(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 July 2024 (04.07.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/141768 A2

(51) International Patent Classification:
A61N 5/06 (2006.01)

(21) International Application Number:
PCT/IB2022/000735

(22) International Filing Date:
29 December 2022 (29.12.2022)

(25) Filing Language: English

(26) Publication Language: English

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with declaration under Article 17(2)(a); without abstract; title not checked by the International Searching Authority*

WO 2024/141768 A2

(54) Title: OPTICAL STIMULATION SYSTEMS AND METHODS FOR IMPLANTING AND USING

(57) Abstract:

OPTICAL STIMULATION SYSTEMS AND METHODS FOR IMPLANTING AND USING

FIELD

The present disclosure is directed to the area of implantable optical stimulation systems and methods of implanting and using the systems. The present disclosure is also directed to methods for implanting optical stimulation leads and light sources.

BACKGROUND

Implantable optical stimulation systems can provide therapeutic benefits in a variety of diseases and disorders. For example, optical stimulation can be applied to the brain either externally or using an implanted stimulation lead to provide, for example, deep brain stimulation, to treat a variety of diseases or disorders. Optical stimulation may also be combined with electrical stimulation.

Stimulators have been developed to provide therapy for a variety of treatments. A stimulator can include a control module (for generating light or electrical signals sent to light sources in a lead), one or more leads, and one or more light sources coupled to, or disposed within, each lead. The lead is positioned near the nerves, muscles, brain tissue, or other tissue to be stimulated.

BRIEF SUMMARY

One aspect is a method for implanting and using an optical stimulation system including an optical lead, a base unit including a light source, and a control module, wherein the base unit is coupleable, or coupled, to the optical lead and the control module. The method includes forming a first burr hole in a skull of a patient for

implantation of the optical lead; forming a second burr hole in the skull and spaced apart from the first burr hole and configured to receive at least a portion of the base unit; coupling the optical lead to the base unit; coupling the base unit to the control module; implanting the optical lead through the first burr hole into the skull of the patient; and receiving the portion of the base unit into the second burr hole.

In at least some aspects, the second burr hole has a larger diameter than the first burr hole. In at least some aspects, the method further includes fastening the base unit to the skull. In at least some aspects, the method further includes implanting the control module in the patient. In at least some aspects, the implanting includes implanting the control module in a subclavicular region of the patient.

In at least some aspects, the method further includes tunneling at least a connector lead from the base unit to the control module. In at least some aspects, the method further includes, prior to implanting the optical lead, inserting a cannula through the first burr hole into the brain of the patient, wherein the implanting includes implanting the optical lead through the cannula. In at least some aspects, the method further includes fastening the optical lead to the skull and the implanting.

In at least some aspects, the method further includes after the implanting, optically stimulating the patient using the optical stimulation system. In at least some aspects, the method further includes after the optically stimulating, obtaining a PET scan to assess effectiveness of the optical stimulation.

Another aspect is a method for implanting an optical stimulation system including an optical lead, a base unit including a light source, and a control module, wherein the base unit is coupleable, or coupled, to the optical lead and the control module. The method includes coupling the base unit to the control module prior to implanting the optical lead; coupling the optical lead to the base unit prior to implanting the optical lead; testing the optical lead and the light source in the base unit using the control module to determine that power is delivered from the control module to the light source, light is produced by light source and delivered to the optical lead, and the light is emitted from the optical lead at at least one emission region disposed on a distal

portion of the optical lead; and after the testing, implanting the optical lead into a brain of a patient.

In at least some aspects, the method further includes, prior to the testing, implanting the control module into the patient. In at least some aspects, the method further includes, prior to the testing, implanting at least a portion the base unit into the patient.

In at least some aspects, the testing includes determining a value of an optical power of light emitted from the at least one emission region of the optical lead for a plurality of different light source current values. In at least some aspects, the testing further includes using the values of optical power determined by the testing in a comparison test based on previously measured optical power values. In at least some aspects, the comparison test includes comparing a slope of the values of optical power determined by the testing with a slope of the previously measured optical power values. The slope can be, for example, the slope of the values of optical power as a function of current applied to the light source.

A further aspect is a method for implanting an optical stimulation system including an optical lead, a base unit including a light source, and a control module, wherein the base unit is coupleable, or coupled, to the optical lead and the control module. The method includes forming a first burr hole in a skull of a patient for implantation of the optical lead; inserting a cannula through the first burr hole into a brain of the patient; delivering a contrast agent through the cannula to the brain of the patient; visualizing at least one ventricle of the brain of the patient using the contrast agent; and, after the visualizing, implanting the optical lead through the cannula into the brain of the patient using the visualization to guide placement of the optical lead.

In at least some aspects, the method further includes, prior to implantation surgery, imaging the brain of the patient. In at least some aspects, the method further includes, prior to implantation surgery, using the imaging to plan a trajectory for the optical lead into the brain of the patient. In at least some aspects, the method further includes using the trajectory or an actual position of the optical lead in the brain of the

patient to estimate an optical power of the optical lead for a set of optical lead parameters delivered to a target site in the brain of the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

Non-limiting and non-exhaustive embodiments of the present invention are described with reference to the following drawings. In the drawings, like reference numerals refer to like parts throughout the various figures unless otherwise specified.

For a better understanding of the present invention, reference will be made to the following Detailed Description, which is to be read in association with the accompanying drawings, wherein:

FIG. 1A is a schematic side view of one embodiment of a lead/light source arrangement including a light source, an optical lead, and a connector lead;

FIG. 1B is a schematic side view of one embodiment of a control module configured to electrically couple to a connector lead or lead extension;

FIG. 2 is a schematic cross-sectional view of one embodiment of the optical lead of FIG. 1A;

FIG. 3 is a schematic side view of one embodiment of a lead extension configured to electrically couple a lead to the control module of FIG. 1B; and

FIG. 4 is a schematic overview of one embodiment of components of an optical or optical/electrical stimulation system including an electronic subassembly.

DETAILED DESCRIPTION

The present disclosure is directed to the area of implantable optical stimulation systems and methods of implanting and using the systems. The present disclosure is also directed to methods for implanting optical stimulation leads and light sources.

Optical stimulation employs light (for example, visible, infrared, near-infrared, ultraviolet, or the like or any combination thereof) directed at target tissue to achieve a therapeutic effect. The interaction of electromagnetic radiation, such as light, with

biological tissues such as, plant (for example, via chlorophyll and photosynthesis) or animal tissues, depends on the wavelength of the radiation. The wavelength of the light also determines, at least in part, light propagation and absorption in the tissue. One example of the effect of electromagnetic radiation is the synthesis of vitamin D in response to sunlight.

Specific effects can be achieved by light interaction with photo-accepting molecules, such as the enzyme cytochrome-C-oxidase. In the case of irradiation in the near-infrared range (600 to 900 nm), cytochrome-C-oxidase specifically absorbs photons at 670nm and transfers the photonic energy into an electron transport chain within mitochondria. This ultimately produces adenosine triphosphate (ATP) which can result in increased metabolism and the promotion of survival or proliferation.

In Parkinson's disease, metabolic involvement at the end of the neurodegenerative process includes activity in the mitochondria of the dopaminergic cells of the substantia nigra compacta (SNc) whose death is responsible for Parkinsonian syndrome. MPTP (1-methyl-4-phenyl-1-2-3-6 tetrahydropyridine) is a toxicant that produces the same cellular effects, especially at the mitochondrial level. As a result, this molecule is used to create experimental models of Parkinson's disease. An optical stimulation device has been tested on animal models to demonstrate the feasibility of the chronic implantation of the optical stimulation devices and the absence of side effects of optical stimulation using near-infrared light. Such experiments, conducted, for example, in fasciculari Macaques with induced Parkinsonian syndrome by systemic injection of MPTP, demonstrated the neuroprotective properties of irradiation in the range of near-infrared at 670nm of the SNc.

In preclinical results, the neuroprotective effect is manifested by significant reduction of motor symptoms arising from MPTP, as well as by significant reduction in dopaminergic neuronal loss, highlighted by the immuno-histochemical analysis of the brains of the animals.

Clinical rating scales are an important tool for measuring the effect of optical stimulation on Parkinson's disease progression. Positron emission tomography (PET) imaging has been demonstrated to be useful for quantifying neurodegeneration. The assessment of dopaminergic transmission by PET imaging can be used to assess the severity and progression of degenerative processes of Parkinson's disease. Examples of dopaminergic tracers include dopamine synthesis enzymes (such as [^{18}F]DOPA which reflects the activity of the dopamine synthesis enzyme (dopa decarboxylase)) and dopamine transporters (such as [^{11}C]PE2I) or its dopamine receptors type 2 (D_2), such as [^{11}C]raclopride).

Conventionally, dopaminergic transmission has been extensively measured by PET using the radiotracer [^{18}F]DOPA, which reflects the activity of the dopamine synthesis enzyme (dopa decarboxylase). It is found, however, that in the early stages of Parkinson's disease, [^{18}F]DOPA may underestimate some degenerative compensatory processes. In addition, [^{18}F]DOPA is a synthetic enzyme common to different monoamines (dopamine, serotonin, norepinephrine), which makes [^{18}F]DOPA a delicate marker to manipulate and not very specific.

Other more specific PET tracers include [^{11}C]PE2I, which is a ligand with a selective affinity for the dopamine transporter (DAT) and allows an accurate measurement of dopamine density. Studies in monkeys and patients with Parkinson's disease show a drop in DAT density in the substantia nigra and in the striatum, which is reflected by a decrease in tracer fixation or non-movable binding potential (BP_{ND}) of [^{11}C]PE2I within these structures, indicating severe dopamine degeneration.

The decrease in BP_{ND} of [^{11}C]PE2I is correlated with the severity of Parkinson's symptoms. DAT fixation in de novo Parkinson's patients can predict the evolution of motor and non-motor symptoms in the long term. PET imaging of the DAT can also assess potential neuroprotective effects. DAT imaging has also been used in clinical trials in Parkinson's patients to measure possible neuroprotective effects of pharmacological agents.

Post-mortem or *in vivo* imaging studies in Parkinson's patients and animal models of Parkinson's disease suggest that 50-75% of nigrostriatal dopaminergic neurons degenerate before the first motor symptoms appear. In Parkinson's primates (injected with MPTP), the first motor symptoms were described when dopaminergic loss reaches 43% of cell bodies in the substantia nigra and 80% of the axonal extremities.

In Parkinson's patients, a post-mortem study indicates that the loss of striatal axonal endings is 70% at the onset of clinical symptoms. A study in very early d*e novo* Parkinson's patients using functional PET imaging of the dopamine transporter ligand PE2I (DAT) showed, as compared to normal subjects, an initial loss of pre-synaptic dopaminergic function in the posterior putamen of 53% in non-apathetic Parkinson's patients and 65% in apathetic Parkinson's patients.

It is documented that the annual neuronal loss is of the order of 10% and that within 3 years the control subjects will have lost about 30%. In at least some embodiments, a therapeutic goal of intraventricular optical stimulation by near-infrared light is to protect the remaining neurons.

In at least some embodiments, patient criteria for optical stimulation can include one or more of the following: diagnosis of Parkinson's disease, confirmed dopaminergic denervation of a predefined amount (for example, at least 30%), diagnosis of an early stage of the disease (for example, a recent diagnosis or tremor at 2 or less on the MDS-UPDRS scale), whether symptoms are severe enough to require medication, the maount of medication used to control the disease, or the like or any combination thereof. Other criteria can also be used.

In at least some embodiments, the optical stimulation can produce a decrease in the dopaminergic denervation rate of at least 5, 10, 15, or 20% or more. In at least some embodiments, the optical stimulation can delay the onset of motor disorders and non-motor disorders (e.g., axial and cognitive disorders) associated with Parkinson's

disease. In at least some embodiments, optical stimulation can be provided in conjunction with conventional dopamine replacement therapy.

To be effective, optical stimulation must illuminate the target tissue. In at least some embodiments, the transmission of light from a light emitter (e.g., a light source or an emission region of an optical fiber, as described in more detail below) to a target can be estimated using, for example, absorption and scattering parameters of the brain structures and tissue between the light emitter and the target. As an example, estimates can be made using optical parameters for white and gray matter. The optical parameters can be designated as the absorption coefficient: μa, diffusion coefficient: μs and anisotropy: g, which can be combined to obtain a single reduced diffusion coefficient: $\mu s' = \mu s * (1 - g)$. Examples of these optical parameters include gray matter – μa = 0.02 mm^{-1}, μs' = 0.84 mm^{-1}, and g – 0.90 – and white matter - μa = 0.07 mm^{-1}, μs' = 2.5 mm^{-1}, and g – 0.85.

In some instances, optical stimulation can produce tissue heating which can have deleterious effects. Magnetic resonance imaging (MRI) can be used for mapping the heat released from the optical stimulation lead and the determination of the energy to delivered by the light source (e.g., a laser diode). Ideally, heat is monitored to limit the change in temperature to below 2 °C to reduce the risk of cellular degradation. A light source in the near-infrared range (670nm) was applied to two rats resulting in an average of 8°C of heating at 120mW. In at least some embodiments, the maximum power at 670 nm is limited to 20 mW. It will be understood that other limitations can be selected for different wavelengths, different stimulation targets or patients, or the like.

Optical stimulation systems are described herein for illuminating target tissue. In at least some embodiments, the optical stimulation systems, or portions of the optical stimulation systems, are implantable. In at least some embodiments, the implantable optical stimulation system only provides optical stimulation. In other embodiments, the stimulation system can include both optical and electrical stimulation. In at least some of these embodiments, the optical stimulation system can be a modification of an

electrical stimulation system to also, or instead, provide optical stimulation. Optical stimulation may include, but is not necessarily limited to, stimulation resulting from response to particular wavelengths or wavelength ranges of light or from thermal effects generated using light or any combination thereof.

Figure 1A and 1B illustrate elements of an optical stimulation system including a lead/light source arrangement 100 illustrated in Figure 1A and a control module 146 (e.g., an implantable pulse generator (IPG)) illustrated in Figure 1B. In at least some embodiments, the control module may be originally designed for use with an electrical stimulation system and adapted for use as an optical stimulation system via the lead/light source arrangement 100.

The lead/light source arrangement 100 includes a base unit 128 with a light source 120 disposed in a housing 130, an optical lead 122 with one or more emission regions 132 disposed along a distal portion of the optical lead from which light is emitted, and a connector lead 134 with one or more terminals 136 for coupling to the control module 146 or a lead extension 160 (Figure 3), as described below. In addition to the light source 120, the base unit 128 can optionally include a light monitor 124. Independently, the optical lead 122 and connector lead 134 may be permanently, or removably, coupled to the base unit 128. If removably coupleable to the base unit 128, the optical lead 122, the connector lead 134, or both will have corresponding arrangements (for example, terminals, contacts, or optical fiber coupling elements) for transmission of light (for the optical lead) from, or electrical signals (for the connector lead) to, the base unit 128. The one or more emission regions 132 may include a tip emission region that emits distally away from the optical lead, as illustrated in Figure 1A, or may include a side emission region that emits from a side of the optical lead or any combination thereof.

The light source 120 can be any suitable light source including, but not limited to, light emitting diodes (LEDs), organic light emitting diodes (OLEDs), laser diodes, lamps, light bulbs, or the like or any combination thereof. In at least some embodiments, the optical stimulation system can include multiple light sources 120. In

at least some of these embodiments, each of the multiple light sources 120 emits light having a different wavelength or different wavelength range.

A light source 120 can emit light at any suitable wavelength or wavelength range including, but not limited to, visible, near-infrared, infrared, or ultraviolet wavelengths or wavelength ranges or any combination thereof. In at least some embodiments, the optical stimulation system includes a light source that emits in the near-infrared wavelength range (for example, in the range of 600 to 900 nm or in the range of 600 to 700 nm or in the range of 640 to 680 nm or 670 nm or the like). In at least some embodiments, the optical stimulation system includes a light source that emits in the green or blue wavelength ranges (for example, in the range of 450 to 550 nm or in the range of 495 to 545 nm or the like) or any other suitable visible wavelengths. A wavelength or wavelength range of a light source may be selected to obtain a specific therapeutic, chemical, or biological effect.

In at least some embodiments, a calibration table or calibration formula is provided for the light source to correlate the input power or current to the output light emission (e.g., output power). U.S. Patent Application Publication No. 2021/0016111, incorporated herein by reference in its entirety, describes embodiments of optical stimulation systems that incorporate a calibration table or calibration formula.

A photodetector (for example, light monitor 124 or an independent light monitoring device), such as a photodiode, can be used to measure the output light emission. The light emission can be quantified at the light source or at the emission region(s) of the optical lead. In at least some embodiments, the photodetector is integrated with the light source, but independent photodetectors can also, or instead, be used to measure light emission at the light source or at the light emission region(s) of the optical lead. In at least some embodiments, the photodetector returns a photocurrent whose value is measured by reading the corresponding voltage (U_{photo}) over a known resistance. In at least some embodiments, the light emission is quantified in mV or in mW. In at least some embodiments, the current to the light source (in mA) is progressively increased and the optical power (in mW or mV or both) is recorded using

a photodetector. As an example, when U_{photo} = 1mV, P_o = 0 mW and when U_{photo} = 410 mV, P_o = 20 mW. These values can be used to calibrate the light source and, in at least some embodiments where light emission is measured at the emission region(s), the optical lead. In at least some embodiments, the calibration is specific to the light source, optical lead, or both.

The calibration table or calibration formula of the specific implant light source/optical lead can be stored in the memory of the control module or other device in order to produce the desired optical power (in mW) when setting the light source current (in mA). In at least some embodiments, the calibration table or calibration formula can be written as $P_{opt}(mW) = f(I_o(mA))$ where P_{opt} is the optical power and I_o is the light source current. In at least some embodiments, the calibration table or calibration formula (e.g., a calibration curve) can be measured or verified during the implantation surgery using at least three points. In at least some embodiments, verification occurs if the measurements (or slope of a calibration curve or any other suitable test of the calibration) during surgery is within a threshold percentage (for example, 5 or 10% or any other suitable percentage) of the measurements (or slope of a calibration curve or any other suitable test of the calibration) from an earlier calibration.

The base unit 128 can also include additional elements such as electrical components associated with the light source 120 or light monitor 124, a heat sink, optical components (for example, a lens, polarizer, filter, or the like), a light shield to reduce or prevent light emission out of the housing of the base unit or to reduce or prevent extraneous light from penetrating to the light monitor 124 or the like. The housing 130 of the base unit 128 can be made of any suitable material including, but not limited to, plastic, metal, ceramic, or the like, or any combination thereof. If the base unit 128 is to be implanted, the housing 130 is preferably made of a biocompatible material such as, for example, silicone, polyurethane, titanium or titanium alloy, or any combination thereof. In at least some embodiments, for deep brain stimulation the base unit 128 is mounted on the skull or in a burr hole formed in the skull of the patient. In at least some embodiments, the base unit 128 can include a jacket or coating of a

relatively soft or flexible material, such as silicone, to provide protection for the skin and skull from the hard housing 130.

One example of base unit 128 includes a laser diode as a light source 120 disposed in a hermetic housing 130 of titanium surrounded by silicone. In one example of placement, the base unit 128 is disposed in a burr hole and attached to the skull using screws or other fasteners.

In at least some embodiments, the optical lead 122 can be, or include, an optical fiber, fiber optic, or any other suitable optical waveguide. In at least some embodiments, the optical lead 122 can include a jacket (such as lead body 141 of Figure 2) around the optical fiber, fiber optic, or other suitable optical waveguide. An optical lead 122 may also include one or more optical components, such as a lens, diffuser, polarizer, filter, or the like, at the distal portion of the lead (for example, at the terminal end of the optical waveguide 138) to modify the light transmitted through the optical waveguide.

An optical lead may be more than a single optical fiber, fiber optic, or other suitable optical waveguide. In at least some embodiments, the optical lead 122, as illustrated in cross-section in Figure 2, includes a lead body 141 and one or more optical waveguides 138 (for example, one or more optical fibers) for transmission of light from the light source 120 with emission along the one or more emission regions 132 disposed on the distal portion of the optical lead, as illustrated in Figure 1A. In at least some embodiments that include a light monitor 124, the optical lead 122 may include one or more optical waveguides 140 (or other optical transmission media) that receive light emitted from the light source 120 and transmitted by the optical waveguide 138 in order to measure or monitor the light emitted at the one or more emission regions 132 of the optical lead. The optical waveguide(s) 140 transmit light from the one or more emission regions 132 of the optical lead to the light monitor 124 in the base unit 128. The optical lead 122 may also include one or more optical components, such as a lens, diffuser, polarizer, filter, or the like, at the distal portion of the lead (for example, at the

terminal end of the optical waveguide 140) to modify the light received by the optical waveguide(s) 140.

One example of an optical lead 122 includes an optical fiber that is attached (for example, glued) to the light source at one end and coated with a silicone jacket or sheath to form the lead body 141. In at least some embodiments, the optical lead 122 has an outer diameter of no more than 2.5, 2, 1.5, 1.25, or 1 mm. In at least some embodiments, the optical lead 122 can include a marker (for example, a metal ring) that assists in radiological tracking of the optical lead within the patient. In at least some embodiments, the emission region 132 of the optical lead 122 is coated with an antireflection coating.

The connector lead 134 includes conductors (e.g., wires – not shown) disposed in a lead body extending along the connector lead 134 to the terminals 136 on the proximal end of the connector lead. As an alternative, the connector lead 134 may be permanently attached to a control module or other device where the conductors then attach to contact points within the control module or other device. The conductors carry electrical signals to the base unit 128 and the light source 120 and, optionally, other electrical components in the base unit for operation of the light source 120. The conductors may also carry electrical signals from the optional light monitor 124 in the base unit 128 to the control module or other device. These electrical signals may be generated by the light monitor 124 in response to light received by the light monitor.

Figure 1B is a schematic side view of one embodiment of proximal ends 142 of one or more leads (for example, connector lead 134 of Figure 1A) or lead extensions 160 (see, Figure 3) coupling to a control module 146 (or other device) through one or more control module connectors 144. The one or more proximal ends 142 include terminals 148 (for example, terminals 136 of connector lead 134).

The control module connector 144 defines at least one port 150a, 150b (and port 150, Figure 3) into which a proximal end 142 can be inserted, as shown by directional arrows 152a and 152b. The control module 146 (or other device) can define any

suitable number of ports including, for example, one, two, three, four, five, six, seven, eight, or more ports.

The control module connector 144 also includes connector contacts, such as connector contact 154, disposed within each port 150a and 150b. When the proximal end 142 is inserted into the ports 150a and 150b, the connector contacts 154 can be aligned with a plurality of terminals 148 disposed along the proximal end(s) 142. Examples of connectors in control modules are found in, for example, U.S. Patent No. 7,244,150 and 8,224,450, which are incorporated by reference.

The control module 146 typically includes a connector housing 145 and a sealed electronics housing 147. An electronic subassembly 110 and an optional power source 112 are disposed in the electronics housing 147.

In a least some embodiments, the light source 120 can be disposed in the control module 146 instead of a base unit 128. In these embodiments, the connector lead 134 is not needed and, instead, light is transmitted into the optical lead 122 from the control module, optionally through a lead extension that also incorporated optical fibers, fiber optics, or any other suitable optical waveguide.

Figure 3 is a schematic side view of a portion of another embodiment of components of an optical stimulation system including a lead extension 160 that is configured to couple one or more proximal ends 142 of a lead (for example, connector lead 134 of Figure 1A) to the control module 146. In Figure 3, the lead extension 160 is shown coupled to a single port 150 defined in the control module connector 144.

A lead extension connector 162 is disposed on the lead extension 160. In Figure 3, the lead extension connector 162 is shown disposed at a distal end 164 of the lead extension 160. The lead extension connector 162 includes a connector housing 166. The connector housing 166 defines at least one port 168 into which terminals 148 of the proximal end 142 of the lead can be inserted, as shown by directional arrow 170. The connector housing 166 also includes a plurality of connector contacts, such as connector contact 172. When the proximal end 142 is inserted into the port 168, the connector

contacts 172 disposed in the connector housing 166 can be aligned with the terminals 148 for electrical coupling.

In at least some embodiments, the proximal end 174 of the lead extension 160 is similarly configured as a proximal end 142 of a lead. The lead extension 160 may include a plurality of electrically conductive wires (not shown) that electrically couple the connector contacts 172 to a proximal end 174 of the lead extension 160 that is opposite to the distal end 164. In at least some embodiments, the conductive wires disposed in the lead extension 160 can be electrically coupled to a plurality of terminals (not shown) disposed along the proximal end 174 of the lead extension 160. In at least some embodiments, the proximal end 174 of the lead extension 160 is configured for insertion into a connector disposed in another lead extension (or another intermediate device). In other embodiments (and as shown in Figure 3), the proximal end 174 of the lead extension 160 is configured for insertion into the control module connector 144.

Figure 4 is a schematic overview of one embodiment of components of an optical stimulation system 400 (or combination optical/electrical stimulation system) including an electronic subassembly 110 disposed within a control module 146 (Figure 1B) (for example, an implantable or external pulse generator or implantable or external light generator). It will be understood that the optical stimulation system can include more, fewer, or different components and can have a variety of different configurations including those configurations disclosed in the stimulator references cited herein. In at least some embodiments, the optical stimulation system may also be capable of providing electrical stimulation through optional electrodes 126.

In at least some embodiments, selected components (for example, a power source 112, an antenna 418, a receiver 402, a processor 404, and a memory 405) of the optical stimulation system can be positioned on one or more circuit boards or similar carriers within a sealed housing of a control module. Any suitable processor 404 can be used and can be as simple as an electronic device that, for example, produces signals to direct or generate optical stimulation at a regular interval or the processor can be capable of receiving and interpreting instructions from an external programming unit

408 or remote control 409 that, for example, allows modification of stimulation parameters or characteristics.

Any suitable memory 405 can be used. The memory 405 illustrates a type of computer-readable media, namely computer-readable storage media. Computer-readable storage media may include, but is not limited to, nonvolatile, non-transitory, removable, and non-removable media implemented in any method or technology for storage of information, such as computer readable instructions, data structures, program modules, or other data. Examples of computer-readable storage media include RAM, ROM, EEPROM, flash memory, or other memory technology, magnetic storage devices, or any other medium which can be used to store the desired information and which can be accessed by a processor.

The processor 404 is generally included to control the timing and other characteristics of the optical stimulation system as the processor 404 is coupled to the light source 120. For example, the processor 404 can, if desired, control one or more of the timing, pulse frequency, interval between pulses, amplitude, and duration of the optical stimulation. In addition, the processor 404 can select one or more of the optional electrodes 126 to provide electrical stimulation, if desired. In some embodiments, the processor 404 selects which of the optional electrode(s) are cathodes and which electrode(s) are anodes.

The processor 404 provides electrical signals to operate the light source 120 including, for example, directing or driving the generation of light by the light source, pulsing the light source, or the like. For example, the processor 404 can direct current from the power source 112 via the connector lead 134 (Figure 1A) to operate the light source 120 in the base unit 128 (Figure 1A). In at least some embodiments, the light source 120 is coupled to one or more optical waveguides (such as an optical fiber or other optical transmission media) disposed in an optical lead 122. In at least some embodiments, the optical lead 122 is arranged so that one or more of the optical waveguides emits light from the distal portion of the optical lead (for example, the

distal end or at one or more positions along the distal portion of the lead or any combination thereof).

Optionally, the processor 404 is also coupled to a light monitor 124 that is used to monitor or measure light from the light source 122. For example, the light monitor 124 can produce electrical or other signals in response to the light received by the light monitor. Any suitable light monitor 124 can be used including, but not limited to, photodiodes, phototransistors, photomultipliers, charge coupled devices (CCDs), light dependent resistors (LRDs), photo-emissive cells, photo-conductive ells, photo-voltaic cells, photo-junction devices, or the like or any combination thereof. The light monitor 124 may be used to measure or monitor the light emitted by the light source 120 or from the optical waveguide(s) (or other optical transmission media) of the optical lead 122. In at least some embodiments, the light monitor 124 may be coupled to one or more optical waveguides (or other optical transmission media) of the optical lead 122 to transmit the light along an optical lead for measurement or monitoring. Examples of monitoring of light can be found in U.S. Patent No. 11,524,174 and U.S. Patent Applications Publication Nos. 2021/0008389 and 2021/0016111, all of which are incorporated herein by reference in their entireties.

Any power source 112 can be used including, for example, a battery such as a primary battery or a rechargeable battery. Examples of other power sources include super capacitors, nuclear or atomic batteries, fuel cells, mechanical resonators, infrared collectors, flexural powered energy sources, thermally-powered energy sources, bioenergy power sources, bioelectric cells, osmotic pressure pumps, and the like. As another alternative, power can be supplied by an external power source through inductive coupling via an antenna 418 or a secondary antenna. The external power source can be in a device that is mounted on the skin of the user or in a unit that is provided near the user on a permanent or periodic basis. In at least some embodiments, if the power source 112 is a rechargeable battery, the battery may be recharged using the antenna 418 and a recharging unit 116. In some embodiments, power can be provided to the battery for recharging by inductively coupling the battery to the external recharging unit 116.

In at least some embodiments, the processor 404 is coupled to a receiver 402 which, in turn, is coupled to an antenna 418. This allows the processor 404 to receive instructions from an external source, such as programming unit 408 (e.g., a clinician programmer) or the remote control 409, to, for example, direct the stimulation parameters and characteristics. The signals sent to the processor 404 via the antenna 418 and the receiver 402 can be used to modify or otherwise direct the operation of the optical stimulation system. For example, the signals may be used to modify the stimulation characteristics of the optical stimulation system such as modifying one or more of stimulation duration and stimulation amplitude. The signals may also direct the optical stimulation system 400 to cease operation, to start operation, to start charging the battery, or to stop charging the battery. In other embodiments, the stimulation system does not include the antenna 418 or receiver 402 and the processor 404 operates as initially programmed.

In at least some embodiments, the antenna 418 is capable of receiving signals (*e.g.*, RF signals) from an external programming unit 408 (such as a clinician programmer or any other device) or remote control 409 which can be programmed by a user, a clinician, or other individual. The programming unit 408 or remote control 409 can be any unit that can provide information or instructions to the optical stimulation system 400. In at least some embodiments, the programming unit 408 or remote control 409 can provide signals or information to the processor 404 via a wireless or wired connection. One example of a suitable programming unit is a clinician programmer or other computer operated by a clinician or other user to select, set, or program operational parameters for the stimulation. A remote control 409 can be, for example, a device that is worn on the skin of the user or can be carried by the user and can have a form similar to a pager, cellular phone, or remote control, if desired. In at least some embodiments, a remote control used by a patient may have fewer options or capabilities for altering stimulation parameters than a clinician programmer.

Optionally, the optical stimulation system 400 may include a transmitter (not shown) coupled to the processor 404 and the antenna 418 for transmitting signals back to the programming unit 408, remote control 409, or another unit capable of receiving

the signals. For example, the optical stimulation system 400 may transmit signals indicating whether the optical stimulation system 400 is operating properly or not or indicating when the battery needs to be charged or the level of charge remaining in the battery. The processor 404 may also be capable of transmitting information about the stimulation characteristics so that a user or clinician can determine or verify the characteristics.

In some embodiments, the optical stimulation system may also be an electrical stimulation system and include electrodes 126 on the optical lead 122 or on a separate electrode lead. Examples of electrical stimulation systems with leads that can be adapted for use in the optical stimulation systems described herein are found in, for example, U.S. Patents Nos. 6,181,969; 6,295,944; 6,391,985; 6,516,227; 6,609,029; 6,609,032; 6,741,892; 7,244,150; 7,450,997; 7,672,734;7,761,165; 7,783,359; 7,792,590; 7,809,446; 7,949,395; 7,974,706; 8,831,742; 8,688,235; 6,175,710; 6,224,450; 6,271,094; 6,295,944; 6,364,278; and 6,391,985; U.S. Patent Applications Publication Nos. 2007/0150036; 2009/0187222; 2009/0276021; 2010/0076535; 2010/0268298; 2011/0004267; 2011/0078900; 2011/0130817; 2011/0130818; 2011/0238129; 2011/0313500; 2012/0016378; 2012/0046710; 2012/0071949; 2012/0165911; 2012/0197375; 2012/0203316; 2012/0203320; 2012/0203321; 2012/0316615; 2013/0105071; 2011/0005069; 2010/0268298; 2011/0130817; 2011/0130818; 2011/0078900; 2011/0238129; 2011/0313500; 2012/0016378; 2012/0046710; 2012/0165911; 2012/0197375; 2012/0203316; 2012/0203320; and 2012/0203321, all of which are incorporated by reference in their entireties.

In at least some embodiments, some or all of the components of the optical stimulation system are implanted into the patient. In particular, at least the distal end of the optical lead 122 is implanted into the patient, for example, into the brain of the patient. The use of the optical stimulation system for treating Parkinson's disease by stimulating the substantia nigra is presented herein as an example for implantation, operation, and use of elements of the optical stimulation system. It will be understood that the optical stimulation systems and methods described herein can be used or

adapted for treating other diseases and disorders and for targeting stimulation sites other than the substantia nigra.

In at least some embodiments, the optical lead 122 is introduced prefrontally into the frontal horn of the lateral ventricle, passes into the third ventricle, and stops before the floor of the third ventricle. The axis of the trajectory aims at the midpoint of the line joining the centers of the substantia nigra compacta. In at least some embodiments, the optical lead is attached to a base unit 128, with the light source 120, implanted in a cranial vault and powered by a control module implanted in a subclavicular position. It will be recognized that other trajectories can be used, particularly for other sites of stimulation.

The following is an example of one embodiment of a surgical method for implanting and placing elements of an optical stimulation system. Prior to surgery, MRI or CT imaging (or both) is performed on the lead implantation site. In at least some embodiments, at least a portion of the imaging is performed within 1 to 5 days of the surgery. Using the imaging, a trajectory is defined with the optional assistance of surgical planning software. The trajectory can include an entry point, a target site (or end point), and a trajectory line. As an example, with the substantia nigra as the target, the entry point can be defined on the pre-coronal area with the trajectory proceeding over the second frontal gyrus defined by drawing a line between the target and the foramen of Monro. The trajectory may pass through the foramen of Monro (for example, the right foramen of Monro for a right-handed patient). This alignment with the target determines the entry point at the convexity of the skull, close to the coronal suture. The trajectory may be modified in view of blood vessels. The trajectory passes through the frontal lateral ventricle, then the foramen of Monro, and ends on the floor of the third ventricle in a position set between the middle of the two substantia nigra pars reticulata (SNr).

The surgery is typically performed under general anesthesia and under stereotactic conditions with the patient's head being fixed in a stereotactic frame. The patient is placed in a supine position with sterile preparation of the head and

subclavicular region. Radiographic methods are used to visualize the implantation of the lead.

An incision is made into the subclavicular region and a subcutaneous pocket is formed for the control module 146 (e.g., the implantable pulse generator.) In at least some embodiments, in distinction from typical electrical stimulation implantation, the implantation of the control module 146 is performed before the implantation of the optical lead 122 as the power source 112 of the control module 146 is used to test the light source 120 and optical lead prior to implantation of the optical lead. The base unit 128 containing the light source 120 is coupled to the control module 146, optionally through a lead extension 160.

An incision is made in the ipsi-lateral parietal region. The connector lead 134 and optional lead extension 160 are tunneled subcutaneously from the temporo-parietal zone to the control module 146 between the two incisions.

Next, with the head fixed in the stereotactic frame, a skin incision is made in the right frontal region. In at least some embodiments, a semi-circular incision is made at the entry point extending for up to approximately 5 cm. This incision is larger than typical for electrical stimulation leads as two burr holes are created – one for the optical lead 122 and one for the base unit 128. Craniotomy is performed to form a drill hole at the entry point for the implantation of the optical lead 122. In at least some embodiments, the drill hole is relatively large, for example 10-12 mm in diameter.

Another burr hole is formed for the base unit 128, which houses the light source. As an example, this second burr hole can have a diameter of 15-30 mm, centered approximately 30-50 mm behind the coronal suture and 15-25 mm from the midline. A template of the base unit 128 may be used during the craniotomy to ensure the burr hole is correctly sized. The base unit 128 is inserted into the burr hole and fixed with fasteners, such as maxillofacial screws or adhesive (e.g., dental adhesive) or the like or any combination thereof.

A cannula can be inserted through the first burr hole. One example of a suitable cannula is the neuroguide™ guide tube from Renishaw Healthcare Inc. (West Dundee, Illinois, United States). In at least some embodiments, the cannula (and other items, such as the optical lead 122) are inserted using a robotic arm or the like, although manual insertion can also be performed. Iopamiron or other suitable contrast agent can be injected followed by performance of ventriculography. This procedure can delimit one or more marks such as the anterior white commissure, the posterior white commissure, the foramen of Monro, the third ventricular floor, the shape of the lateral ventricle or the third ventricle, or the like or any combination thereof. The final position of the end of the cannula is within the third ventricle after having passed the foramen of Monro. In at least some embodiments, the end of the cannula is fixed 8-12 mm from the target.

The optical lead 122 and the base unit 128 are tested prior to insertion into the cranium. The base unit 128 is coupled to the control module 146 (or to a testing control module), which is turned on. In at least some embodiments, the control module (or testing control module) is set to direct the light source 120 of the base unit 128 to generate light continuously to facilitate efficient testing. Light is generated by the light source 120 in the base unit 128 and measured or otherwise observed to ensure that an appropriate amount of light is exiting the distal end of the optical lead. This procedure verifies the optical integrity of the optical lead. A light monitor 124 of the optical lead 122 or an external light measurement device can be used for the testing and measurements.

In at least some embodiments, the optical lead 122 and the base unit 128 are attached testing control module for this testing instead of the control module 146 that is part of the system, as the control module 146 may already be implanted. In at least some embodiments, the testing control module is identical to the control module 146. In at least some embodiments, the testing control module is reused and sterilized between implantation surgeries. In at least some embodiments, a sterilized lead extension 160 is connected between the testing control module and the base unit 128.

In at least some embodiments, an external light measurement device may not be sterile. The external light measurement device can be maintained within a sterile bag and can be positioned relative to the distal end of the optical lead 122 using a sterilized tool that holds both a light gathering element of the external light measurement device (within the sterile bag) and the distal end of the optical lead in a fixed position for the measurement(s) and testing. In at least some embodiments, the testing includes measurements of optical power (for example, three measurements at different current values applied to the light source 120). These measurements (or a slope of the measurements or any other suitable testing measure) are compared to values (or a slope or any other suitable testing measure) from earlier measurements or calibration to ensure that the optical lead 122 and light source 120 are consistent with the earlier measurements or calibration. In at least some embodiments, the operating room may be darkened to facilitate visual observation of the generated light.

The optical lead 122 is inserted through the cannula into the patient. Care is taken to ensure that the optical lead 122 is not bent too much to avoid breaking or damaging the optical fiber(s) or other optical waveguide(s) in the optical lead. The final position of the distal end of the optical lead 122 can be verified using imaging, for example, x-ray fluoroscopy. The cannula is removed and the optical lead 122 is then secured by suture or any other suitable lead securement element or combination of elements. For example, adhesive, such as dental cement or biological glue, can be used to fix the optical lead 122 within the burr hole. The proximal portion of the optical lead, outside the burr hole, is tunneled or otherwise inserted under the skin. The final arrangement is confirmed using imaging, such as x-ray fluoroscopy or CT imaging.

Subsequent to the surgery (for example, within hours, 1, 2, 3, 5, or 7 days or any other suitable time period), the optical stimulation system is turned on. In at least some embodiments, the current applied to the light source 120 is increased to a desired level. The patient may be observed during this time for stimulation effects, although it will be understood that many effects are not observable within the time period of the clinician visit as those effects may take longer to manifest. The patient can be taught how to use

the remote control 409 to control stimulation to the extent allowed by the clinician and optical stimulation system.

In at least some embodiments, optical stimulation is provided using a duty cycle with on-periods and off-periods. In at least some embodiments, the percentage of time that is within the on-periods is at least 1, 5, 10, 15, 20, 25%, or more. As an example of stimulation parameters, the light source is operated to provide illumination at 670 nm with a pulse frequency of 150 Hz, an output power of 15mW, and a duty cycle of 1 minute on and 4 or 5 minutes off.

Follow-up visits can be performed regularly in which neurological and general examinations can be conducted. In at least some visits, the examination can measure or test physiological responses using, for example, MPS-UPDRS assessments; the Archimedes spiral test; the presence of tremor in the limbs, such as the hands; the presence of micro-pupillary tremors; gait analysis; freezing of gait; rate or speed of left and right feet; assessments of non-motor skills using any suitable assessment methodology or test; or the like or any combination thereof. Examples of cognitive assessments include, but are not limited to, MMSE (Mini Mental State Exam), ADAS-Cog, neuropsychiatric measures such as NPI-Q (Neuropsychiatric Inventory Questionnaire), sleep inventories such as PSQI (Pittsburgh sleep quality index), or the like. Examples of other assessment methodologies and tests include, but are not limited to, ECMP (Behavioral Assessment of Parkinson's Disease), LARS (Lille Apathy Rating Scale), BDI-II (Beck Depression Inventory, version II), NMS (Non-Motor Symptoms Scale), and PDQ-39 (Parkinson's Disease Questionnaire).

In at least some visits, the examination can include imaging, such as, for example, CT, PET (described below), x-ray fluoroscopy, or any other suitable type of imaging. In at least some embodiments, the examination can include exporting data from the control module 146, remote control 409, or any other suitable device that is in contact with the optical stimulation system. Such data may be used to monitor items such as, for example, device performance, patient practices, patient compliance,

temperature during charging of the control module 146 or operation of the light source 120, or the like or any combination thereof.

PET can be used to investigate the non-displaceable binding potential (BP_{ND}) of the [^{11}C]PE2I. A PET-scan can facilitate the evaluation of optical stimulation on dopaminergic transmission using, for example, the ligand [^{11}C]PE2I binding to the dopamine transporter (DAT) or any other suitable marker. An anatomical brain MRI or the like can be used to calibrate the PET images on the brain structures. This MRI is generally performed prior to implantation of the optical lead 122.

PET imaging can include intravenous injection of a radiotracer bolus, such as the [^{11}C]PE2I (DAT ligand). In at least some embodiments, a low-dose CT scan sequence can be acquired before each PET scan to correct tissue attenuation during PET data reconstruction.

In at least some embodiments, the images are analyzed by voxel-by-voxel or by larger regions. In at least some embodiments, the images are normalized in the MNI (Montreal Neurological Institute) space or any other suitable normalize space. For example, the PET images are registered on the individual MRI; the parameters are calculated to transform the native space of the individual MRI to the space of a gray matter template; and (iii) the PET images are normalized using these transformation parameters. The PET images can be smoothed using an isotropic Gaussian filter or any other suitable smoothing function or filter to reduce variance due to interindividual anatomical variability and to increase the signal-to-noise ratio.

A voxel analysis can be performed on regions of interest. The anterior commissure can be used as a reference to define the anterior-posterior boundary of these regions on consecutive axial sections. The ventral territory of the striatum (anatomically corresponding to the anterior territories of the caudate nucleus and putamen) can be manually delimited on consecutive coronal sections. The regional values of BP_{ND} of [^{11}C]PE2I can be calculated using the values of all the voxels within each region of interest.

In at least some embodiments, the optical power delivered to a particular region of the brain can be determined. In at least some embodiments, the determined optical power can correspond to a dosage. The following is one example of a measurement protocol. CT-scan(s) and MRI data (for example, T1 and T2 weighted images) are obtained and are preferably registered to each other. The CT-scan(s) and MRI data are used to segment the brain into different regions. Examples of regions include, but are not limited to, the skull, white matter, gray matter, cerebrospinal fluid, substantia nigra, eye, optical nerve, red nucleus, or the like. Some or all of these regions (and possibly other regions) can be defined or otherwise used for any particular analysis. For example, the CT scan(s) can be used to segment the skull and the MRI data can be used to segment the white and gray matter, as well as other soft tissue regions.

Optical parameters can be obtained, determined, or estimated for each region. The optical parameters can include, for example, one or more of the following (which may be defined for a particular wavelength or wavelength range of interest): an absorption coefficient, a scattering coefficient, an anisotropy factor, or the like or any combination thereof. In at least some embodiments, optical parameters can be found in the literature or otherwise estimated.

The light source has associated operational parameters, such as one or more of the following: size, orientation, position, wavelength, power, or the like or any combination thereof. A Monte Carlo simulation, for a given period of time or number of photons, is performed using the operational parameters of the light source 120 and the optical parameters of the regions of the brain that are illuminated to determine or estimate light propagation in the brain and the optical power or dosage at points within the brain. It will be understood that other simulation techniques can be used in place of the Monte Carlo simulation. A dosage for a particular stimulation target (or any other region) in the brain can be determined using the Monte Carlo simulation by only considering the amount of light received by the particular stimulation target (or other region).

The above specification provides a description of the manufacture and use of the invention. Since many embodiments of the invention can be made without departing from the spirit and scope of the invention, the invention also resides in the claims hereinafter appended.

5

CLAIMS

1. A method for implanting and using an optical stimulation system comprising an optical lead, a base unit comprising a light source, and a control module, wherein the base unit is couppleable, or coupled, to the optical lead and the control module, the method comprising:

forming a first burr hole in a skull of a patient for implantation of the optical lead;

forming a second burr hole in the skull and spaced apart from the first burr hole and configured to receive at least a portion of the base unit;

coupling the optical lead to the base unit;

coupling the base unit to the control module;

implanting the optical lead through the first burr hole into the skull of the patient; and

receiving the portion of the base unit into the second burr hole.

2. The method of claim 1, wherein the second burr hole has a larger diameter than the first burr hole.

3. The method of claim 1 or 2, further comprising fastening the base unit to the skull.

4. The method of any of claims 1 to 3, further comprising implanting the control module in the patient.

5. The method of claim 4, wherein the implanting comprises implanting the control module in a subclavicular region of the patient.

6. The method of any of claims 1 to 5, further comprising tunneling at least a connector lead from the base unit to the control module.

7. The method of any of claims 1 to 6, further comprising, prior to implanting the optical lead, inserting a cannula through the first burr hole into the brain of the patient, wherein the implanting comprises implanting the optical lead through the cannula.

8. The method of any of claims 1 to 7, further comprising fastening the optical lead to the skull and the implanting.

9. The method of any of claims 1 to 8, further comprising after the implanting, optically stimulating the patient using the optical stimulation system.

10. The method of claim 9, further comprising after the optically stimulating, obtaining a PET scan to assess effectiveness of the optical stimulation.

11. A method for implanting an optical stimulation system comprising an optical lead, a base unit comprising a light source, and a control module, wherein the base unit is coupleable, or coupled, to the optical lead and the control module, the method comprising:

coupling the base unit to the control module prior to implanting the optical lead;

coupling the optical lead to the base unit prior to implanting the optical lead;

testing the optical lead and the light source in the base unit using the control module to determine that power is delivered from the control module to the light source, light is produced by light source and delivered to the optical lead, and the light is emitted from the optical lead at at least one emission region disposed on a distal portion of the optical lead; and

after the testing, implanting the optical lead into a brain of a patient.

12. The method of claim 11, further comprising, prior to the testing, implanting the control module into the patient.

13. The method of claim 11 or 12, further comprising, prior to the testing, implanting at least a portion the base unit into the patient.

14. The method of any of claims 11 to 13, wherein the testing comprises determining a value of an optical power of light emitted from the at least one emission region of the optical lead for a plurality of different light source current values.

15. The method of claim 14, wherein the testing further comprises using the values of optical power determined by the testing in a comparison test based on previously measured optical power values.

16. The method of claim 15, wherein the comparison test comprises comparing a slope of the values of optical power determined by the testing with a slope of the previously measured optical power values.

17. A method for implanting an optical stimulation system comprising an optical lead, a base unit comprising a light source, and a control module, wherein the base unit is coupleable, or coupled, to the optical lead and the control module, the method comprising:

forming a first burr hole in a skull of a patient for implantation of the optical lead;

inserting a cannula through the first burr hole into a brain of the patient;

delivering a contrast agent through the cannula to the brain of the patient;

visualizing at least one ventricle of the brain of the patient using the contrast agent; and

after the visualizing, implanting the optical lead through the cannula into the brain of the patient using the visualization to guide placement of the optical lead.

18. The method of claim 17, further comprising, prior to implantation surgery, imaging the brain of the patient.

19. The method of claim 18, further comprising, prior to implantation surgery, using the imaging to plan a trajectory for the optical lead into the brain of the patient.

20. The method of any of claims 17 to 19, further comprising using the trajectory or an actual position of the optical lead in the brain of the patient to estimate an optical power of the optical lead for a set of optical lead parameters delivered to a target site in the brain of the patient.

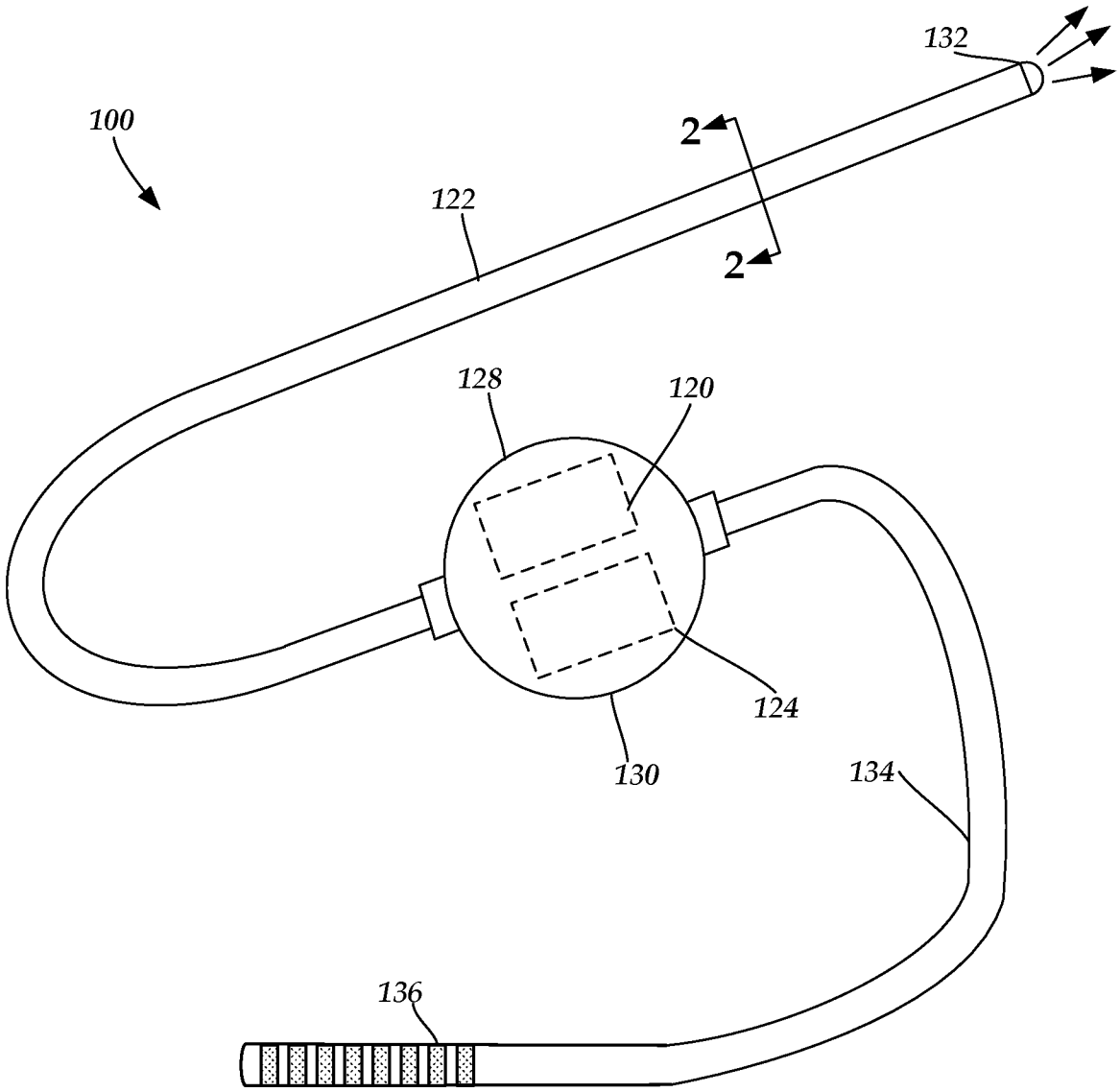

Fig. 1A

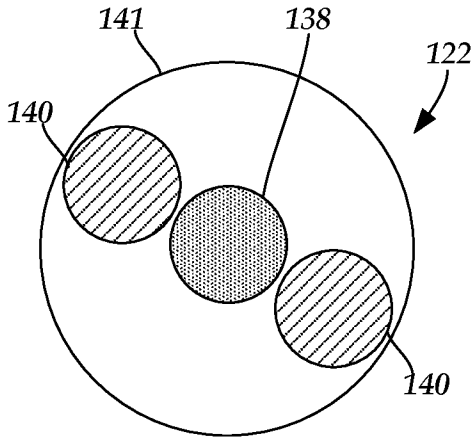

Fig. 2

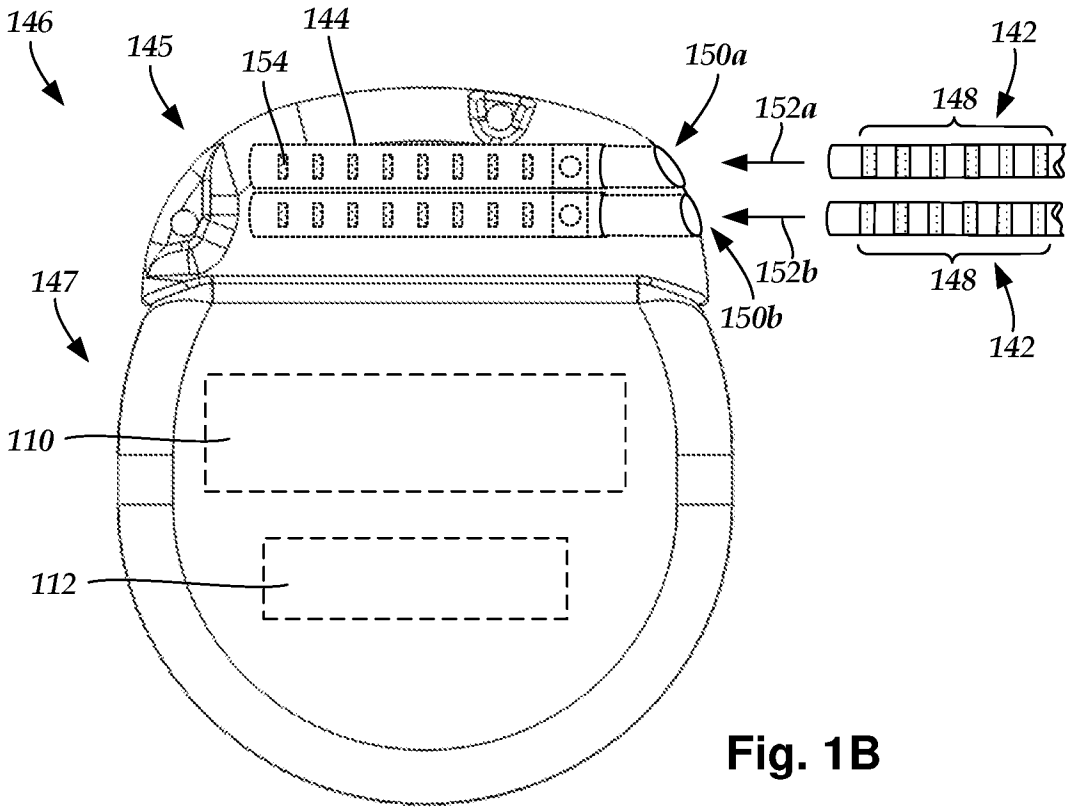

Fig. 1B

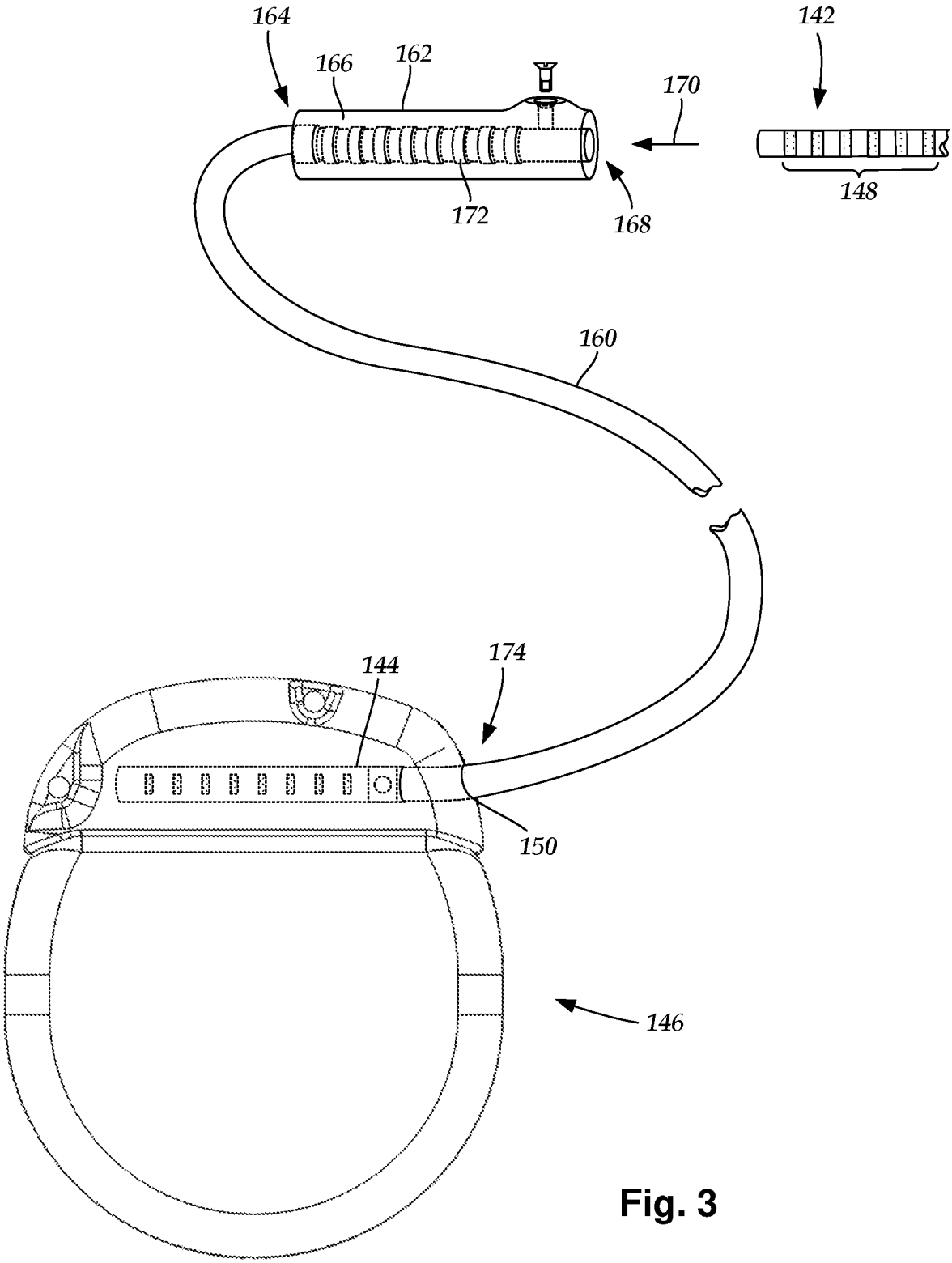

Fig. 3

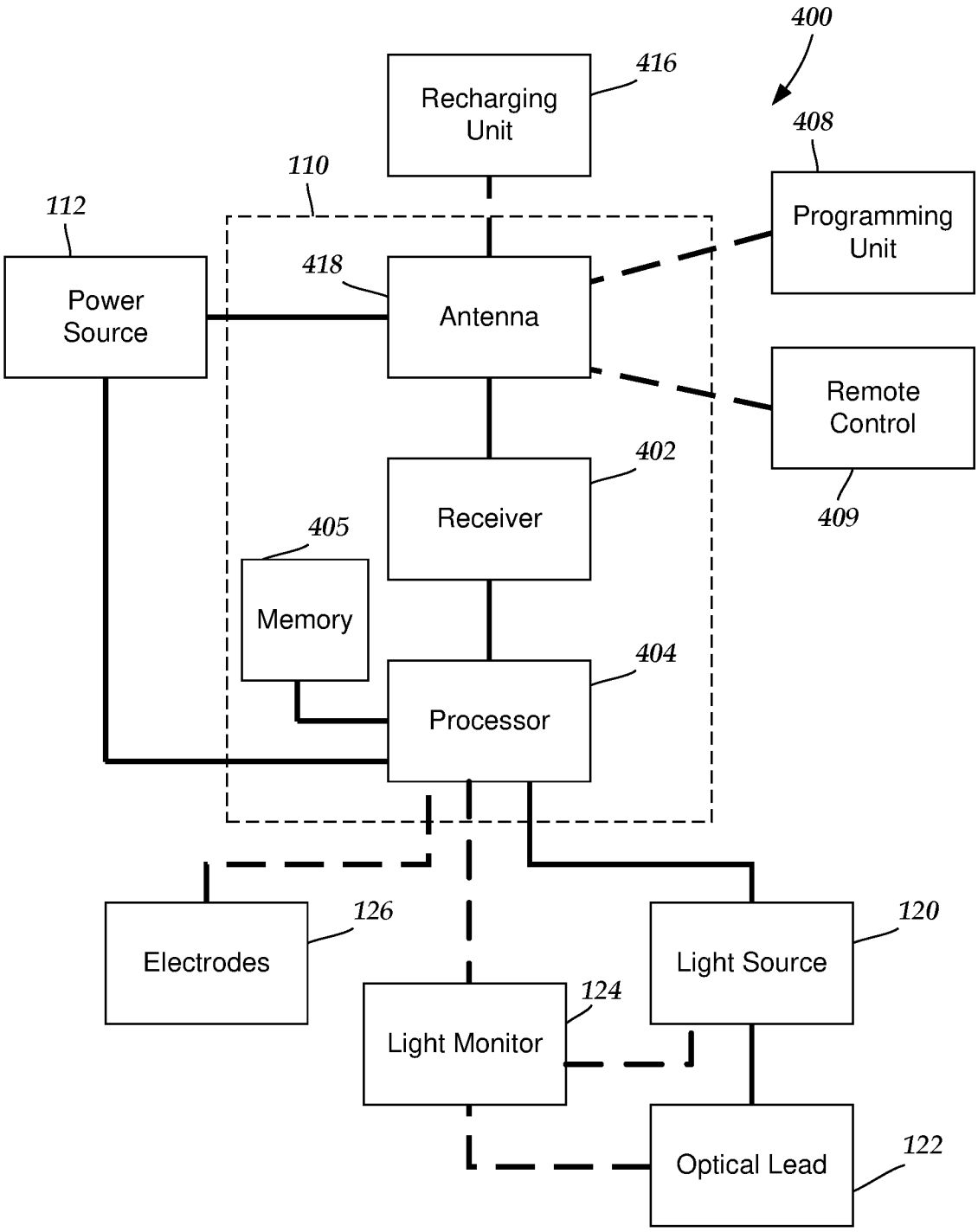
400
Recharging Unit
416
408
110
112
Programming Unit
418
Power Source
Antenna
Remote Control
402
409
Receiver
405
Memory
404
Processor
Electrodes
126
120
Light Source
124
Light Monitor
Optical Lead
122

Fig. 4

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13*ter*.1(c) and Rule 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing(day/month/year)
1H330680DI1SLE		21 July 2023 (21-07-2023)
International application No.	International filing date(day/month/year)	(Earliest) Priority date(day/month/year)
PCT/IB2022/000735	29 December 2022 (29-12-2022)	
International Patent Classification (IPC) or both national classification and IPC		
A61N5/06		
Applicant		
BENABID ALIM-LOUIS		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below

1. [X] The subject matter of the international application relates to:
   - a. [ ] scientific theories
   - b. [ ] mathematical theories
   - c. [ ] plant varieties
   - d. [ ] animal varieties
   - e. [ ] essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
   - f. [ ] schemes, rules or methods of doing business
   - g. [ ] schemes, rules or methods of performing purely mental acts
   - h. [ ] schemes, rules or methods of playing games
   - i. [X] methods for treatment of the human body by surgery or therapy
   - j. [ ] methods for treatment of the animal body by surgery or therapy
   - k. [ ] diagnostic methods practised on the human or animal body
   - l. [ ] mere presentations of information
   - m. [ ] computer programs for which this International Searching Authority is not equipped to search prior art
2. [X] The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
   [ ] the description [X] the claims [ ] the drawings
3. [ ] A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:
   - [ ] furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in a form, language and manner acceptable to it.
   - [ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).

4. Further comments:

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	OBLINGER, Sabine Tel:+49 (0)89 2399-7714

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

Claims 1-20, thus all the claims relate to subject-matter considered by this Authority to be covered by the provisions of Article 17.2(a)(i) and Rule 39.1(iv) PCT as the said claims define therapeutic an surgical methods (implantation of an optical stimulation system). Consequently, no search has been carried out for those claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.