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(71) Applicant: THE CLEVELAND CLINIC FOUNDATION [US/US]; 9500 Euclid Avenue, Mail Code Gcic-10, Cleveland, OH 44195 (US).

(72) Inventor: PAPAY, Francis A.; 30548 Royal Woods Place, Westlake, OH 44145 (US).

(74) Agent: SOLOMON, Steven J. et al.; TUCKER ELLIS LLP, 950 Main Street, Suite 1100, Cleveland, OH 44113-7213 (US).

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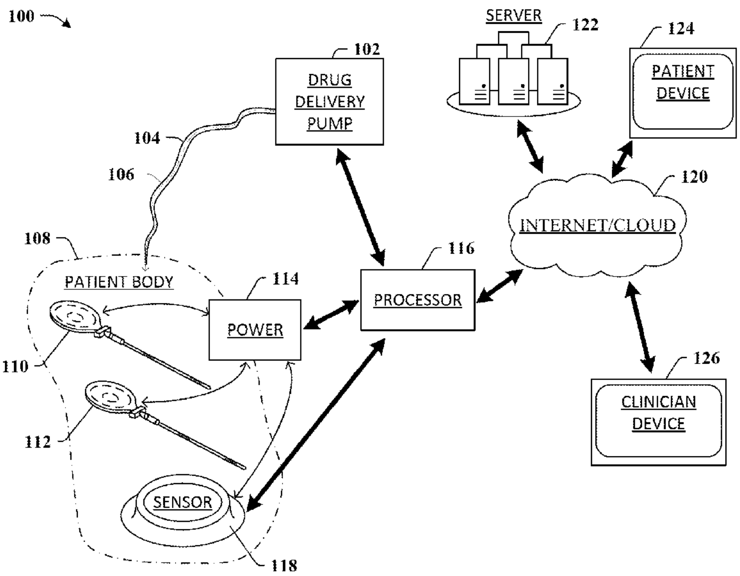

FIG. 1

(57) Abstract: A drug delivery system is provided and includes an electronic stimulation implant, a drug delivery pump, and a computing device coupled to the electronic stimulation implant and the drug delivery- pump. The electronic stimulation implant is configured to be implanted adjacent to a nerve and/or blood vessel of a subject. The computing device stores instructions that, when executed, causes one or more processors to activate the electronic stimulation implant to deliver stimulation energy to the nerve/blood vessel to modulate a blood brain barrier of the subject to increase its permeability. The processor activates, when instructed, the drug delivery pump to deliver a therapeutic agent to the subject via the blood brain barrier once its permeability has been suitably adjusted. The processor further can instruct the electronic stimulation implant to adjust or cease the first stimulation energy- once drug delivery- is complete to reduce the permeability' of the blood brain barrier.

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CLOSED-LOOP DRUG DELIVERY SYSTEM WITH BLOOD BRAIN BARRIER MODULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application Serial No. 63/600,257 filed November 17, 2023, the contents of which are incorporated by reference.

FIELD OF THE INVENTION

[0002] The present disclosure relates to a system and methods for timed modulation of the permeability of the blood brain barrier of a subject with the coordinated timing of the delivery of therapeutic agents to the central nervous system of the subject while the blood brain barrier is rendered more permeable. In addition, this system can be used to render the blood brain barrier less permeable through timed modulation to control (or inhibit) the amount of noxious autogenous intravascular and other inflammatory factors allowed into the brain parenchyma.

BACKGROUND

[0003] The blood brain barrier (BBB) is a selective, semipermeable membrane that lines the capillary blood vessels that supply the brain, and serves to inhibit the passage of potentially harmful molecules in the blood into the brain. The BBB represents a significant obstacle to the delivery of therapeutic agents to the central nervous system. As the size of a therapeutic molecule increases, modulating the BBB to be permeable enough to allow its passage becomes more difficult. For example, chemotherapy and other immune modulating agents can contain very large antibodies that can be more effective when delivered directly to the central nervous system, which requires that the BBB be rendered more permeable. Chemotherapy agents and other immunotherapies, particularly utilizing relatively large molecules, are often administered several times over a short period (e.g., every few hours or days). Such frequent and periodic modulation of the blood brain barrier (BBB) for effective drug delivery can be cumbersome.

BRIEF SUMMARY OF THE INVENTION

[0004] According to a first aspect, a drug delivery system includes an electronic stimulation implant, a drug delivery pump, and a computing device, which can include a timer, coupled to the electronic stimulation implant(s) and the drug delivery pump. The electronic stimulation implant is configured to be implanted adjacent to one or more nerve(s) and/or ganglion nerve bundle(s) of a subject to deliver stimulation energy to the nerve to modulate a blood brain barrier of the subject to control (increase and/or decrease) permeability of the blood brain barrier. The drug delivery pump is configurable to deliver (e.g. via intravascular, intrathecal, intraventricular, subdural, or directly) one or more therapeutic agent(s) to the subject through the blood brain barrier. The computing device comprises a non-transitory, computer-readable medium storing instructions that, when executed by one or more processors of the computing device, cause the one or more processors to: activate the electronic stimulation implant to deliver the stimulation energy to the nerve(s) or nerve ganglion bundle(s) for a first time period; activate the drug delivery pump to deliver the therapeutic agent to the subject via the blood brain barrier over a second time period; deactivate the drug delivery pump to stop delivery of the therapeutic agent to the subject; and deactivate the electronic stimulation implant to stop delivering the stimulation energy to the nerve or change the electrical characteristics of the stimulation energy to cause reversal (closure, less permeability) of the blood brain barrier.

[0005] According to a second aspect, a drug delivery method includes the step of applying stimulation energy to a nerve, nerve ganglion bundle and/or blood vessel of a subject. The stimulation energy may be electrical, ultrasonic, and/or electromagnetic energy. For example, low frequency energy may be applied to the nerve(s), and particularly to the craniofacial/skull based nerves, to stimulate the blood vessels of the blood brain barrier, thereby causing vasodilation to increase permeability of the blood brain barrier. Additionally or alternatively, high-frequency ultrasonic energy may be applied directly to a brain parenchymal blood vessel(s) to cause vasodilation to increase permeability of the blood brain barrier. The method further includes the steps of measuring a real-time parameter of the subject; determining that a blood brain barrier is permeable based on the real-time parameter meeting or exceeding a permeability threshold; operating a drug delivery pump to deliver a therapeutic agent; thereafter deactivating the drug delivery pump; and thereafter, stopping or changing the electrical characteristics of the application of the stimulation energy to lessen the permeability of the blood brain barrier. The stimulation energy is adapted to increase or decrease permeability of the blood brain barrier of the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIGURE 1 shows a schematic diagram of embodiments of a system for drug delivery through the blood brain barrier as described herein.

[0007] FIGURE 2 shows a flow diagram of an example method for drug delivery through the blood brain barrier as described herein.

[0008] FIGURE 3 illustrates an exemplary time-plot of electrical stimulatory frequency delivered by an electronic stimulation implant over time to permeate the blood brain barrier.

[0009] FIGURE 4 illustrates a schematic block diagram of an example system for drug delivery that includes several stimulation devices to stimulate blood vessels, ganglion nerve bundles and/or nerves to modulate permeability the blood brain barrier.

[0010] FIGURE 5 illustrates an exemplary plot of the frequencies delivered by two electronic stimulation implants or devices over time that together modulate the permeation of the blood brain barrier by the stimulation of different neural targets (e.g., Vagus Nerve, Sphenopalatine Ganglion).

DETAILED DESCRIPTION

[0011] The present disclosure relates to systems and methods to improve delivery of therapeutic agents past the blood brain barrier (BBB) and into the central nervous system of a patient. The system facilitates delivery of such agents across the BBB, but also is useful to control or minimize the passage of noxious inflammatory factors across the BBB in a permeable state and into the brain parenchyma to cause pathophysiologic changes. Electronic stimulation (e.g. with radiofrequency or electrical field energy) of skull base ganglia and nerves, such as the Sphenopalatine (Pterygopalatine) ganglion, the Trigeminal nerve, the Vagus nerve, and even more broadly, other nerve(s) in or communicating with the parasympathetic system of the cranial ganglia, can modulate the permeability of the BBB. Upon stimulation of such nerve(s), the BBB may become more or less permeable depending on the frequency or other characteristics of the stimulation energy, in order to allow therapeutic agents to enter the central nervous system from the bloodstream that otherwise would have been blocked, and disallow intravascular autogenous inflammatory cellular noxious factors to pass into the brain's neural tissues causing pathophysiologic changes.

[0012] It also has been shown that focal ultrasound stimulation of intracranial blood vessels also can impact the permeability of the BBB focally associated with those vessels, thereby increasing permeability to facilitate passage of larger molecules such as antibodies, gene therapies, stem cells, and the like. A combination of both ultrasound stimulation and electrical stimulation of parasympathetic nerves will augment the volume and permeability factors of the blood brain barrier. Delivery of large molecular therapeutic agents to the central nervous system can be useful in treating various central nervous diseases such as, for example, brain tumors, Alzheimer's disease, central nervous system lymphomas, leukemias and certain other cancers, central nervous system infections, and autoimmune and genetic central nervous system diseases.

[0013] It is noted that normal or excessive permeability of the BBB can allow the passage of intravascular noxious autogenous inflammatory factors that can affect the inflammation and pathophysiology of the brain parenchyma in both acute and chronic diseases of the central nervous system. Controlling the BBB permeability to limit transmission of such factors can be useful when treating central nervous disease conditions. An example would be to modulate, and thereby limit, the permeability of the BBB after a vascular stroke to inhibit passage of intravascular inflammatory factors that might otherwise pass (or be more likely to pass) and initiate peri-stroke infarct inflammation. Such a methodology can limit the volume of the post-stroke infarct (neuron cell death).

[0014] In some instances, the therapeutic molecular agents are so large that material increase in BBB permeability would be required to facilitate their passage. In such cases, several nerves and/or blood vessels can be stimulated through several different forms of stimulation energy (e.g. ultrasound and electrical) to provide a compounding modulation effect to materially increase the BBB permeability to allow such larger therapeutic molecules to pass through the BBB. For example, low frequency electrical energy applied to the nerve(s), and particularly the craniofacial/skull base nerves, can increase BBB permeability. Whereas, high-frequency ultrasonic energy applied to blood vessels also can increase BBB permeability for the treated blood vessels. In some embodiments, at least two different energy types can be applied to the cranium (e.g., blood vessels and/or nerves) to provide a compounded stimulation effect to materially increase BBB permeability. In some other embodiments, at least two different parts of the cranium (e.g., two different blood vessels, two different nerves, a blood vessel and a nerve) may be stimulated with a same energy type to provide a compounded stimulation effect to materially increase BBB permeability. The same or distinct modalities of stimulation at different locations can be applied simultaneously to yield a compounding effect to materially increase the permeability of the BBB, thereby rendering passage accessible to relatively large molecular species for specific treatments.

[0015] After beginning the stimulation of the nerve(s) and/or blood vessel(s) to increase permeability, it may be desirable to wait for a period of time before beginning delivery of the therapeutic agent to ensure the BBB has become sufficiently permeated. Accordingly, it may be desirable to ensure that the therapeutic agent is not administered until the BBB has been assessed to be sufficiently permeable. By waiting to deliver the therapeutic agent into the body until after the BBB is sufficiently permeable, unnecessary exposure and/or unwanted circulation of the therapeutic agent to other parts of the body outside of the BBB is reduced. The stimulation of the nerve(s) and/or blood vessel(s) to increase BBB permeability may continue until the therapeutic agent delivery is complete. Once complete, the stimulation may be stopped such that the BBB returns to its baseline state. Alternatively, different modalities of stimulation energy, and/or energies of different characteristics (e.g. different frequency) can be applied at suitable locations as described above to facilitate decreasing the permeability of the BBB. For example, relatively high-frequency electrical energy can be applied to the parasympathetic ganglion or nerve bundles to lessen permeability of the BBB, returning it to its baseline state.

[0016] In some instances, one or more sensors may be arranged on or within the patient's body to measure real-time parameters of the patient that indicate whether the BBB has been sufficiently permeated for the passage of a particular therapeutic agent. The real-time parameters may include blood pressure, blood sugar, white blood cell count, red blood cell count, and/or levels of proteins, biomarkers, inflammatory markers, electrolytes, vitamins, and the like in the blood or cerebrospinal fluid (CSF), as well as other parameters that have been or can be measured periodically or in real time and correlated to BBB permeability. For example, elevated levels of albumin and/or immunoglobulins in the CSF can indicate BBB permeability; elevated levels of the S100B protein in the blood can indicate BBB permeability; and elevated levels of inflammatory markers (e.g., IL-6, TNF-α, IL-1β) in the blood or CSF can indicate BBB permeability. The one or more sensors may also be image devices configured to capture image data from the patient to determine BBB permeability. For example, dynamic contrast-enhanced MRI imaging can track the passage of a contrast agent, such as gadolinium across the BBB to determine where the BBB has become permeated. Diffusion Tensor Imaging can detect microstructural changes in brain tissue that correlate with BBB permeability. 18F-

FDG PET scans can measure glucose uptake in the brain, which can correspond to BBB permeability since glucose transport is regulated by the BBB. Cerebral blood flow can also be measured through MRI or PET scans, where changes in the blood flow can indicate BBB permeability changes, especially when combined with contrast agents that indicate BBB permeability. MRI scans can also measure brain tissue water content, which if imbalanced can show BBB permeability. Electrophysiological markers can also show BBB permeability, such as measurement of a patient's transendothelial electrical resistance to measure the tightness of cell junctions, where lower values indicate an increase in BBB permeability; and measurement of a patient's brain wave patterns (e.g., EEG changes). Changes in the osmotic balance across the BBB measured via osmotic agents (e.g., mannitol) can also indicate BBB permeability.

[0017] The presence and concentration of the therapeutic agent in different parts of the body or body systems, as well as the residuary concentration in the blood stream following administration of a known dose, may also be correlated to provide an indication whether the BBB has been sufficiently permeated for the intended delivery of the therapeutic agent to the central nervous system. As will be realized, certain real-time parameters will be more amenable to measurement in an ambulatory setting in order to supply feedback data for regulating the delivery of therapeutic agent. Whereas other such parameters will require a hospital or clinical setting. The clinician can select a suitable real-time parameter to be measured and used to supply feedback data indicative of BBB permeability given the nature and setting of the particular therapy.

[0018] Disclosed is a closed-loop drug-delivery system configured to modulate the permeability of the BBB and to deliver therapeutic agents to the central nervous system via the BBB, wherein the delivery of the agent is timed or synchronized to correspond to one or more time periods when the BBB has been sufficiently permeated via modulation. The system also can utilize feedback signals from one or more sensors that continuously or periodically detects one or more real-time parameters from the patient indicative of or correlated to BBB permeability in order to optimize therapeutic-agent delivery according to a timed or sequenced algorithm, e.g. corresponding to selected time periods. Delivery of the therapeutic agent into a subject can be delayed until BBB permeability is determined; and preferably until said permeability has been determined to have reached a degree adequate to permit passage of the therapeutic agent into the central nervous system. Similarly, once delivery of the therapeutic agent has ceased, the system also can be used to detect, via the one or more sensors, real-time parameter(s) to provide an indication when the BBB permeability has been sufficiently reduced; or reduced back to a baseline state. The disclosed system preferably is a closed-loop system that in desirable embodiments can be implemented using human-portable components, which allows a patient to receive therapeutic agents that need to permeate the BBB in an ambulatory setting outside of the hospital. This can materially reduce cost and increase patient quality of life, especially if the delivery of therapeutic agents is conducted on a frequent schedule.

[0019] Turning now to FIG. 1, an example of a drug delivery system 100 for modulating the BBB and administering therapeutic agents to a patient's central nervous system is shown. The system 100 includes a drug delivery pump 102, a first electronic stimulation implant 110, and a processor 116 connected to the drug delivery pump 102 and the first electronic stimulation implant 110. The first electronic stimulation implant 110 is operably coupled to a patient body 108 internally or externally. For example, the first electronic stimulation implant 110 can be implanted within the patient body 108 adjacent to a nerve and configured to deliver stimulation energy (such as electrical energy at different frequencies) to the nerve to modulate the BBB. Alternatively, the first stimulation implant 110 can be implanted adjacent to or to target a particular intracranial brain blood vessel with suitable stimulation energy (e.g. ultrasonic energy) to modulate the blood brain barrier and increase its permeability. In other examples, the first electronic stimulation implant 110 is located entirely or partially external to the patient body 108, such as on the outside of the patient's head wherein the stimulation implant 110 can act as a transducer effective to transmit RF energy to generate a perineural electrical field directed to the patient's skull base ganglion or craniofacial nerves as desired. In yet some other examples, the implant 110 can be powered through resonance induction (or other) stimulation energy through the skin to underlying skull base ganglion, craniofacial nerves, or to blood vessels as desired. Optionally, an externally disposed stimulation implant also can have leads that penetrate the skin and extend into the patient's head, toward or adjacent to the nerve(s) and/or blood vessel(s) to be stimulated. increase or decrease the permeability of the BBB.

[0020] The drug delivery system 100 can further include a second electronic stimulation implant 112 operably coupled to the patient body 108 internally or externally, similar as the first stimulation implant 110 discussed above. The first and second electronic stimulation implants 110, 112 may have different structures and/or may target different areas (e.g., nerves, blood vessels, etc.) of the patient body 108 to augment the modulation of the BBB. A power supply 114 is coupled to the first and/or second electronic stimulation implants 110, 112.

[0021] The processor 116 can be coupled to, or part of a computing device that includes, a non-transitory, computer-readable medium that stores machine-readable instructions. When the instructions are executed, the processor 116 is configured to activate the first and/or second electronic stimulation implants 110, 112 to provide stimulation energy to nerves and/or blood vessels of the patient body 108. Stimulation of the nerves and/or blood vessels will modulate, e.g. increase, the permeability of the BBB such that it is rendered to a permeable state suitable to accommodate passage of desired therapeutic molecules. After some the implants 110, 112 have been activated, the processor 116 can activate the drug delivery pump 102 pursuant to the machine-readable instructions, in order to deliver the therapeutic agent to the patient body 108 where it may permeate the BBB. At an appropriate time, the processor 116 then deactivates the drug delivery pump 102 to stop the delivery of the therapeutic agent, and stops or adjusts the stimulation energy in order to reduce the permeability of the BBB (e.g. to return it to its baseline permeability state) once it no longer need be permeable to facilitate drug delivery. Simply stopping delivery of stimulation energy in many cases should result in the BBB returning to its baseline permeability. However, actively modulating the BBB to reduce its permeability with relatively high-frequency energy, for example, may prove an appropriate therapy to accelerate reducing BBB permeability to protect the central nervous system.

[0022] Lines of communication between the components of the system 100 are shown schematically as arrows in FIG. 1. Such communication can be wireless, wired or a combination thereof. The communication between the various components can be two-way, meaning that, for example, the drug delivery pump 102 sends data to the processors 116 and the processor 116 may send data to the drug delivery pump 102. Such two-way communications can allow several components to send and receive feedback signals to ensure the system 100 is performing as intended; e.g. in accordance with a programmed or operative algorithm. For example, if the drug delivery pump 102 notifies the processor 116 that the drug delivery pump 102 has no more therapeutic agent available to deliver, the processor 116 may send an instruction to the implants 110, 112 to stop delivery of the stimulation energy until the drug delivery pump 102 is refilled.

[0023] The illustrated system 100 further includes a sensor 118, which is also connected to the processor 116. The sensor 118 is coupled to the patient body 108 internally or externally and is configured to detect a real-time parameter of the patient in real-time or periodically. Examples of real-time parameters that could be detected include blood pressure, blood sugar, white blood cell count, red blood cell count, other vital signs, as well as metabolic parameters such as serum-levels of certain proteins, electrolytes, vitamins, other matabolytes or blood components, and of the therapeutic agent, each as it may be correlated to or indicative of the permeability of the BBB. The real-time parameter can be selected based on the extent to which it is either directly correlated to, or indicative of, the permeability of the BBB. The processor 116 is configured to compare the detected parameter to a permeability threshold indicative of the BBB permeability for that detected parameter. The processor 116 can be configured, e.g. according to machine-readable instructions, to adjust the delivery of stimulation energy to one or more nerve(s) and/or blood vessels via one or more stimulation implants 110, 112 in order to suitably modulate the permeability of the BBB in real-time during delivery of a therapeutic agent, based on feedback control using parameter data for one or more detected real-time parameters. For example, if such parameter data indicates that the BBB is becoming relatively less permeable during therapeutic-agent delivery, then an algorithm can be configured so that the processor 116 activates or increases the magnitude (or frequency, if applicable) of the stimulation energy in order to increase permeability. On the other hand, if the parameter data indicates that the BBB is becoming relatively more permeable, or permeable to an undesirable degree, then the processor can reduce the delivery of stimulation energy (or adjust its characteristics, such as its frequency) via the stimulation implant(s) in order to reduce BBB permeability.

[0024] The processor 116 can modulate the application of the stimulation energy in response to successive or continuous measurements of the real-time parameter by the sensor 118 to ensure that permeability of the BBB continues to at least meet a threshold permeability before the drug delivery pump 102 delivers a full dose of the therapeutic agent and/or while the drug delivery pump 102 continues to deliver the full dose of the therapeutic agent to the patient body 108.

[0025] After one of the implant(s) 110, 112 starts supplying a stimulation energy, the drug delivery pump 102 may supply a test dose of the therapeutic agent to the patient. The sensor 118 may then detect a real-time parameter that has been or can be correlated to whether the test dose of the therapeutic agent has entered the patient's central nervous system. As an illustrative example, if the therapeutic agent is one that would tend to produce a measurable change in blood pressure, heart rate, or brain activity, then a suitable sensor adapted to detect one of these real-time parameters could be used to provide an indication whether the BBB was penetrated by the test dose. Upon finding, via inference or correlation from the detected real-time parameter, that the test dose of the therapeutic agent reached the patient's central nervous system, the processor 116 can deduce that the stimulation energy has yielded a sufficient increase in BBB permeability to deliver the therapeutic agent, and thus activate the drug delivery pump 102 to provide a full dose of the therapeutic agent to the patient body 108. Conversely, if the detected real-time parameter does not exhibit a change that would correlate to or imply delivery of the therapeutic agent across the BBB, then the processor 116 can deduce that the stimulation energy has not sufficiently modulated the BBB. The processor 116 may then operate the implant(s) 110, 112 to adjust the frequency and/or magnitude of stimulation energy. It also may activate another implant or device to apply a different form of energy, or to apply energy to different ones of the patient's nerves and/or blood vessels to help modulate the BBB permeability. After adjusting the stimulation energy, the processor 116 may repeat the test dose delivery and collection of sensor data from the sensor 118 to once again determine whether the therapeutic agent has entered the patient's central nervous system. This process can be repeated as part of an algorithm to modulate the BBB permeability prior to commencement of delivery of the full dose of therapeutic agent, as well as during delivery thereof to ensure sufficient or optimal BBB permeability.

[0026] As another example, the sensor 118 can be coupled to another nerve interface to detect neuroactivity of a different nerve and provide an electrical signal corresponding to the neuroactivity. The sensor 118 can be programmed to routinely collect and deliver data concerning the real-time parameter of the patient to the processor 116. The sensor 118 can also be programmed to collect and deliver data concerning the real-time parameter upon an instruction requested by or given to the processor 116; e.g. via a user interface. The real-time parameter measured by the sensor 118 can provide important feedback to the processor 116 such that the processor 116 can determine whether the drug delivery pump 102 and implants 110, 112 are functioning properly. This way, unnecessary permeation of the BBB is mitigated, which protects the patient's central nervous system. Additionally, untimely delivery of the therapeutic agent, such as delivery of the therapeutic agent when the BBB is not sufficiently permeable, also is mitigated, which reduces therapeutic agent waste and improves clinical outcomes. Parameter data similarly can be used during therapeutic-agent delivery to maintain suitable or optimal BBB permeability during the course of treatment as described above.

[0027] As yet another example, one or more sensors 118 may also be used to determine whether the BBB has returned back to its baseline impermeable state after a cycle of administering a dose of the therapeutic agent. After therapeutic-agent delivery is complete, the processor 116 can deactivate the implant(s) 110, 112 such that the implant(s) 110, 112 no longer supply the stimulation energy to the patient body 108. Alternatively, the processor 116 can adjust the stimulation energy provided by the implant(s) 110, 112 to actively induce permeability reduction of the BBB or return to its baseline state. For example, BBB permeability can be increased when cranial or facial nerves or nerve ganglia are stimulated with energy that activates the parasympathetic nervous system, thereby causing vasodilation within small-diameter cerebral vessels. Such vasodilation may be induced by low-frequency energy stimulation, e.g. at frequencies less than 100 Hz. To reduce the permeability of the BBB, a different stimulation energy may be applied to the same or different cranial or facial nerves to activate the sympathetic nervous system to promote vasoconstriction, thereby reducing BBB permeability to restrict the passage of harmful substances and inflammatory factors entering brain parenchyma. Relatively high-frequency energy may be used to activate the sympathetic nervous system in this manner, e.g. frequencies of greater than 100 Hz. The stimulation energy used to reduce BBB permeability may be a different frequency, come from a difference source, and/or be directed towards one or more different facial/cranial nerve(s) as described above, as well as different blood vessel(s), compared to the stimulation energy used to increase BBB permeability. Additionally, a combination of stimulation energies and/or nerves/blood vessels may be used to stimulate multiple nerve(s) and/or blood vessel(s) to modulate the BBB permeability, e.g. either increasing or decreasing, as desired according to a particular operative algorithm at appropriate time(s) and/or during appropriate time period(s).

[0028] Once the stimulation energy is deactivated, or suitably high-frequency stimulation energy is applied to the desired cranial/facial nerve(s), for example, the permeability BBB should reduce from its increased state, ideally returning to its baseline impermeable (or semi-permeable) state. The sensor 118 may be activated to collect a real-time parameter for some predetermined time period after the deactivation of (or suitable change in) the stimulation energy designed to reduce BBB permeability, and the processor 116 may compare the real-time parameter data to an impermeability threshold to determine if and when the BBB successfully returns to its baseline impermeable state. The impermeability threshold can be the same as or different than the permeability threshold. If the processor 116 determines that the BBB is still permeable, the processor 116 may repeat the sensor data collection and comparison for another predetermined time period. After one or more findings of the BBB remaining permeable, the processor 116 may conduct some other protocol according to its instructions to ensure the BBB returns to its permeable state and/or to inform the patient or a clinician that the BBB is still permeable, in order that appropriate interventions might be considered.

[0029] Each of the drug delivery pump 102, the first electronic stimulation implant 110, the second electronic stimulation implant 112, the sensor 118, and the processor 116 can include any configuration of one or more electrical components to collect data, supply energy or therapeutic agents to the patient body 108, and/or communicate with at least one other component of the system 100. The system may include other electronic components, such as a power supply (e.g., battery), a microprocessor (in addition to the one or more processor(s) already described), an electronic data storage unit (e.g., memory), a digital interface (e.g., an analog-to-digital converter (ADC) or digital-to-analog converter (DAC)), a signal processor (e.g., filter, amplifier), a recorder, a user interface (e.g., display, touchscreen, keyboard), electrodes (as the aforementioned sensor 118 and/or stimulation implants 110,112) to measure real-time parameters of the patient body 108 and/or to supply stimulation energy to the patient body 108, and/or a transponder for establishing wireless communication to or with a remote terminal such as a computer, tablet or smartphone.

[0030] The communication between the various components of the system 100 may be automatic. In some other instances, a user, such as the patient, clinician, or caregiver, can monitor the communication between the various components of the system 100 and determine when to activate the implant(s) 110, 112 and drug delivery pump 102. For example, a patient device 124, such as a cell phone, laptop, or other device having a user interface, may be connected to the drug delivery pump 102, processor 116, implant(s) 110, 112, and/or sensor 118 such that the patient has the ability to send instructions to the components through the patient device 124. A clinician may similarly use a clinician device 126 coupled to the system 100 to monitor the patient's treatment and adjust the treatment (e.g., drug delivery timing, dosage) as needed. The patient device 124 and/or clinician device 126 may have direct wireless communication with the components of the system 100 or may be indirectly connected to the components of the system 100 through the internet/cloud 120 via WiFi or other network connection. For example, the processor 116 may be connected to the internet/cloud 120, which facilitates communication with a server 122. This allows for the transfer of data between the server 122 and processor 116, the patient device 124, and/or the clinician device 126.

[0031] In some other embodiments, the system 100 may have its own user interface such that that displays data from the drug delivery pump 102, the implants 110, 112, and/or the sensor(s) 118, and which allows a user (e.g. the patient, a caregiver or a clinician) to supply instructions to the drug delivery pump 102, and/or to the implants 110, 112 for operation of the system 100. The drug delivery pump 102 may be coupled to a therapeutic agent source (e.g., I.V. bag, syringe, cartridge) and be configured to deliver 104 a particular dosage of the therapeutic agent over a particular period of time to the patient body 108. In some embodiments, the drug delivery pump 102 comprises an infusion tube 106. The infusion tube 106 or other component of the drug delivery pump 102 can be coupled to the patient body 108 in various ways to deliver the therapeutic agent intravenously, intrathecally, intra-arterially, intraventricularly, or combinations thereof. In some embodiments, the therapeutic agent source and/or the infusion tube 106 are semi-permanently attached to the drug delivery pump 102 and the patient body 108 such that they remain connected to the patient body 108 even when the drug delivery pump 102 and implant(s) 110, 112 are deactivated. In other embodiments, the therapeutic agent source and/or the infusion tube 106 may be connected to the drug delivery pump 102 and/or the patient body 108 upon a notification from the processor 116 that it is time for another dosage of the therapeutic agent. Prior to the notification, the therapeutic agent is not delivered to the patient body 108. This can increase treatment efficacy by minimizing unwanted circulation of the therapeutic agent outside of the BBB, and instead ensuring delivery where it will provide the desired therapy, in central nervous system. The patient or caregiver may then disconnect the therapeutic agent source and/or the infusion tube 106 upon completion of the dosage delivery.

[0032] The processor 116 may be housed within the drug delivery pump 102, within a different component of the system 100, or it may contain its own separate housing. The processor 116 may communicate with the power supply 114 of the implant(s) 110, 112 to activate the delivery of stimulation energy by the implant(s) 110, 112. The implant(s) 110, 112 can be powered by RF energy to generate a perineural electrical field that stimulates or over stimulates the nerve or nerve ganglia. In some other embodiments, the implant(s) 110, 112 and/or sensor 118 are powered through electromagnetic resonance induction, where the implant(s) 110, 112 and/or sensor 118 are within the patient body 108 but are powered by a power supply 114 located outside of the patient body 108. In such embodiments, the patient places a power supply 114 close to the implant(s) 110, 112 and/or sensor 118 when notified by the processor 116 to provide power to the implant(s) 110, 112 and/or sensor 118 within the patient body 108 through electromagnetic induction. The patient may hold the power supply 114 near the implant(s) 110, 112 and/or sensor 118 until the drug delivery cycle is complete. Thus, the power supply 114 may directly power the stimulation energy provided by the implant(s) 110, 112. In some other embodiments, the power supply 114 for the implant(s) 110, 112 and/or sensor 118 can include rechargeable batteries and be despised inside the patient's body 108. In such a case, the patient may rest his/her head (if that is where the power supply 114 is located, for example) on a power pad for a charging time period to recharge the power supply 114. The implant(s) 110, 112 and sensor 118 may share one or more power supplies 114 or each may have its own, local power supply 114. After charging the associated power supply(ies) 114, the implant(s) 110, 112 can provide the stimulation energy to the patient body 108 using the stored energy in the power supply 114. In yet some other embodiments, the implant(s) 110, 112 and/or sensor 118 may utilize a power supply that relies on batteries that are not rechargeable, in which case the batteries must be replaced once exhausted. Such non-rechargeable power supplies ideally will not be implanted within the patient body.

[0033] FIG. 2 shows a flow diagram for an example method 200 of using the disclosed drug delivery system 100.

[0034] At step 202, a signal is received indicating that it is time to administer a dose of a therapeutic agent to a patient. The signal is based on a predetermined dosage schedule within the instructions of the processor 116, a command input by a user (e.g., patient, caregiver, clinician) at a user interface (e.g., patient device 124, clinician device 126), and/or data from the sensor 118 indicative of the patient body 108 being ready for the dosage. For example, if the sensor 118 routinely measures the patient's blood pressure and the processor 116 subsequently determines that the patient's real-time blood pressure has met a suitable blood pressure threshold indicative of an appropriate degree of BBB permeability for the desired treatment, the processor 116 may provide a signal to the drug delivery pump 102 and/or and implants 110, 112 to start the dosage cycle by proceeding to step 204.

[0035] At step 204, stimulation energy is applied to, e.g. a facial nerve of the patient to facilitate increased permeability of the BBB of the patient. The stimulation energy is applied by the one or more of the implants 110, 112 or other stimulation devices. The stimulation energy is applied over a first time period, where the start of the first time period begins at step 204.

[0036] At step 206, the processor 116 collects sensor data from the sensor 118 related to a real-time parameter of the patient body 108. The stimulation energy may continue to be provided during step 206 to continue to stimulate the nerve (for example) to modulate the BBB permeability.

[0037] At step 208, the processor 116 may compare the real-time parameter to a threshold that is indicative of or correlated to the BBB being in a sufficiently permeable state for the desired treatment. The threshold can be dependent on the patient (e.g., weight, height, age) as well as the type and size of the therapeutic agent to be delivered to the patient body 108.

[0038] After the comparison in step 208, the next step of the method 200 depends on the comparison result from step 208.

[0039] At step 210, if the comparison indicates that the BBB is suitably permeable, then the method 200 proceeds to step 212. At step 212, the drug delivery pump is activated to deliver the therapeutic agent to the central nervous system through the permeable BBB of the patient.

[0040] At step 218, if the comparison indicates that the BBB is not permeable, then the method 200 proceeds to step 220. At step 220, the processor 116 adjusts one or more parameters of the stimulation energy. The processor 116 may adjust the stimulation energy by changing the output, such as the frequency, of the stimulation energy delivered by one or more of the implant(s) 110, 112 and/or may activate another implant or stimulation device to stimulate other nerves and/or blood vessels effective to modulate the permeability of the BBB. After step 220, the method may again repeat steps 206 and 208 to collect new sensor data to determine if the adjustments at step 220 achieved a desirable state of permeability for the BBB. Steps 206, 208, 218, and 220 may continuously repeat until at step 210 the comparison indicates that the BBB has reached a suitably permeable state for the method proceeds to step 212.

[0041] At step 212, the drug delivery pump 102 is activated for a second time period that begins at the start of step 212. The duration of the second time period can be based on the therapeutic agent to be delivered and the anticipated time needed to deliver the full dose. While the drug delivery pump 102 is activated in step 212, the delivery of stimulation energy commenced at step 204 continues in order to maintain suitable BBB modulation to ensure that it remains permeable to the therapeutic agent during delivery. As also seen in Fig. 2, steps 206, 208, 210, 218 and 220 can be executed cyclically while the delivery pump is operating to deliver the therapeutic agent, based on real-time or periodic feedback from the real-time parameter(s) in order to modulate the BBB to ensure it remains suitable permeable during drug delivery.

[0042] As will be appreciated, the second time period for drug delivery overlaps with the first time period for delivery of stimulation energy to ensure the BBB remains in a suitably permeable state during drug delivery. The collection of sensor data in step 206 as well as steps 208 and 210 may characterized as occurring during a third time period, not necessarily the same as either the first or second time periods, but optionally overlapping with one or both of them as desired in order to supply feedback data concerning real-time parameters during delivery of stimulation energy and therapeutic-agent delivery. The start of the second time period relating to step 212 starts preferably after the start of the first time period relating to step 204 and preferably after the start of the third time period relating to step 206. The start of the third time period may be delayed from the start of the first time period by some predetermined interval to give the BBB time to become more permeable before starting collection of sensor data indicative of the BBB permeability.

[0043] At step 214, the drug delivery pump 102 sends a feedback signal to the processor 116 indicating the dose of the therapeutic agent has been delivered to the central nervous system. At step 214, the second time period relating to drug delivery ends.

[0044] At step 216, the processor 116 instructs the implant(s) 110, 112 and/or other stimulation devices to adjust or cease the stimulation energy to decrease permeability of the BBB. In some embodiments, step 216 includes the implant(s) 110, 112 and/or other stimulation devices applying a different stimulation energy to one or more nerve(s) or blood vessel(s) to reduce the permeability of the BBB. At step 216, the first time period relating to stimulation energy application to increase BBB permeability ends. The first time period may start before and end after the second time period to ensure the BBB is in a suitably permeable state during drug delivery over the second time period.

[0045] The method 200 may then proceed from step 216 back to step 202 when it is time for another dose administration of the therapeutic agent.

[0046] As will be appreciated, the one or more processor(s) 116, the drug delivery pump 102 and the stimulation implant(s) 110, 112 are coupled together to provide a closed-loop drug delivery system 100, wherein the pump delivers a therapeutic agent to the body based on instructions from the processor(s), during time period(s) when the implant(s) is/are similarly controlled by the processor(s) to ensure a suitably permeable BBB. Moreoer, data from one or more sensor(s) also supplied to the processor(s) can provide an indication both when and the degree to which it is desirable to adjust the delivery of stimulation energy to modulate BBB permeability, as well as to adjust the delivery of the therapeutic agent via the pump to ensure it is being delivered only when the BBB is suitably permeable to accommodate passage of the therapeutic agent. In this sense, the system is a closed loop insofar as the processor is operative to modulate BBB permeability, and operate the pump to deliver therapeutic agent during suitable times in a closed control loop. Data from the aforementioned sensor(s) further can be used to moderate that closed loop to ensure optimal stimulation of nerves/blood vessels and drug-delivery rates during a course of drug delivery.

[0047] In some embodiments, the method 200 omits steps 206, 208, 210, 218, and 220 such that step 204 proceeds directly to step 212. In some such embodiments, the start of the second time period relating to step 212 may be delayed from the start of the first time period relating to step 204 by some predetermined time that is or has been correlated to a presumptive state of the BBB that is sufficiently permeable to accommodate drug delivery. In these embodiments, the system still is a closed-loop system insofar as control of the pump to facilitate drug delivery remains controlled by the processor(s) based on (and ideally confined to a time period when) the BBB being (has been) rendered sufficiently permeable via stimulation energy, also controlled by the processor(s). However, this closed-loop architecture will not benefit from the feedback control afforded by steps 206, 208, 210, 218 and 220. It should be noted that in these and other embodiments, it is possible for the first and second time periods to start at the same time; although this may not be desired.

[0048] It will be appreciated that the method of FIG. 2 is exemplary and that additional steps, such as the use of additional stimulation devices or implants, additional sensor measurements, and the like, are also within the scope of this disclosure. Other steps not mentioned above also may be omitted.

[0049] FIG. 3 illustrates an example frequency versus time plot to illustrate modulation of stimulation energy that can be provided by the first electronic stimulation implant 110. The time between t0 to t1 represents a time period in the drug delivery method before the first electronic stimulation implant 110 is activated to deliver a stimulation energy. Between time t0 and t1, a first frequency f1 is supplied to the first electronic stimulation implant 110. The first frequency f1 is often zero to save power supply but in some embodiments can be greater than zero such that the first electronic stimulation implant 110 supplies at least some kind of frequency (e.g., f1) at all times. At time t1, the first electronic stimulation implant 110 is activated to deliver a second frequency f2. The second frequency f2 corresponds to the stimulation energy intended to cause the BBB to change from a baseline impermeable state into a desirably permeable state. The second frequency f2 may be applied continuously or as a series of pulses. At time t2, the sensor 118 may measure a real-time parameter. At time t3, the processor 116 may compare the real-time parameter to a permeability threshold. At time t4, the processor 116 may determine that the real-time parameter has not met the permeability threshold, and that the frequency of the first electronic stimulation implant 110 needs to be adjusted. For example, at t4, the frequency of the first electronic stimulation implant 110 is changed from f2 to f3. While in FIG. 3, f1 is shown less than f2, and f2 is shown less than f3, it will be appreciated that f3 could be less than f2 and/or less than f1. Similarly, f2 could be less than f1. At t5, the sensor 118 may again measure a real-time parameter. At t6, the processor 116 may compare the real-time parameter to the permeability threshold and determine that the threshold has been met or exceed. After time t6, the drug delivery pump 102 may begin supplying the therapeutic agent to the patient body 108 through the permeable BBB. The drug delivery pump 102 may stop supplying the therapeutic agent at time t7. At time t8, the first electronic stimulation implant 110 may stop supplying (or adjust the characteristics of) the stimulation energy applied to return the BBB permeability to its baseline state (e.g., f1) since drug delivery has concluded.

[0050] Thus, in this example the time period beginning at t1 and ending at t8 may correspond to the first time during which the first electronic stimulation implant 110 supplies the stimulation energy f2 and f3 (the latter representing an adjustment based on sensor data suggesting that the BBB had not yet been sufficiently permeable at f2). The time period beginning at t6 and ending at t7 may correspond to the second time period during which the drug delivery pump 102 supplies the therapeutic agent to the patient body 108. The time period beginning t2 and ending at t6 may correspond to the third time period during which the system 100 uses the real-time parameter from the sensor 118 (measured continuously or periodically) to determine whether the BBB is sufficiently permeable.

[0051] Turning to FIG. 4, the drug delivery system 100 can include several stimulation devices to provide different types or magnitudes of stimulation energy to various parts of the patient body 108. As already described, the system 100 can include a first electronic stimulation implant 110 and a second electronic stimulation implant 112. The system 100 can further include a third stimulation device 402 and/or a fourth stimulation device 404. The third and fourth stimulation devices 402, 404 are coupled to and controlled by the processor 116. The third and/or fourth stimulation devices 402, 404 may provide high-frequency ultrasonic energy and/or electromagnetic frequency energy to a blood vessel and/or nerve in the cranium to permeate the BBB. The third and/or fourth stimulation devices 402, 404 may be located internally, externally, or a combination thereof to the patient body 108. Each of the third and/or fourth stimulation devices 402, 404 can be powered using various techniques such as those described above (e.g., batteries, rechargeable batteries, electromagnetic induction, etc.) with respect to the implants 110, 112. In some other embodiments, the first and/or second electronic stimulation implants 110, 112 are omitted from the drug delivery system 100 and one of the third and/or fourth stimulation devices 402, 404 are used for BBB modulation.

[0052] By directing more than one kind of energy (e.g., low frequency energy, high-frequency ultrasonic energy, and/or electromagnetic frequency energy) at one or more nerves and/or blood vessels in the cranium, various implants/devices 110, 112, 402, 404 can provide a compounding modulation effect on the BBB permeability to allow larger therapeutic agents into the central nervous system past the BBB.

[0053] The stimulation parameters may vary depending on the location of the desired nerve and/or blood vessel to be activated. In some instances, stimulation energy provided to a nerve is often hemispherical such that only one side of the BBB can be made sufficiently permeable to facilitate drug delivery; stimulation energy that is electromagnetic provided to a blood vessel is regional; and stimulation energy that is high-frequency ultrasound provided to a blood vessel is focal. For example, parasympathetic neuromodulation that opens up the BBB hemispherically can be combined with ultrasonic and/or electromagnetic energy to augment the focal effect of the BBB permeability. Therefore, a drug delivery system 100 may be designed to include one or more devices (e.g., 110, 112, 402, 404) coupled to a processor 116 to create permeation in a desired area of the BBB based on the type of therapeutic agent to be delivered. When a drug delivery system 100 comprises more than one stimulation device, such as those shown in FIG. 4, each device's timing and energy type/amount can be modulated during the drug delivery method. Even if a drug delivery system 100 comprises multiple stimulation energy devices, only one or two may be activated during the drug delivery method, depending on how easily the BBB can be modulated for permeability.

[0054] Turning now to FIG. 5, another example of a frequency versus time plot is illustrated. The time and frequencies illustrated may indicate the same or similar steps as described with respect to FIG. 3. For example, in FIG. 5, a first stimulation device may be activated to provide a second frequency f2 to particular nerve and/or blood vessel of the patient at time t1, as shown by line 502. Then, at time t4, if the processor 116 determines that the real-time parameter has not met the permeability threshold based on the frequency f2 provided by the first stimulation device, then the processor 116 may activate a second stimulation device at time t4 to provide a third frequency f3 to a particular nerve and/or blood vessel of the patient, as shown by line 504. When both devices are activated, the sensor data at t5 and t6 may be indicative of the BBB being sufficiently permeated. Both stimulation devices may remain activated until time t8 at which the drug delivery method has concluded for a particular dose of therapeutic agent. As shown by line 504, the second stimulation device may be activated during a fourth time period between time t4 and t8. The start of the fourth time period may follow the start of the first time period or may be simultaneous with the start of the first time period. The start of the delivery of the therapeutic agent may occur after the start of the first and fourth time periods. After the drug delivery phase concludes at time t7, the first and/or second stimulation devices may each stop providing stimulation energy and/or adjust the stimulation energy to reduce BBB permeability at time t8. The magnitude and frequencies of stimulation energy supplied by each stimulation device at time t8 may be the same or different.

[0055] Illustrative embodiments have been described, herein above. It will be apparent to those skilled in the art that the above apparatuses and methods may incorporate changes and modifications without departing from the general scope of this disclosure. The disclosure is intended to include all such modifications and alterations disclosed herein or ascertainable herefrom by persons of ordinary skill in the art without undue experimentation.

What is claimed is:

1. A drug delivery system comprising:

a first electronic stimulation implant configured to be implanted adjacent to a nerve and/or a blood vessel of a subject and configured to deliver first stimulation energy thereto to modulate a blood brain barrier of the subject to adjust a permeability of the blood brain barrier;

a drug delivery pump configurable to deliver a therapeutic agent to the subject through the blood brain barrier;

a computing device coupled to the first electronic stimulation implant and the drug delivery pump, the computing device comprising a non-transitory, computer-readable medium storing instructions that, when executed by one or more processors of the computing device, cause the one or more processors to:

activate the first electronic stimulation implant to deliver the first stimulation energy during a first time period effective to increase the permeability of the blood brain barrier;

activate the drug delivery pump to deliver the therapeutic agent to the subject across the blood brain barrier during a second time period;

deactivate the drug delivery pump to stop delivery of the therapeutic agent to the subject at an end of the second time period; and

at or after the end of the second time period, adjust or cease the first stimulation energy to decrease the permeability of the blood brain barrier.

2. The drug delivery system of claim 1, further comprising a second electronic stimulation implant, the instructions being configured such that during either or both of the first time period and the second time period, a second stimulation energy is supplied by the second electronic stimulation implant, to a blood vessel and/or nerve different than the first stimulation energy, to increase the permeability of the blood brain barrier, wherein the first stimulation energy and the second stimulation energy are combined to yield a compound effect on increasing the permeability of the blood brain barrier.

3. The drug delivery system of claim 1, wherein the instructions are configured such that at or after the end of the second time period, a second stimulation energy, different from the first stimulation energy, is applied to decrease the permeability of the blood brain barrier.

4. The drug delivery system of claim 3, wherein the first stimulation energy is adjusted at or after the end of the second time period, and wherein the adjusted first stimulation energy and the second stimulation energy are combined to yield a compound effect on reduction of the blood brain barrier permeability.

5. The drug delivery system of claim 4, further comprising a second electronic stimulation implant, the second stimulation energy being supplied via the second electronic stimulation implant to a different blood vessel or nerve than the adjusted first stimulation energy.

6. The drug delivery system of claim 1, wherein the instructions are configured such that the start of the second time period occurs after the start of the first time period.

7. The drug delivery system of claim 1, wherein the instructions are configured such that the first time period overlaps with the second time period, and wherein the activation of the drug delivery pump is started after the start of the first time period.

8. The drug delivery system of claim 1, wherein the instructions are configured such that the deactivation of the drug delivery pump occurs before the adjustment or deactivation of the first stimulation energy to decrease the blood brain barrier permeability.

9. The drug delivery system of claim 1, wherein the first time period and the second time period are predetermined and are based on a molecular size of the therapeutic agent to be delivered across the blood brain barrier.

10. The drug delivery system of claim 1, further comprising an ultrasound device configurable to deliver ultrasonic energy to a blood vessel of the subject to increase the permeability of the blood brain barrier of the subject.

11. The drug delivery system of claim 10, wherein the instructions, when executed by the one or more processors, further cause the one or more processors to activate the ultrasound device to deliver the ultrasonic energy to an intracranial blood vessel, to a parasympathetic nerve ganglion, or to a parasympathetic nerve.

12. The drug delivery system of claim 11, wherein the ultrasound device is activated during a time period overlapping with both the first time period and the second time period, and wherein the start of the second time period is after the start of the first time period.

13. The drug delivery system of claim 1, further comprising a sensor coupled to the computing device and configured to detect a real-time parameter of the subject.

14. The drug delivery system of claim 13, wherein the instructions of the computing device are configured to further cause the one or more processors to:

determine whether the blood brain barrier is permeable based on the real-time parameter; and

start the second time period upon determining that the blood brain barrier is permeable.

15. The drug delivery system of claim 14, wherein the instructions are configured such that the determination of whether the blood brain barrier is permeable is conducted by comparing the real-time parameter to a threshold value indicative of blood brain barrier permeability.

16. The drug delivery system of claim 14, wherein the sensor is configured to detect whether a particular molecule is present in blood of the subject.

17. The drug delivery system of claim 16, wherein the particular molecule is the therapeutic agent.

18. The drug delivery system of claim 14, wherein the instructions of the computing device are configured to further cause the one or more processors to operate the first electronic stimulation implant to adjust the first stimulation energy delivered to the nerve and/or blood vessel based on sensor data for the real-time parameter to ensure that the blood brain barrier remains permeable during the second time period.

19. A drug delivery method comprising:

a) applying first stimulation energy to a first nerve and/or blood vessel of a subject adapted to increase permeability of a blood brain barrier of the subject;

b) measuring a real-time parameter of the subject;

c) determining that the blood brain barrier of the subject is permeable based on the real-time parameter meeting or exceeding a permeability threshold;

d) operating a drug delivery pump to deliver a therapeutic agent;

e) thereafter deactivating the drug delivery pump; and

f) thereafter, adjusting or deactivating the first stimulation energy to decrease the permeability of the blood brain barrier.

20. The drug delivery method of claim 19, further comprising repeating steps (a)-(f) according to a predetermined drug delivery schedule.

21. The drug delivery method of claim 19, step a) further comprising applying a second stimulation energy to a nerve and/or a blood vessel of the subject different than that to which the first stimulation energy is applied, adapted to increase the permeability of the blood brain barrier, wherein the first stimulation energy and the second stimulation energy are combined to yield a compound effect on increasing the permeability of the blood brain barrier.

22. The drug delivery method of claim 19, step f) further comprising applying a second stimulation energy to a nerve and/or a blood vessel of the subject different than that to which the first stimulation energy is applied, adapted to decrease the permeability of the blood brain barrier, wherein the adjusted first stimulation energy and the second stimulation energy are combined to yield a compound effect on decreasing the permeability of the blood brain barrier.

23. The drug delivery method of claim 19, further comprising modulating application of the first stimulation energy in response to successive or continuous measurements of the real-time parameter to ensure that permeability of the blood brain barrier continues to at least meet the permeability threshold while the drug delivery pump continues to deliver the therapeutic agent.

24. The drug delivery method of claim 19, wherein the first stimulation energy comprises one or more of: high-frequency ultrasonic energy applied to a brain parenchymal blood vessel(s) of the subject or electromagnetic frequency energy applied to a brain parenchymal blood vessel(s) of the subject.

25. The drug delivery method of claim 19, further comprising, after step a) but before step b), operating the drug delivery pump to deliver a test dose of the therapeutic agent, wherein the

real-time parameter of the subject is indicative of whether the test dose of the therapeutic agent entered the central nervous system of the subject through the blood brain barrier, and wherein at step d), the drug delivery pump is operated to deliver a full dose of the therapeutic agent.

26. The drug delivery method of claim 19, wherein the first stimulation energy is applied to a skull base parasympathetic facial nerve of the subject.

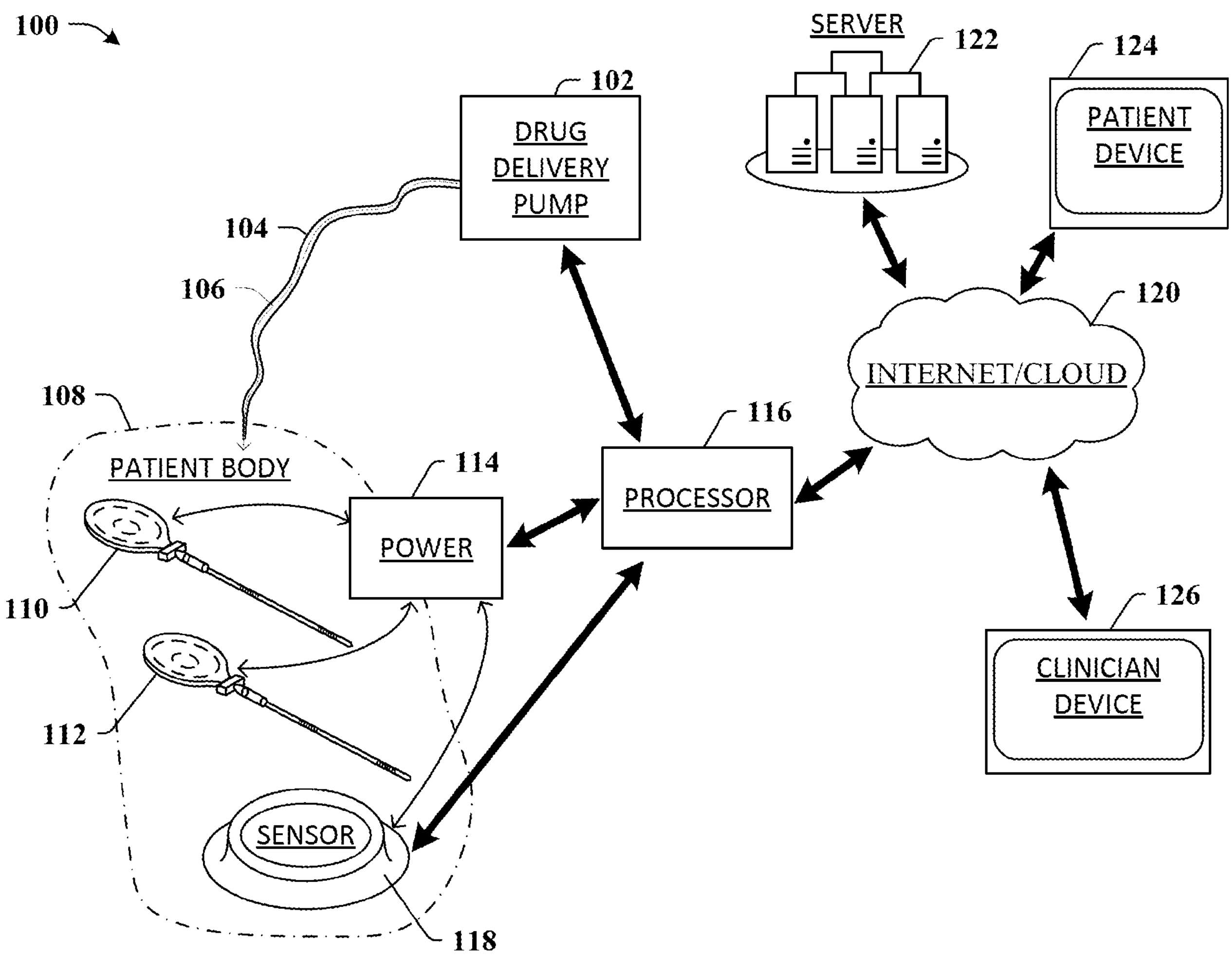
100
SERVER
122
124
PATIENT DEVICE
102
DRUG DELIVERY PUMP
104
106
120
INTERNET/CLOUD
108
116
PATIENT BODY
114
PROCESSOR
POWER
110
126
CLINICIAN DEVICE
112
SENSOR
118

FIG. 1

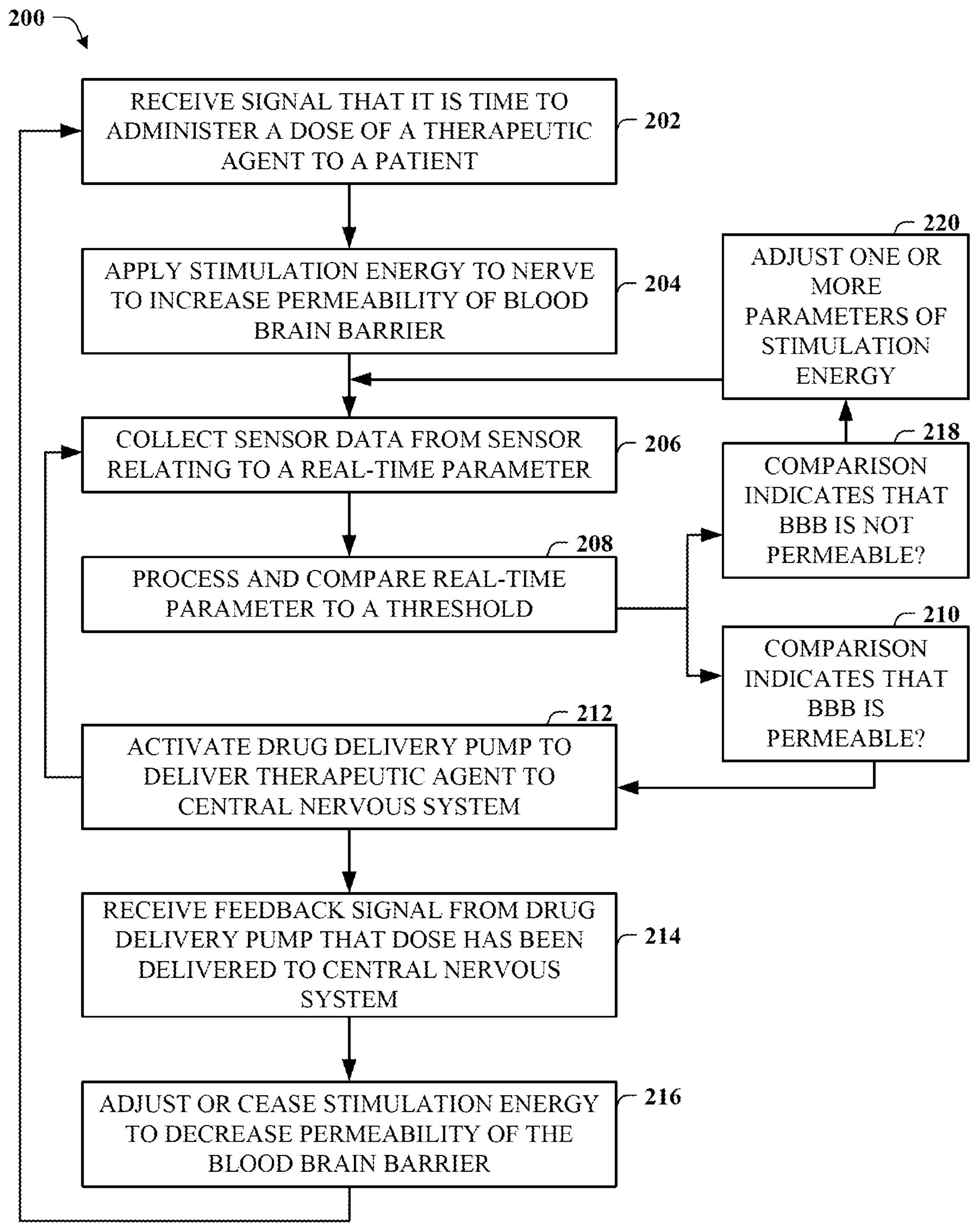
200
RECEIVE SIGNAL THAT IT IS TIME TO ADMINISTER A DOSE OF A THERAPEUTIC AGENT TO A PATIENT
202
APPLY STIMULATION ENERGY TO NERVE TO INCREASE PERMEABILITY OF BLOOD BRAIN BARRIER
204
COLLECT SENSOR DATA FROM SENSOR RELATING TO A REAL-TIME PARAMETER
206
PROCESS AND COMPARE REAL-TIME PARAMETER TO A THRESHOLD
208
ACTIVATE DRUG DELIVERY PUMP TO DELIVER THERAPEUTIC AGENT TO CENTRAL NERVOUS SYSTEM
212
RECEIVE FEEDBACK SIGNAL FROM DRUG DELIVERY PUMP THAT DOSE HAS BEEN DELIVERED TO CENTRAL NERVOUS SYSTEM
214
ADJUST OR CEASE STIMULATION ENERGY TO DECREASE PERMEABILITY OF THE BLOOD BRAIN BARRIER
216
ADJUST ONE OR MORE PARAMETERS OF STIMULATION ENERGY
220
COMPARISON INDICATES THAT BBB IS NOT PERMEABLE?
218
COMPARISON INDICATES THAT BBB IS PERMEABLE?
210

FIG. 2

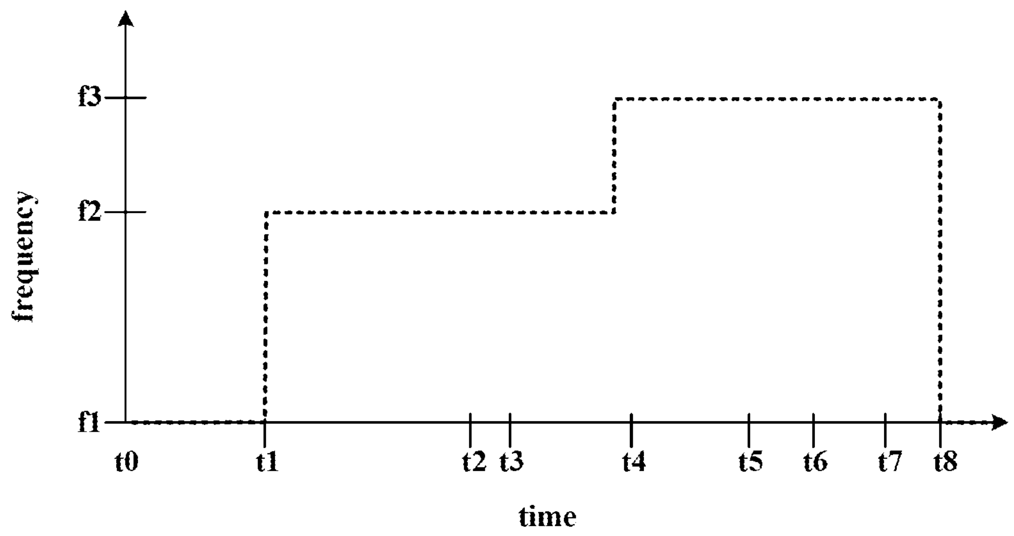
f3
f2
f1
frequency
t0
t1
t2
t3
t4
t5
t6
t7
t8
time

FIG. 3

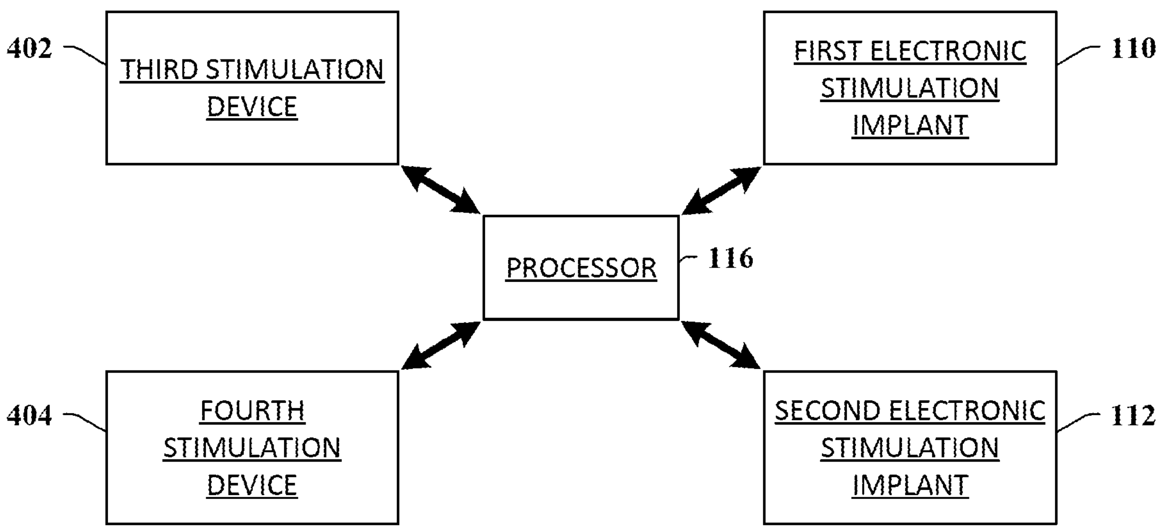
402
THIRD STIMULATION DEVICE
FIRST ELECTRONIC STIMULATION IMPLANT
110
PROCESSOR
116
404
FOURTH STIMULATION DEVICE
SECOND ELECTRONIC STIMULATION IMPLANT
112

FIG. 4

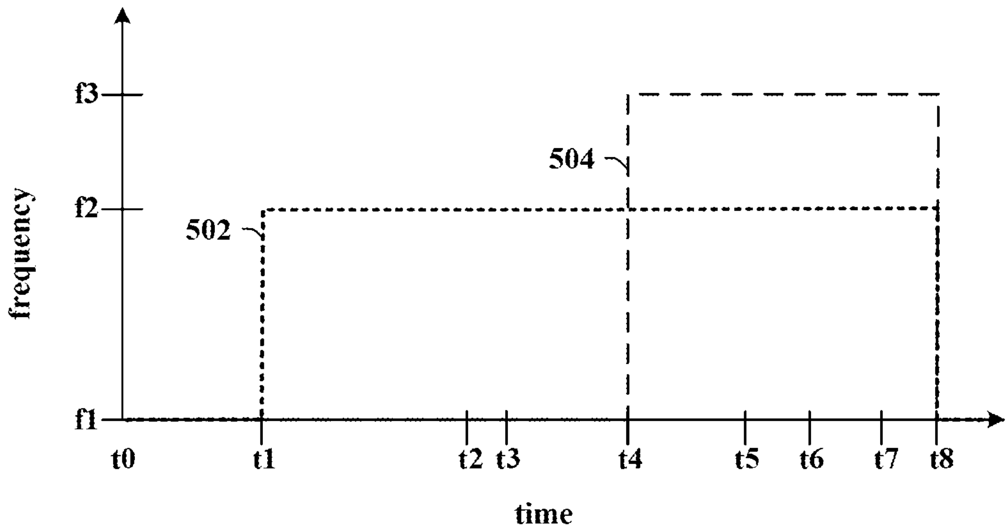

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/056393

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/36 A61M5/142
ADD.

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 A61M

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 657 316 B2 (BOSTON SCIENT NEUROMODULATION [US]) 2 February 2010 (2010-02-02) abstract; figure * pages 36-42	1-18
A	CN 113 368 386 A (CIXI INSTITUTE OF BIOMEDICINE WENZHOU MEDICAL UNIV) 10 September 2021 (2021-09-10) the whole document	1-18
A	WO 2004/010923 A2 (BRAINSGATE LTD [IL]; GROSS YOSSI [IL] ET AL.) 5 February 2004 (2004-02-05) the whole document	1-18
A	US 2012/253261 A1 (POLETTO CHRISTOPHER [US] ET AL) 4 October 2012 (2012-10-04) the whole document	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2025	04/02/2025

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Scheffler, Arnaud

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/056393

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-26
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 19-26

The method of drug delivery applying first stimulation energy as defined in claims 19-26 is regarded to be a method for treatment of the human or animal body by therapy/surgery. Therefore, the subject-matter of claims 19-26 has not been searched (Art.17(2)(a)(i) and Rule 39.1). Moreover, according to Article 34(4)(a)(i) PCT and Rule 67.1(iv) PCT, no international preliminary examination is required to be carried out on the subject-matter of these claims. By analogy, it is considered that medical methods do not avoid exclusion merely through computer implementation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/056393

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