by comparing the neural activity response to the diagnostic stimulation with previously obtained neural activity response to previous diagnostic stimulation.

[0021] According to some embodiments, the processing circuitry is further configured to estimate locations of the predetermined brain regions based on the obtained EEG signal.

[0022] According to some embodiments, the electric current stimulation unit includes a transcranial direct current stimulation (tDCS) device subject. According to some embodiments, the electric current stimulation unit includes a transcranial alternate current stimulation (tACS) device.

[0023] Certain embodiments of the present disclosure may include some, all, or none of the above advantages. One or more technical advantages may be readily apparent to those skilled in the art from the figures, descriptions and claims included herein. Moreover, while specific advantages have been enumerated above, various embodiments may include all, some or none of the enumerated advantages.

[0024] In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the figures and by study of the following detailed descriptions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] Examples illustrative of embodiments are described below with reference to figures attached hereto. In the figures, identical structures, elements or parts that appear in more than one figure are generally labeled with a same numeral in all the figures in which they appear. Alternatively, elements or parts that appear in more than one figure may be labeled with different numerals in the different figures in which they appear. Dimensions of components and features shown in the figures are generally chosen for convenience and clarity of presentation and are not necessarily shown in scale. The figures are listed below.

[0026] FIG. **1** schematically illustrates a setting of treating chronic pain, according to some embodiments;

[0027] FIG. **2***a* schematically illustrates a repetitive evaluation process, according to some embodiments;

[0028] FIG. **2***b* schematically illustrates a singular evaluation process, according to some embodiments;

[0029] FIG. **3** schematically illustrates a session of evaluation and treatment, according to some embodiments;

[0030] FIG. **4** schematically illustrates an EEG response to a stimulation burst in a healthy brain, according to some embodiments;

[0031] FIG. **5** schematically illustrates a diagnostic stimulation intensity operation range, according to some embodiments;

[0032] FIG. **6** schematically illustrates a method for establishing a motor threshold value for evaluation, according to some embodiments;

[0033] FIG. **7** schematically illustrates a method for providing diagnostic stimulated EEG response bursts, according to some embodiments;

[0034] FIG. **8** schematically illustrates a high-level method for treating chronic pain, according to some embodiments;

[0035] FIG. **9** schematically illustrates a subjective method for treating chronic pain, according to some embodiments;

[0036] FIG. **10** schematically illustrates an iterative method for treating chronic pain, according to some embodiments;

[0037] FIG. **11** schematically illustrates a method for treating chronic pain with tCS stimulation, according to some embodiments;

[0038] FIG. **12** schematically illustrates tDCS sessions, according to some embodiments; and

[0039] FIG. **13** schematically illustrates a method for treating chronic pain with tDCS stimulation, according to some embodiments.

DETAILED DESCRIPTION

[0040] In the following description, various aspects of the disclosure will be described. For the purpose of explanation, specific configurations and details are set forth in order to provide a thorough understanding of the different aspects of the disclosure. However, it will also be apparent to one skilled in the art that the disclosure may be practiced without

specific details being presented herein. Furthermore, well-known features may be omitted or simplified in order not to obscure the disclosure.

[0041] Chronic pain has been found associated with affecting the brain structure and function, which are expressed in abnormal anatomical and functional connectivity in various brain regions/areas related to the processing of pain, in addition to causing grey matter loss. These changes in the brain are explained by a neurological/neuro-structural property called neuroplasticity.

[0042] Neuroplasticity is manifested in two directions of neural behavior: potentiation, which is when a neural response is increased over time (training) by parts producing strengthening of neuronal connection, or depression, which is when a neural response is decreased over time by parts producing weakening of neuronal connections.

[0043] Neuroplasticity can be expressed in both synaptic-neuroplasticity and structural neuroplasticity, and in both, the constructive and destructive directions: synaptic potentiation, synaptic depression, structural potentiation and structural depression.

[0044] In synaptic potentiation, the activity of the synapse is increased such that for an action potential, more neurotransmitters are released from the axon terminal into the synapses, or the change may occur in the post synaptic membrane in that the number of neuro-transmitter receptors may increase, or changes to the types of the neurotransmitter receptors, or change in the responses that occur in the second messenger such that the sensitivity to neurotransmitters increases and an increased response per action potential is observed.

[0045] On the other hand, synaptic depression can be manifested by a decrease in the neurotransmitter release per action potential, or the number of the receptors is decreased and/or the type of the receptors is changed or changes to second messengers and a decreased response is observed per action potential.

[0046] In structural potentiation, the amount, length and strength of dendritic branches and amount and structure of axon terminal forming synapses increases, and the connection between the neurons becomes stronger.

[0047] In structural depression, the amount, length and strength of dendritic branches and amount and structure of axon terminal forming synapses increases, and the connection between neurons becomes weaker.

[0048] In a normal brain, neuroplasticity comes into effect in that activating a link/connection between neurons commonly promotes potentiation, and the more a connection between neurons is activated, the more the link becomes stronger. On the other hand, not utilizing a link between neurons commonly results in a weakening of the link between the neurons.

[0049] In people suffering from chronic pain, the neural structure and the behavior of the neural activity in some pain related brain regions is affected. Therefore, according to some embodiments, the affected brain regions may be detected by measuring a neural activity response to a diagnostic stimulation, and a treatment stimulation may be applied for stimulating and/or inhibiting the neural activity in the affected brain regions for reducing the chronic pain.

[0050] According to some embodiments, the affected brain region may include the motor cortex and/or the primary somatosensory cortex (which are stimulated usually by 10/20 electrode positioning of C3, C4, Cz and possibly C5, C6, Cp1, Cp2 corresponding to painful area and or prefrontal cortex (electrodes Fp1, Fp2, F3, F4) and possibly insular cortex (electrodes C5, C6).

[0051] According to some embodiments, the neuroplasticity and/or excitability of the neuro structures in the specific brain regions may be evaluated by providing a diagnostic stimulation to the specific brain regions, and measuring the neural activity response of the neural structures in the targeted brain regions. According to some embodiments, a healthy neuroplasticity may be indicated by a change in the neural activity response over stimulations.

[0052] According to some embodiments, after evaluating the neuroplasticity and/or excitability of the neuro structures in the targeted brain region(s), a stimulation treatment to the brain region(s) may be provided. Such a stimulation treatment may affect the neuroplasticity and/or excitability of the neuro-structures, thereby providing a treatment to the chronic pain.

[0053] As used herein, the term "stimulation" refers to an intervention to the normal behavior/activity of the neurons/neuro-structures, and may be used for either inhibiting or stimulating a neural activity.

[0054] According to some embodiments, the stimulation is an electric stimulation. According to some embodiments, the stimulation is an electrically induced electric stimulation. According to some embodiments, the stimulation is a magnetically induced electric stimulation. According to some embodiments, the stimulation is a Transcranial-Magnetic-stimulation.

[0055] According to some embodiments, the stimulation includes inducing a magnetic flux/field to the brain or portions thereof. According to some embodiments, the magnetic stimulation may include a Transcranial-Magnetic-stimulation (TMS). According to some embodiments, the stimulation may include multiple TMS magnetic pulses at determined intensities. According to some embodiments, the TMS intensity may refer to the flux of the induced magnetic field. According to some embodiments, the TMS intensity may be measured/presented in Tesla units. According to some embodiments, the TMS intensity may be measured/presented as a percentage of a reference value.

[0056] According to some embodiments, measuring the reactive activity may be facilitated by measuring an electric/electromagnetic activity of neural structures in the brain. According to some embodiments, measuring the reactive activity may be facilitated by utilizing at least one electrode, configured to measure variations of electric/electromagnetic fields indicative of an activity of specific neural networks in the brain. According to some embodiments, measuring the reactive activity may be facilitated by utilizing an EEG device/system.

[0057] Reference is now made to FIG. **1**, which schematically illustrates a setting **100** of treating chronic pain of a subject **152** by a care provider **150**, according to some embodiments. As illustrated, care provider **150** places an evaluation stimulating device, such as but not restricted to TMS-inducer **102**, at a certain position on/near the head of subject **152** for inducing stimulation to a target brain region thereof. TMS-inducer **102** is provided with control signals and electric energy from a controller, such as a TMS-controller **112**. TMS-controller **112** is configurable for enabling a controllable stimulation by TMS-unit **112**. According to some embodiments, a controllable stimulation

may include control over the intensity, duration, frequency, flux and/or other stimulation-related parameters and patterns of stimulation.

[0058] At least some brain activity sensors, such as EEG-electrodes **104**, are placed on the head of subject **152**, and configured to measure neural activity of the brain of subject **152** or defined areas thereof for assessing a neural activity response to the diagnostic stimulation. According to some embodiments, EEG-electrodes **104** are in communicational link with an analyzer/controller, such as an EEG-analyzer **114**, configured to obtain EEG signals from EEG-electrodes **104**.

[0059] According to some embodiments, EEG-analyzer **114**, or other processing circuitry (such as remote servers, a cloud computing service, a local computer, distributed computers, and the like), is configured to analyze the obtained EEG signals and detect reactive activity associated with induced electrical stimulation, such as TMS diagnostic stimulations induced by TMS-inducer **102**. According to some embodiments, EEG-analyzer **114** is configured to facilitate evaluation of neuroplasticity and/or excitability of the targeted brain regions of subject **152** (or neural structures thereof) by measuring the intensities of the reactive activity, for example, by comparing the intensities with model/reference activities expected assuming various conditions and/or lack thereof. According to some embodiments, EEG-analyzer **114** is configured to detect neuroplasticity and/or excitability of the targeted brain regions of subject **152** (or neural structures thereof) by measuring the intensities of the reactive activity and comparing the ratios or differences between various pairs therefrom, and comparing the intensities with model/reference activities expected assuming various conditions and/or lack thereof.

[0060] According to some embodiments, EEG-analyzer **114** is configured to analyze the EEG signals relying on their amplitudes, slopes, frequencies, delays, area under curve and the like. According to some embodiments, EEG-analyzer **114** is configured to perform a frequency analysis of the EEG signals. According to some embodiments, EEG-analyzer **114** is configured to perform noise reduction filtration on the EEG-signals. According to some embodiments, EEG-analyzer **114** is configured to perform noise cancelation filtration on the EEG-signals. According to some embodiments, EEG-analyzer **114** is configured to perform a temporal analysis of the EEG signals.

[0061] According to some embodiments, a treatment stimulation mechanism is provided, such as transcranial current stimulation (tCS) device **120**, which is configured to provide treatment brain stimulation to the target brain regions by driving an electric signal through a cathode **122** and an anode **124** placed on subject **152** at desired positions for inducing stimulation to the target brain regions.

[0062] According to some embodiments, a Neuronal stimulator, such as, TMS-unit **102** is configured to induce multiple stimuli pulses. According to some embodiments, the multiple stimuli pulses are substantively equal in intensity. According to some embodiments, the multiple stimuli pulses are substantively equal in duration. According to some embodiments, the multiple stimuli pulses are substantively similar in slopes. According to some embodiments, the multiple stimuli differ in intensity, duration, and/or slopes.

[0063] According to some embodiments, Transcranial current stimulation device **120** is a transcranial direct current stimulation device (tDCS). According to some embodiments, Transcranial current stimulation device **120** is a transcranial alternate current stimulation device (tACS).

[0064] According to some embodiments, the tACS is performed by inducing an alternating current at a frequency in the range of 1-120 Hz at current density of up to 5 A/m^2 to be matched with a desired oscillatory behavior needed, for example to induce 8-12 Hz activity, a 10 Hz tACS frequency will be administered.

[0065] Unbalanced plasticity between relevant cortical brain regions (such as but not limited to the "pain matrix") will indicate chronic pain related changes, as well as plasticity shifts between visual and motor/sensory areas. Plasticity shifts in the prefrontal areas may also be associated with chronic pain.

[0066] According to some embodiments, treatment stimulation is configured to balance the plasticity between motor and/or sensory hemisphere. According to some embodiments, for short term plasticity changes, anodal stimulation may be applied in high plasticity areas to decrease the plasticity, and cathodal stimulation may be applied in low plasticity areas to increase local plasticity, for creating a balanced plasticity.

[0067] According to some embodiments, determination of pain related brain areas may be done by, measuring plasticity changes in pain related brain areas, and source localization of entire EEG data which determines the source brain region of EEG behavior. According to some embodiments, after establishing the brain areas to be treated, stimulation electrode positioning may be placed directly on these areas with supporting electrodes in contralateral and distant areas. The electrode locations may be calculated and optimized by electric flow modeling of a human average head with designated brain areas to be affected.

[0068] For example:

[0069] For right hand pain area to subject displaying high plasticity in left motor area and in left prefrontal area, a possible treatment electrode configuration may include anodal stimulation in C3 and Cp5 position, cathodal stimulation in C4 and Cp6 and anodal stimulation to Fp1 position. This treatment may decrease plasticity post stimulation in left motor area and increase plasticity in the contralateral area, while decreasing plasticity in left prefrontal area.

[0070] For left leg pain area to subject displaying low plasticity in right motor area and high plasticity in left prefrontal area, a possible treatment electrode configuration may include cathodal stimulation in C4 and Cp6 position, anodal stimulation in C3 and Cp5 and anodal stimulation to Fp1 position, for example. This treatment may increase plasticity post stimulation in right motor area and decrease plasticity in the contralateral area, while decreasing plasticity in left prefrontal area.

[0071] According to some embodiments, the devices, systems and/or methods may be used for assessing the progress and/or state of a chronic pain patient. According to some embodiments, the devices, systems and/or methods may be used for measuring a stage/severity of neural changed caused by chronic pain. According to some embodiments, the devices, systems and/or methods may be used for detecting and/or assessing neural network abnormalities.

[0072] According to some embodiments, evaluating the neuroplasticity of target brain regions may be done by providing stimulation to the target brain region and measuring the reactive neural activity of that region. According to

some embodiments, evaluating the neuroplasticity of target brain regions may be done by iteratively providing stimulation to the target brain region, measuring the reactive neural activity of that region, and assessing the changes in reactive neural activity between different iterations.

[0073] Reference is now made to FIG. **2***a*, which schematically illustrates a repetitive evaluation process **200**, according to some embodiments. According to some embodiments, evaluation process **200** may include multiple diagnostic stimulation events, such as diagnostic stimuli pulses **220**, configured to induce stimulation ,evoked by a diagnostic stimulation device, such as a TMS, at determined times and intensities. According to some embodiments, evaluation process **200** further includes sensing brain activity of the user, for example using EEG-monitoring **230** for measuring the response activity to stimuli pulses **220**. According to some embodiments, EEG-monitoring **230** may be continuous throughout the period of stimulation burst **220**. According to some embodiments, EEG monitoring **230** may be intermittent.

[0074] According to some embodiments, stimuli pulses **220** comprise a first stimulus pulse **222***a* followed by a first pulse delay interval **232***a*, a second stimulus pulse **222***b* followed by a second pulse delay interval **232***b*, a third stimulus pulse **222***c* followed by a third pulse delay interval **232***c*, a fourth stimulus pulse **222***d* followed by a fourth pulse delay interval **232***d* and a fifth stimulus pulse **222***e* followed by a fifth pulse delay interval **232***e*.

[0075] According to some embodiments, pulse delay intervals **232***a*, **232***b*, **232***c*, **232***d*, **232***e* are configured to enable distinguishing between EEG recording/monitoring of reaction activity associated with each of stimulus pulse **222***a*, **222***b*, **222***c*, **222***d*, **222***e*.

[0076] According to some embodiments, stimulus pulses **222***a*, **222***b*, **222***c*, **222***d*, **222***e* may be substantively equal in intensity. According to some embodiments, stimulus pulses **222***a*, **222***b*, **222***c*, **222***d*, **222***e* may vary in intensity.

[0077] According to some embodiments, stimulus pulses **222***a*, **222***b*, **222***c*, **222***d*, **222***e* may be substantively equal in duration. According to some embodiments, stimulus pulses **222***a*, **222***b*, **222***c*, **222***d*, **222***e* may vary in duration.

[0078] According to some embodiments, pulse delay intervals **232***a*, **232***b*, **232***c*, **232***d*, **232***e* may be substantively equal in duration. According to some embodiments, pulse delay intervals **232***a*, **232***b*, **232***c*, **232***d*, **232***e* may vary in duration.

[0079] Reference is now made to FIG. **2***b*, which schematically illustrates a singular evaluation process **201**, according to some embodiments. According to some embodiments, an evaluation of the neuroplasticity of the target brain region may be enabled by a non-iterative stimulation event **221** and monitoring of a neural reactive response thereto, for example by EEG-monitoring **233**.

[0080] According to some embodiments, the duration of a pulse is in the range of 0.5 ms to 2 ms. According to some embodiments, the duration of a pulse is in the range of 1 ms to 1.5 ms. According to some embodiments, the duration of a pulse is approximately 1 ms.

[0081] According to some embodiments, the delay intervals are in the range of 100 ms to 2 s. According to some embodiments, the delay intervals are in the range of 250 ms to 1 s. According to some embodiments, the delay intervals are approximately of 500 ms. According to some embodiments, the pulse frequency within a burst is in the range of 0.1 Hz to 10 Hz. According to some embodiments, the pulse frequency within a burst is in the range of 1 Hz to 5 Hz. According to some embodiments, the pulse frequency is approximately 2 Hz.

[0082] According to some embodiments, the reaction activity of the neural network in the brain is expected to vary between consecutive stimulus pulses. This may be attributed to the neuro-structural characters of plasticity and excitability. As a result, the reaction activity associated with the second stimuli pulse may be considerably higher than the reaction activity associated with the first stimuli pulse. Additionally, in later stimulus pulses, a gradual decrease in the reaction activity may be expected.

[0083] The amount/ratio of increased and/or decreased activity may be indicative of the characteristics of the neuronal network (neural structures), such as plasticity and excitation and inhibition. Consequently, one may detect irregularities in these characteristics and associate them with various conditions that may lead to changes in these characteristics.

[0084] According to some embodiments, a stimulation burst may include 1 or more stimuli pulses. According to some embodiments, a stimulation burst may include 2 or more stimuli pulses. According to some embodiments, a stimulation burst may include 3 or more stimuli pulses. According to some embodiments, a stimulation burst may include 4 or more stimuli pulses. According to some embodiments, a stimulation burst may include 5 or more stimuli pulses. According to some embodiments, a stimulation burst may include 2 to 10 stimuli pulses. According to some embodiments, a stimulation burst may include 10 or more stimuli pulses.

[0085] According to some embodiments, a session of evaluation and treatment is provided by performing evaluation (assessment of neuroplasticity) and providing treatment stimulation. According to some embodiments, an efficiency of a treatment may be evaluated by performing another evaluation (assessment of neuroplasticity), and based on the effectiveness assessment, another treatment session may be provided. According to some embodiments, parameters and characteristics of the second and following treatment sessions may be determined based on the assessed effectiveness of the first treatment.

[0086] Reference is now made to FIG. **3**, which schematically illustrates a session **300** of evaluation and treatment, according to some embodiments. According to some embodiments, the subject may undergo a first round of treatment **310**, where he is asked to provide a score indicating a level of pain they feel and record a pre-treatment-pain **324***a* score, then the pre-treatment plasticity of certain brain regions may be evaluated **328***a* for determining a treatment, and a treatment stimulation **332***a* may be provided. Afterwards, the subject may be asked to provide a post treatment pain score **326***a*, and a post treatment plasticity is evaluated **329***a* to assess the first treatment efficacy.

[0087] According to some embodiments, the subject may then, after a period of time, undergo a second round of treatment **312**, in which he is asked again to provide a score indicating a level of pain they feel and record a second pre-treatment-pain **324***b* score, then the plasticity of certain brain regions may be evaluated **328***b* for determining a treatment and progress compared to first round of treatment **310**, and a second treatment stimulation **332***b* may be provided. Afterwards, the subject may be asked to provide a

second post-treatment pain-score **326***b*, and a post treatment plasticity is evaluated **329***b* to assess the second treatment efficacy.

[0088] According to some embodiments, a stimulation session may include 2 or more evaluation periods. According to some embodiments, a stimulation session may include 3 or more evaluation periods. According to some embodiments, a stimulation session may include 5 to 10 evaluation periods. According to some embodiments, a stimulation session may include 10 or more evaluation periods.

[0089] According to some embodiments, an evaluation period may be essentially as described in FIG. **2***a* or FIG. **2***b*.

[0090] For assessing the plasticity and/or excitability of the predetermined brain region(s), TMS stimulation may be applied and the neural activity reaction may be monitored and analyzed. According to some embodiments, some parameters, characteristics and/or features that may be considered for assessing the neuroplasticity characteristics may include one or more of the following: amplitudes, slopes, frequencies, delays, area under curve and the ratios between. According to some embodiments, these parameters may be in response to stimulation pulses, or with association thereto. Reference is now made to FIG. **4**, which schematically illustrates an EEG response activity to a stimulation burst in a normal brain, according to some embodiments. As illustrated, the stimulation burst includes four stimulation pulses; the EEG recording thereof is illustrated in a first pulse recording **406***a*, a second pulse recording **406***b*, a third pulse recording **406***c* and a fourth pulse recording **406***d*. Following each pulse recording, there is a response recording, namely a first response recording **408***a*, a second response recording **408***b*, a third response recording **408***c* and a fourth response recording **408***d*. As illustrated, second response recording **408***b* and third response recording **408***c* are greater than first response recording **408***a*, which may be attributed to the excitability or plasticity characteristics of the relevant neural network, while forth response recording **408***d* is considerably reduced compared to the rest of the responses recorded, which may be attributed to the adaptation characteristics of the relevant neural network.

[0091] According to some embodiments, responses that vary from the normal response or a normal response range may indicate various abnormal neural network characteristics.

[0092] According to some embodiments, the intensity of pulses is determined as a percentage of a reference value. According to some embodiments, the reference value is determined as a percentage from the personal determined motor-threshold value.

[0093] According to some embodiments, a motor threshold is a stimulation intensity at which a motoric reaction may be triggered and/or detected as a consequence thereto.

[0094] According to some embodiments, a motor threshold value is established by increasingly incrementing stimulation intensity, until a motoric reaction is detected. According to some embodiments, the motoric threshold may vary from one person to another. According to some embodiments, using a TMS stimulator to induce focal electrical stimulation in the brain, the motor threshold value may be in the range of 1.5 to 2.5 Tesla. According to some embodiments, the motor threshold value may be in the range of 1.7 to 2.3 Tesla. According to some embodiments, the motor threshold value may be in the range of 1.8 to 2.2 Tesla. According to some embodiments, the motor threshold value may be in the range of 1.9 to 2.1 Tesla. According to some embodiments, the motor threshold value may be in the range of 48% to 52% of the maximal TMS device intensity. According to some embodiments, the motor threshold value may be approximately 50% of the maximal TMS device intensity.

[0095] Once a motor threshold value is established for a certain person, one may evaluate/calculate an "operational range", which is a range of intensity values in which a reaction activity may be observed and activity corresponds to the intensity of the stimuli.

[0096] According to some embodiments, the term "operational range" may be interchangeable with the terms "relevant range" or "active range".

[0097] According to some embodiments, an "operational range" ranges from 60% to 140% of the motor threshold. According to some embodiments, an "operational range" ranges from 80% to 120% of the motor threshold. According to some embodiments, an "operational range" ranges from 50% to 150% of the motor threshold.

[0098] According to some embodiments, the intensity of the stimuli pulses may be a value within the "operational range". According to some embodiments, the intensity of the stimuli pulses may be referred to as an "operational point".

[0099] Reference is now made to FIG. **5**, which schematically illustrates a stimulation intensity operational range, according to some embodiments. As illustrated, the EEG response to low stimulation intensities is relatively unchanged, until the stimulation intensity surpasses a certain value (lower threshold), then the EEG response reacts/increases as the stimulation intensity increases, until the stimulation intensity reaches another value (upper threshold) in which the EEG response no longer responds to increases in the stimulation intensity.

[0100] According to some embodiments, the operational range is a range of intensity values between the lower threshold and the upper threshold.

[0101] Reference is now made to FIG. **6**, which schematically illustrates a method **600** for establishing a motor threshold value, according to some embodiments. According to some embodiments, the TMS device/unit is positioned (step **606**) in a determined position on/near the head of the subject, then a magnetic stimulation pulse is induced (step **608**), then the mechanical response is monitored (step **610**) for detecting triggered motoric movement. According to some embodiments, if a motoric movement is detected, and a motor threshold established (step **612**), the motor threshold value is provided (step **616**), otherwise, the pulse intensity is changed (step **614**) and we iterate the steps from inducing the magnetic stimulation pulse (step **608**).

[0102] According to some embodiments, changes to the pulse intensity (step **614**) include increasing the pulse intensity.

[0103] Reference is now made to FIG. **7**, which schematically illustrates a method **700** for providing a stimulated EEG response session, according to some embodiments. According to some embodiments, an EEG cap is placed on the head of a subject (step **704**), then a TMS device is positioned on/near the head of the subject (step **706**), then a motor threshold ("MT") is established (step **708**), then a magnetic stimulation pulse is induced (step **710**) having an intensity of X % of the established MT. According to some embodiments, the X % is a predetermined percentage of the MT. According to an operational range/value based on the

motor threshold, then the EEG response activity is monitored, (step **712**), then optionally steps **710** and **712** are repeated as the stimulation amplitude is elevated by a predetermined percentage up to a certain level, for example 20% up to 150%, (step **714**) with a "pulse-wait" delay between iterations (step **716**), and the response activity is analyzed (step **722**).

[0104] Reference is now made to FIG. **8**, which schematically illustrates a high-level method **800** for treating chronic pain, according to some embodiments. According to some embodiments, method **800** begins by an evaluation of the plasticity of pain-related brain regions (step **802**), then a treatment by stimulation based on the evaluated plasticity of the brain regions (step **804**) then an evaluation for the treatment efficacy (step **806**), for example by measuring the plasticity once again.

[0105] According to some embodiments, the subjects may be asked to evaluate the pain level they are feeling, and the efficacy of the treatment may be measured by the changes in the pain levels the subject is experiencing.

[0106] Reference is now made to FIG. **9**, which schematically illustrates a method **900** for treating chronic pain, according to some embodiments. According to some embodiments, method **900** begins with obtaining pain levels that the subject is suffering/feeling before the treatment (step **902**), then evaluate the neuroplasticity of pain related brain regions (step **904**), then a stimulation treatment is provided to the pain related brain regions (step **906**), and the pain levels that the user feels after the treatment may be obtained (step **908**) to check whether the treatment was successful.

[0107] Reference is now made to FIG. **10**, which schematically illustrates a method **1000** for iterative evaluation and treatment, according to some embodiments. According to some embodiments, method **1000** begins by providing a diagnostic/examinatorial stimulation to a predetermined brain region (step **1002**) associated with pain, then measuring neural activity response to the diagnostic/examinatorial stimulation (step **1004**), and if more diagnosis/evaluation iterations are required (step **1006**), go back to providing a diagnostic/examinatorial stimulation to a predetermined brain region (step **1002**), otherwise, proceed by evaluating the neuroplasticity and determine stimulation parameters accordingly (step **1008**) and provide a treatment stimulation and evaluate the efficacy thereof (step **1010**), then if more treatments may be required (step **1012**), go back to providing a diagnostic/examinatorial stimulation to a predetermined brain region (step **1002**), otherwise, end treatment session(step **1014**).

[0108] Reference is now made to FIG. **11**, which schematically illustrates a method **1100** for treating chronic pain with tCS stimulation, according to some embodiments. According to some embodiments, the brain activity is monitored by an EEG system (step **1102**), then the brain is stimulated using a TMS machine (step **1104**) and the neural reaction response is analyzed for finding the location of the brain regions based on the EEG electrode positions (step **1106**), and the neuroplasticity and excitability of the brain regions is evaluated (step **1108**), based on the neuroplasticity and the brain region locations, a tDCS/tACS treatment stimulation is configured with characteristics and montage (electrode placements) (step **1110**) for providing a personalized pain treatment stimulation.

[0109] Reference is now made to FIG. **12**, which schematically illustrates tDCS sessions **1200**, according to some embodiments. According to some embodiments, various tDCS parameters may be determined based on the stimulation need, for example strong-anodal-stimulation **1202** may be configured to provide a ramp-up from 0 mA to 2 mA, and drive 2 mA current for 20 minutes and end the stimulation. According to some embodiments, a weak-anodal-stimulation **1204** may be configured to provide a ramp-up from 0 mA to 1 mA, and drive 1 mA current for 10 minutes and then end stimulation. According to some embodiments, strong-kathodal-stimulation **1206** may be configured to provide a ramp-up from 0 mA to −2 mA, and drive −2 mA current for 20 minutes. According to some embodiments, the duration, current value and current direction may be configurable.

[0110] According to some embodiments, anodal stimulation may stimulate the neural activity of a brain region, while a cathodal stimulation may inhibit the activity of the brain region, depending on the electrode locations. According to some embodiments, the electrode polarity is selected (anodal/cathodal/alternate), an electrode montage (number of cathodes and anodes), and location, for example over M1 or S1 or Dorsolateral prefrontal cortex (DLPFC) brain regions, all corresponding to painful area.

[0111] Reference is now made to FIG. **13**, which schematically illustrates a method **1300** for treating chronic pain with tDCS stimulation, according to some embodiments. According to some embodiments, method **1300** begins with stimulating pain-related brain regions (step **1302**), and measuring the neural activity response (step **1304**) to evaluate the plasticity and excitability of the brain regions (step **1306**), then determining tDCS electrode location per brain region (step **1308**), determine stimulation polarity per brain region (step **1310**) and determine stimulation intensity and duration (step **1312**), and provide the direct current stimulation according to the above determined parameters (step **1314**), then assess the efficacy of the treatment (step **1316**), and decide whether more treatment sessions are required (step **1318**). If more sessions are requires, we go back to stimulating the brain regions (step **1302**), if not, we end the treatment (step **1320**).

[0112] According to some embodiments, the parameters/characteristics of a stimulation session may be determined, taking into consideration previous sessions and the efficacy thereof.

[0113] According to some embodiments, a stimulation threshold value is established. According to some embodiments, a stimulation threshold value is a TMS stimulation intensity value, above-which reactive neural activity may be observed/detected.

[0114] According to some embodiments, the TMS stimulation intensity is a "supra-threshold", selected to be of a higher intensity than the stimulation threshold.

[0115] According to some embodiments, the TMS stimulation intensity is a "sub-threshold", selected to be of a lower intensity than the stimulation threshold.

[0116] According to some embodiments, the analysis is conducted after the stimulation session. According to some embodiments, the analysis is conducted during the stimulation session.

[0117] As used herein, the terms "neuron", "neuro-structure", "neural network" may be interchangeable.

[0118] As used herein, the term "TMS" may refer to Transcranial magnetic stimulation, which is a non-invasive method used to stimulate regions of the brain. In TMS, a magnetic field generator, such as a coil or an electromagnet,

is placed near/on the head of the subject receiving the stimulation, an electric current is conducted through the coil and a magnetic flux gradient is induced as a result of the change in current through the coil. According to some embodiments, the coil (or electromagnet coil) is connected to a pulse generator, or controller, or stimulator configured to deliver electric current to the coil.

[0119] As used herein, the terms "tCS", "tDCS" and "tACS" refer to a brain stimulation technique in which electric current is driven though the crania of the user to reach and stimulate a desired region, and the electric current is provided to the crania using at least two electrodes placed at defined places such that driving a current signal via the electrodes through the crania may reach the desired brain region.

[0120] As used herein, the term "EEG" may refer to Electroencephalography, which is typically a non-invasive method for recording electrical activity of the brain along the scalp. An EEG measures voltage fluctuation resulting from ionic current within the neurons/neuro-structures of the brain. According to some embodiments, an EEG may refer to the recording of the brain's spontaneous and/or stimulated electrical activity over a period of time.

[0121] As used herein, the term "plasticity" may refer to neuroplasticity or brain plasticity which may encompass synaptic and/or non-synaptic plasticity, and may refer to changes in neural pathways and synapses and/or structure due to changes in behavior, environment, neural processes, thinking, emotions, injuries and stimulation.

[0122] As used herein, the terms "examinatorial" and "diagnostic" stimulation may be interchangeably used and refer to stimulation(s) that are intended to examine a neural behavior and/or diagnosing a cognitive condition.

[0123] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements, or components, but do not preclude or rule out the presence or addition of one or more other features, integers, steps, operations, elements, components, or groups thereof.

[0124] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced be interpreted to include all such modifications, additions and sub-combinations as are within their true spirit and scope.

1. A method for treating chronic pain of a subject, the method comprising:

inducing a diagnostic stimulation to a predetermined brain region of the subject;

measuring a neural activity response to the diagnostic stimulation;

evaluating a neuroplasticity and/or excitability of neural-structures in the predetermined brain regions based on the neural activity response to the diagnostic stimulation; and

inducing a treatment stimulation to the predetermined brain region based on the evaluated neuroplasticity of the neural structures in the predetermined brain region.

2. The method of claim **1**, wherein the chronic pain is a neuropathic pain.

3. The method of claim **1**, wherein the predetermined brain region is selected from a group comprising: primary motor cortex and primary somatosensory cortex, prefrontal cortex and insular cortex.

4. The method of claim **1**, wherein inducing a diagnostic stimulation to a predetermined brain region of the subject comprises utilizing transcranial magnetic stimulation (TMS).

5. The method of claim **1**, wherein inducing a diagnostic stimulation to a predetermined brain region of the subject comprises providing the subject with a cognitive/behavioral task configured to induce stimulation to the predetermined brain region.

6. The method of claim **1**, wherein measuring a neural activity response to the diagnostic stimulation comprises obtaining electroencephalogram (EEG) measurements indicative of a neural activity of the brain of the user during and/or after inducing the diagnostic stimulation.

7. The method of claim **6**, wherein inducing a treatment stimulation to the predetermined brain region comprises electric brain stimulation.

8. The method of claim **7**, wherein the inducing electric brain stimulation comprises placing a first electrode and a second electrode on the subject, such that an electric signal passing through the user via the first electrode and the second electrode reaches a predetermined brain region.

9. The method of claim **7**, further comprising evaluating specific brain areas for plasticity changes by dipole fitting the EEG measurements and performing a source modeling for detecting the location (source localized areas) of the specific areas and providing treatment stimulation to the source localized areas.

10. The method of claim **7**, wherein the electric brain stimulation comprises transcranial direct current stimulation (tDCS), or transcranial alternating current stimulation (tACS).

11. The method of claim **10**, wherein the tDCS utilizes a current density of no more than 5 A/m2, and has a duration of no more than 30 minutes.

12. The method of claim **10**, wherein the tDCS stimulation is selected to be either Anodal stimulation or Cathodal stimulation for a brain region based on the evaluated neuroplasticity and/or excitability of neural-structures in the predetermined brain regions.

13. (canceled)

14. The method of claim **10**, wherein the tACS is performed by inducing an alternating current at a frequency in the range of 1-120 Hz at current density of 5 A/m2 to be matched with a desired oscillatory behavior needed.

15. (canceled)

16. (canceled)

17. The method of claim **1**, further comprising:

inducing a post-treatment diagnostic stimulation to the predetermined brain region of the subject;

measuring a neural activity response to the post-treatment diagnostic stimulation;

evaluating a post-treatment neuroplasticity and/or excitability of neural- structures in the predetermined brain regions based on the neural activity response to the post-treatment diagnostic stimulation; and

inducing a treatment stimulation to the predetermined brain region based on the evaluated post-treatment neuroplasticity of the neural structures in the predetermined brain region.

18. A system for treating chronic pain of a subject, the system comprising:

a directed inspective/diagnostic stimulation unit, configured to induce a diagnostic stimulation to a predetermined brain region of the subject;

a brain activity sensor, configured to measure a neural activity response to the diagnostic stimulation induced by said directed brain stimulation unit;

a processing circuitry in communication with said brain activity sensor, said processing circuitry is configured to evaluate a neuroplasticity and/or excitability of neural-structures in the predetermined brain region based on the neural activity response to the diagnostic stimulation; and an electric current stimulation unit comprising a first electrode and a second electrode, said electric current stimulation unit is configured to induce a treatment stimulation to the predetermined brain region based on the evaluated neuroplasticity of the neural structures in the predetermined brain region, by driving a current signal through the user via the first electrode and the second electrode such that the current reaches the predetermined brain region.

19. The system of claim **18**, wherein said directed inspective stimulation unit comprises a transcranial magnetic stimulation (TMS) unit.

20. The system of claim **18**, wherein said brain activity sensor comprises an electroencephalography (EEG) device.

21. The system of claim **20**, wherein said processing circuitry is configured to obtain an EEG signal from said EEG device and evaluate a neuroplasticity and/or excitability of neural-structures in the predetermined brain region by comparing the neural activity response to the diagnostic stimulation with previously obtained neural activity response to previous diagnostic stimulation.

22. The system of claim **20**, wherein said processing circuitry is further configured to estimate locations of the predetermined brain regions based on the obtained EEG signal.

23. The system of claim **18**, wherein said electric current stimulation unit comprises a transcranial direct current stimulation (tDCS) device subject or a transcranial alternate current stimulation (tACS) device.

24. (canceled)

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专利名称(译)	慢性疼痛的诊断和治疗		
公开(公告)号	US20180008827A1	公开(公告)日	2018-01-11
申请号	US15/547505	申请日	2016-02-03
申请(专利权)人(译)	NIBS神经科学TECHNOLOGIES LTD.		
当前申请(专利权)人(译)	NIBS神经科学TECHNOLOGIES LTD.		
[标]发明人	DOLEV IFTACH FOGEL HILLA		
发明人	DOLEV, IFTACH FOGEL, HILLA		
IPC分类号	A61N1/36 A61N1/04 A61B5/0484 A61B5/04 A61B5/05 A61N1/20 A61B5/00		
CPC分类号	A61N1/36021 A61B5/04001 A61B5/4836 A61B5/4824 A61B5/0484 A61N1/0456 A61N1/20 A61B5/05		
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摘要(译)

通过诱导对大脑的预定区域的刺激来治疗慢性疼痛的方法，系统和装置，并测量对刺激的神经活动反应并评估预定脑区域中神经结构的神经可塑性和/或兴奋性，然后刺激预定的脑区域治疗慢性疼痛。