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(19) **United States**(12) **Patent Application Publication****Dawant et al.**(10) **Pub. No.: US 2005/0070781 A1**(43) **Pub. Date: Mar. 31, 2005**(54) **ELECTROPHYSIOLOGICAL ATLAS AND APPLICATIONS OF SAME**

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Publication Classification(51) **Int. Cl.⁷** **A61B 5/05**(52) **U.S. Cl.** **600/407; 607/45**(57) **ABSTRACT**

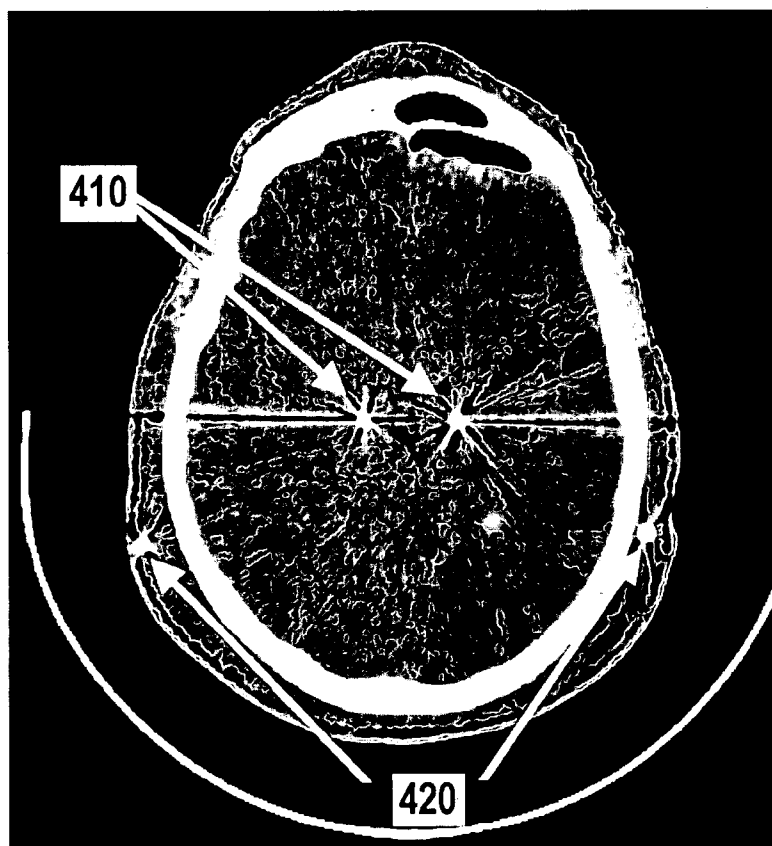
A method of creating an atlas that contains electrophysiological information related to at least one of a plurality of living subjects. In one embodiment, the method includes the steps of choosing a brain image volume as a common image volume of reference, acquiring electrophysiological information for a target of interest, relating the acquired electrophysiological information to spatial coordinates in the brain image volume of the target of interest, and registering the brain image volume of the target of interest to the common image volume of reference so as to create an atlas in which any spatial coordinates of the brain of the target of interest are related to atlas coordinates in the atlas such that the acquired electrophysiological information associated with the related spatial coordinates in the brain image volume of the target of interest can be related to atlas coordinates in the atlas, and vice versa.

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(73) Assignee: **Vanderbilt University**, Nashville, TN(21) Appl. No.: **10/883,233**(22) Filed: **Jul. 1, 2004****Related U.S. Application Data**

(63) Continuation of application No. 10/833,504, filed on Apr. 28, 2004.



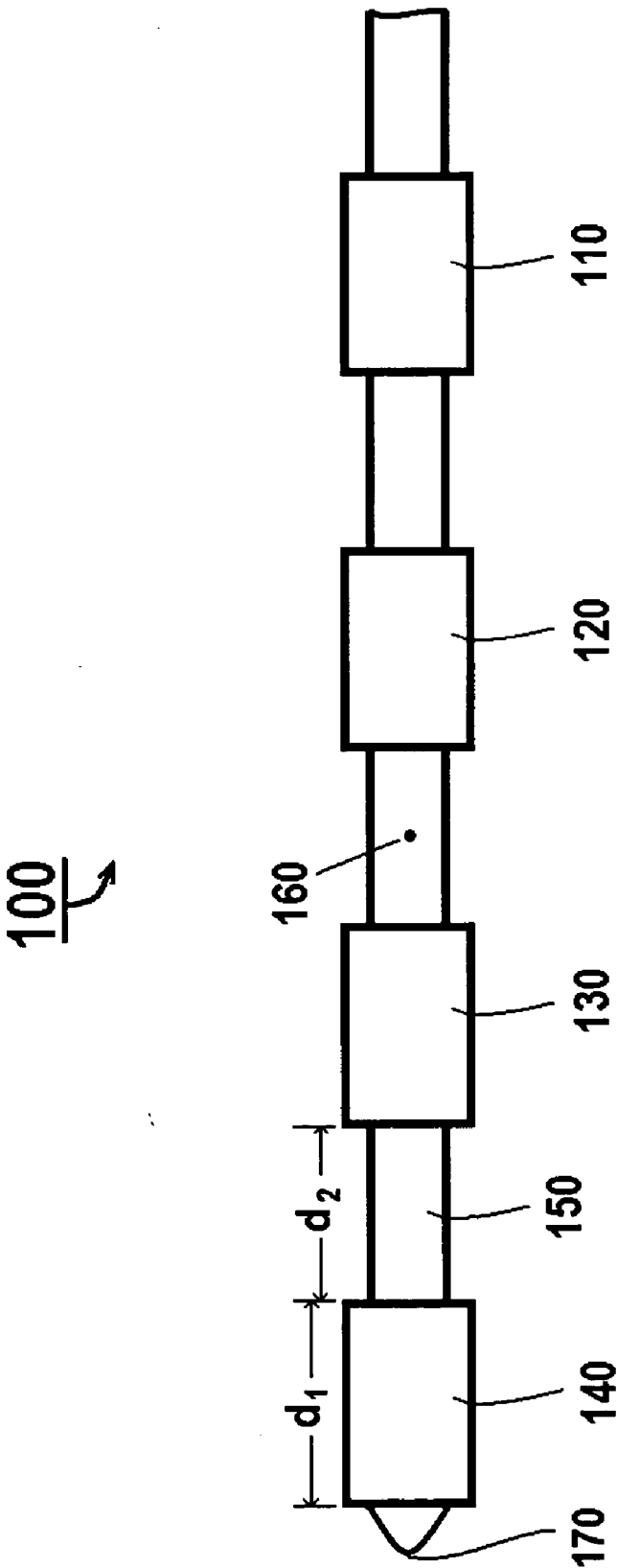


Fig. 1

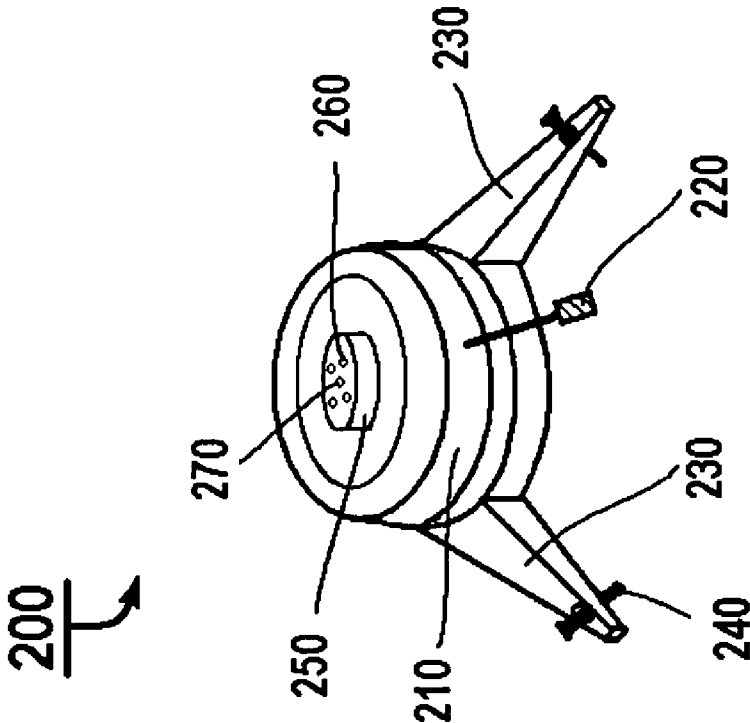


Fig. 2a

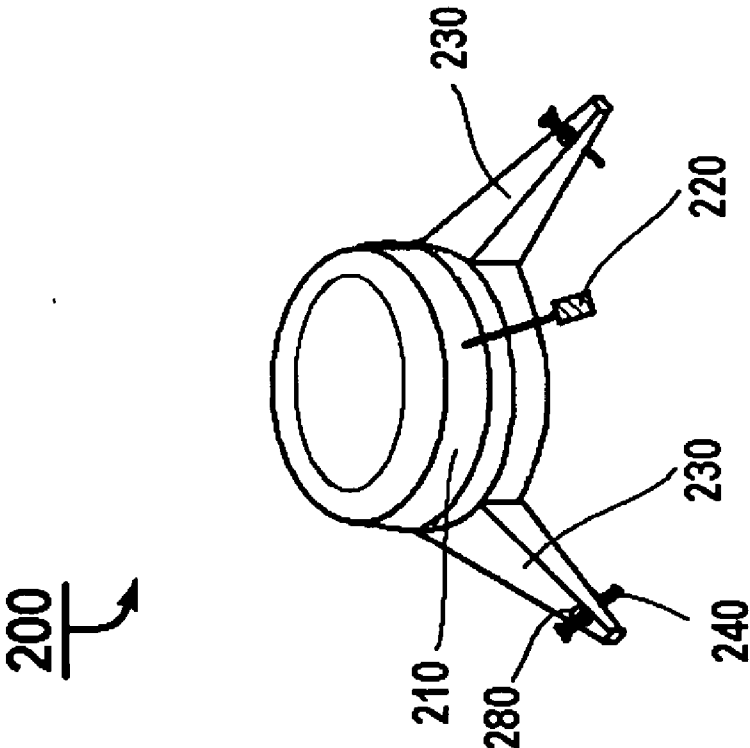


Fig. 2b

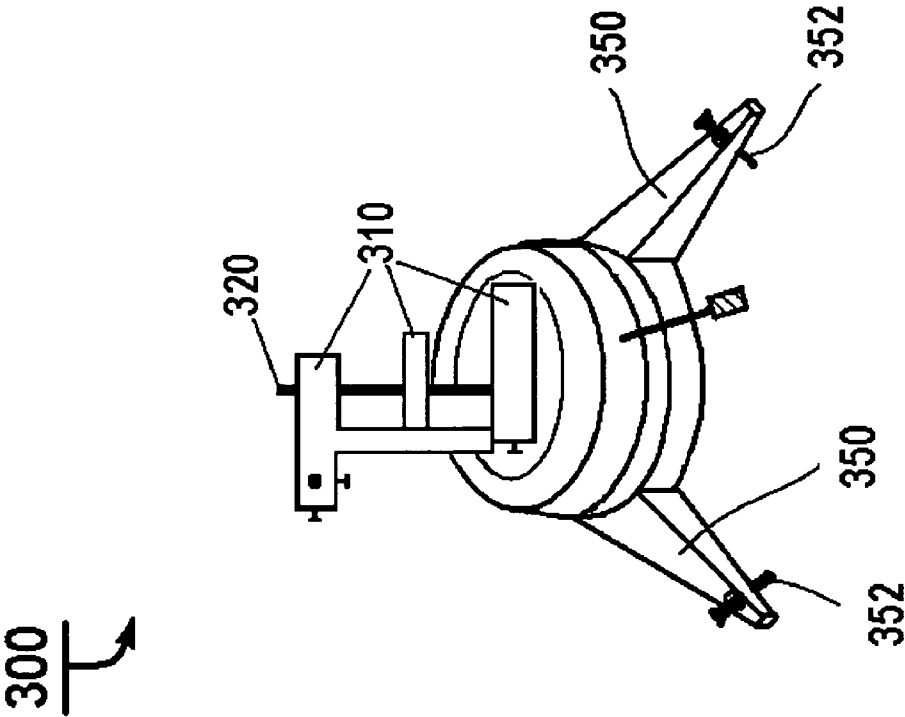


Fig. 3

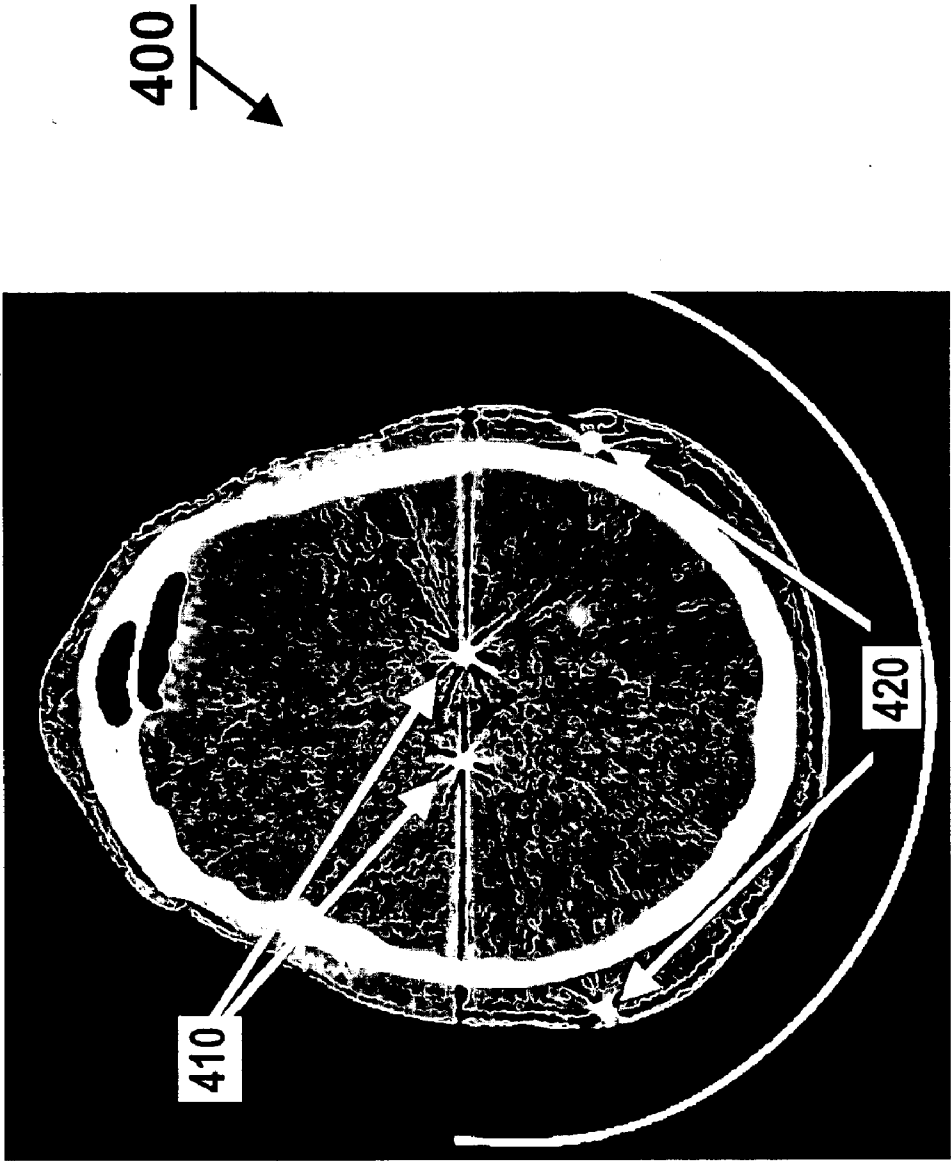


Fig. 4

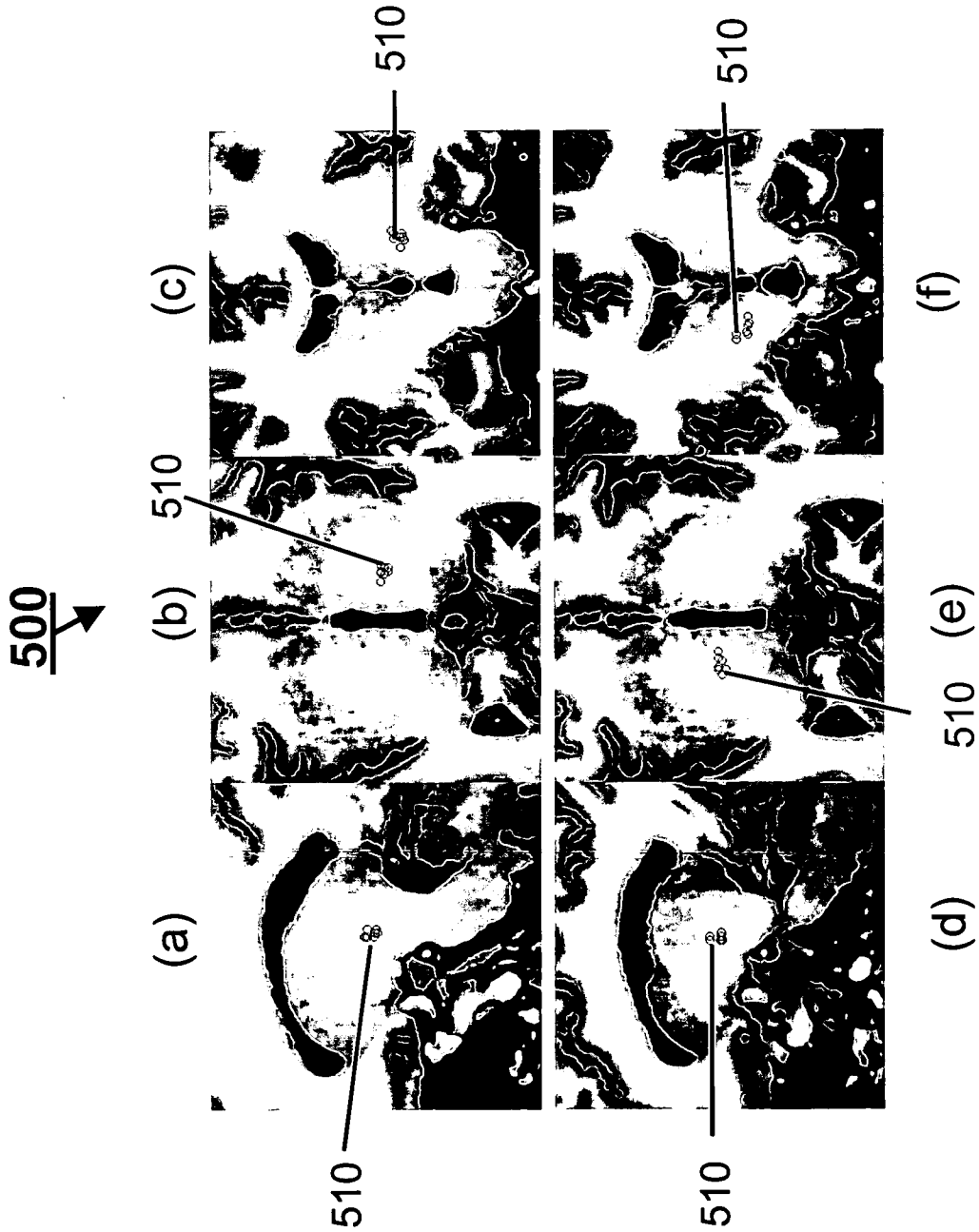


Fig. 5

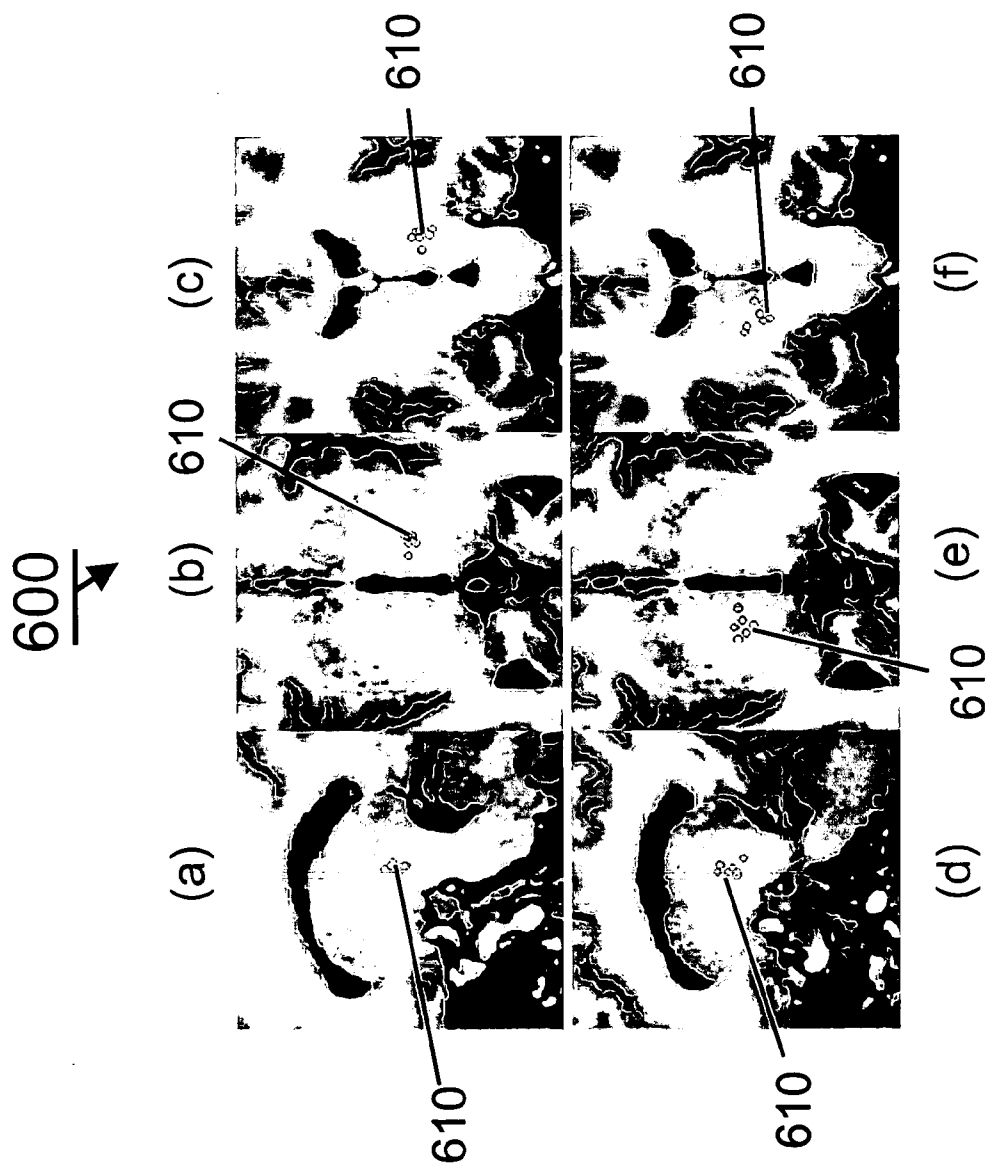


Fig. 6

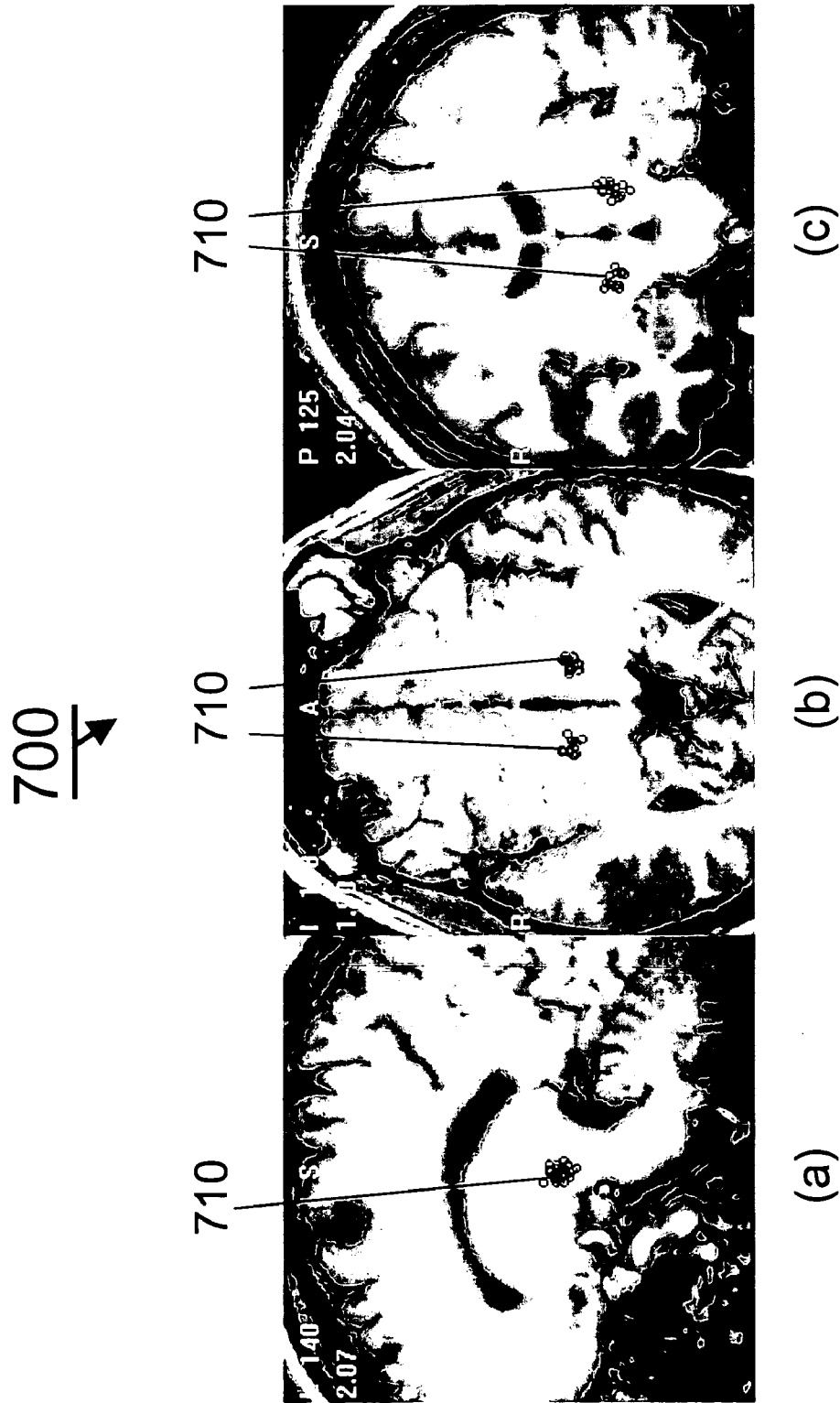


Fig. 7

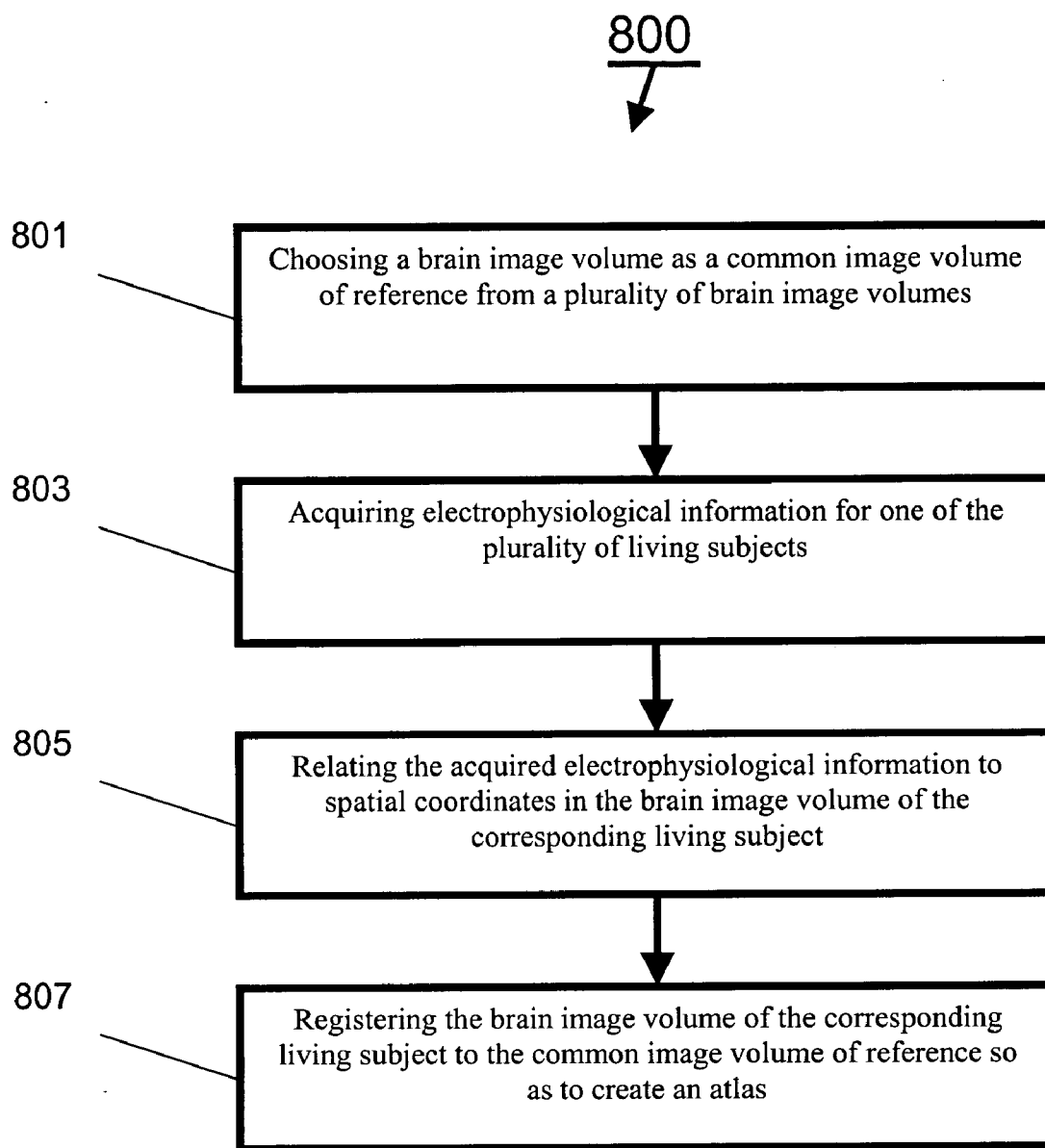


Fig. 8

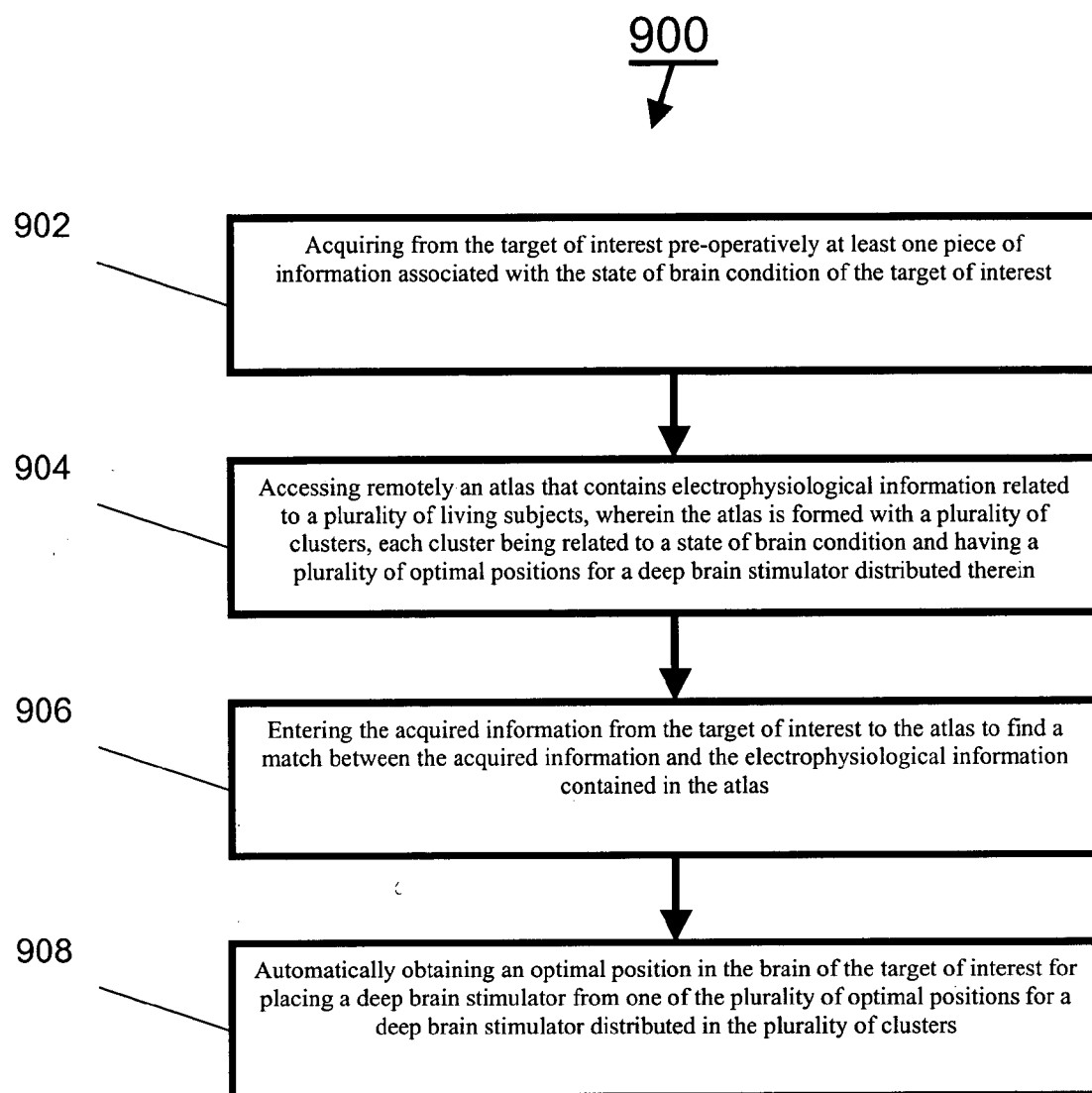


Fig. 9

1000
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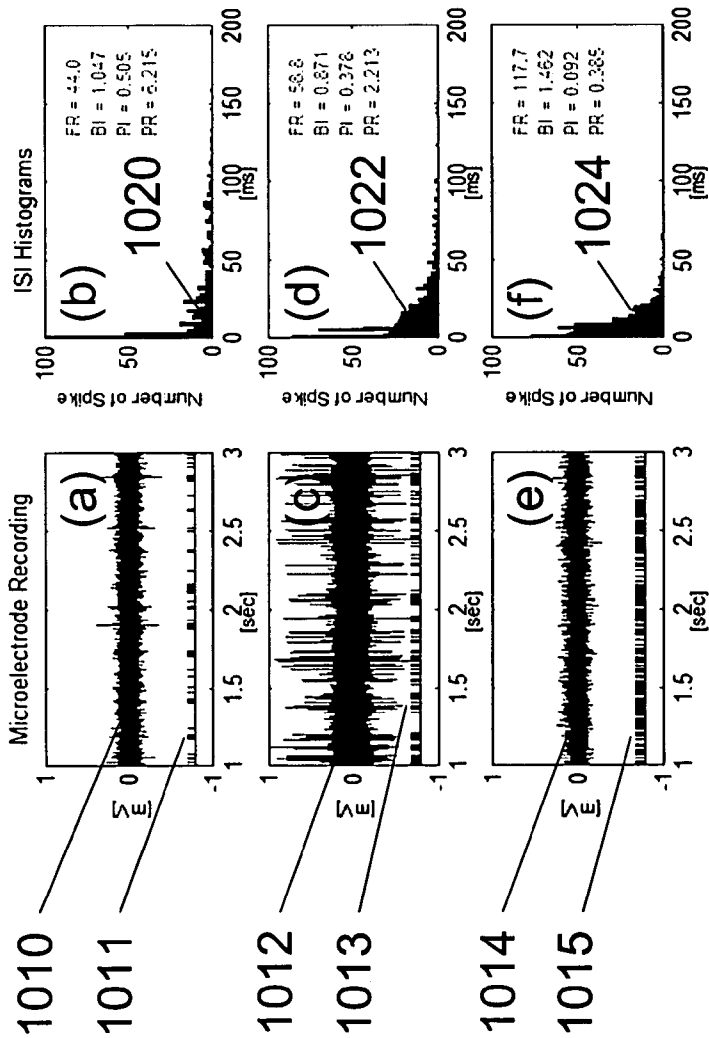
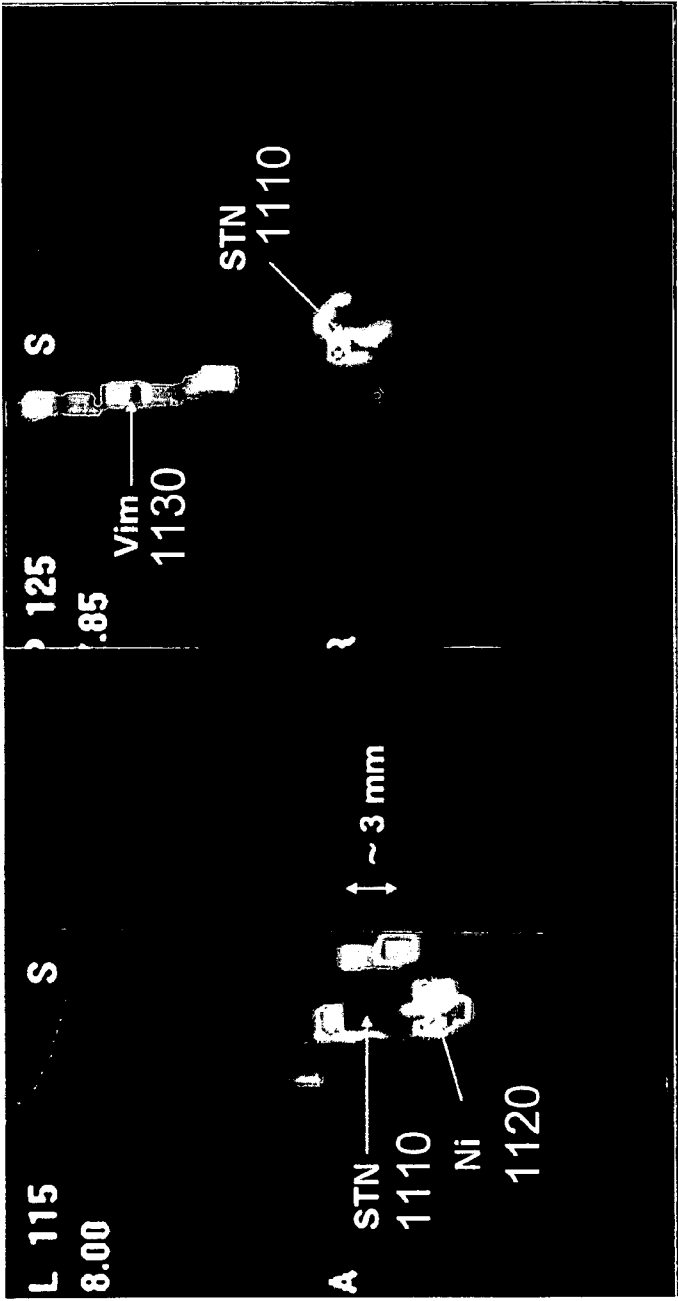


Fig. 10

1100



(a)

(b)

Fig. 11

ELECTROPHYSIOLOGICAL ATLAS AND APPLICATIONS OF SAME

CROSS-REFERENCE TO RELATED PATENT APPLICATION

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 10/833,504, filed Apr. 28, 2004, entitled "APPARATUS AND METHODS OF OPTIMAL PLACEMENT OF DEEP BRAIN STIMULATOR," by Benoit M. Dawant, the disclosure for which is incorporated herein by reference in its entirety, which itself claims the benefit, pursuant to 35 U.S.C. § 119(e), of provisional U.S. patent application Serial No. 60/466,219, filed Apr. 28, 2003, entitled "APPARATUS AND METHODS OF COMPUTERIZED ATLAS-GUIDED POSITIONING OF DEEP BRAIN STIMULATORS," by Benoit M. Dawant, which is incorporated herein by reference in its entirety.

[0002] Some references, which may include patents, patent applications and various publications, are cited and discussed in the description of this invention. The citation and/or discussion of such references is provided merely to clarify the description of the present invention and is not an admission that any such reference is "prior art" to the invention described herein. All references cited and discussed in this specification are incorporated herein by reference in their entireties and to the same extent as if each reference was individually incorporated by reference. In terms of notation, hereinafter, "[n]" represents the nth reference cited in the reference list. For example, [9] represents the 9th reference cited in the reference list, namely, G. Rhode, A. Aldroubi and B. M. Dawant, "The Adaptive-bases algorithm for intensity-based nonrigid image registration," *IEEE Transactions on Medical Imaging*, vol. 22, no. 11, pp 1470-1479, 2003.

FIELD OF THE INVENTION

[0003] The present invention generally relates to an atlas, and in particular to the creation and/or utilization of an atlas that contains electrophysiological information related to one or more living subjects for optimal placement of one or more deep brain stimulators placement in a brain of a target of interest.

BACKGROUND OF THE INVENTION

[0004] Since its first Food and Drug Administration (hereinafter "FDA") approval in 1998, deep-brain stimulation (hereinafter "DBS") has gained significant popularity in the treatment of a variety of brain-controlled disorders, including movement disorders [1, 2]. The therapy of the DBS has significant applications in the treatment of tremor, rigidity, and drug induced side effects in patients with Parkinson's disease and essential tremor. Generally, such treatment involves placement of a DBS electrode lead through a burr hole drilled in the patient's skull, followed by placement of the electrode lead and then applying appropriate stimulation signals through the electrode lead to the physiological target. The placement portion of the treatment, involving stereotactic neurosurgical methodology, is very critical, and has been the subject of much attention and research. In particular, finding the deep brain target and then permanently placing the electrode lead so that it efficiently stimulates such target is very important.

[0005] Yet finding the optimal physiological target in deep brain stimulation implants for the treatment of movement disorders is a particularly complicated task. This is especially true for the treatment of symptoms that cannot be tested at the operating table during the electrode lead implantation. For instance, it is practically impossible to test walking and postural stability in Parkinson's Disease (hereinafter "PD") patients during the DBS lead implantation. Two other major PD symptoms, Rigidity and Akinesia, are also considered difficult to evaluate quantitatively during DBS lead implantation. On the other hand, the surgical targets of interest involve deep brain nuclei or subregions within the subthalamus or globus pallidus intemus. These structures are not visible in any current imaging modalities, such as magnetic resonance imaging (hereinafter "MRI"), X-ray computerized tomography (hereinafter "CT"), or Positron Emission Tomography (hereinafter "PET").

[0006] Ideally, the optimal target for the DBS therapy should be located within the stimulation range of 1 or 2 contacts, each contact measuring 1.5 mm separated by either 1.5 mm or 0.5 mm. Effective stimulation results when the contacts surround the optimal target [3, 4]. For example, as shown in FIG. 1, for placement of a 4-contact electrode lead of a deep brain stimulator 100, which has a tip portion 170, a central body portion 150 and associated contacts 110, 120, 130 and 140 (Medtronic #3387 or #3389 quadripolar lead®, Medtronic, Inc., Minneapolis, Minn.), in the proximity of functional areas which one may refer to as targets or targeted regions, a preferable scenario is that two contacts 110 and 120 of the quadripolar lead 100 lie above and the other contacts 130 and 140 lie below a target. For this example of the lead, each of the contacts 110, 120, 130, and 140 has a length, d_1 , which is substantially around 1.5 mm for a Medtronic #3387 or #3389 quadripolar lead®, and the distance between two neighboring contacts, for example, 130 and 140, is d_2 , where $d_2=1.5$ mm for Medtronic #3387 quadripolar lead®, and $d_2=0.5$ mm for Medtronic #3389 quadripolar lead®, respectively. If the contacts are located as little as 2 mm away from the desired target, ineffective stimulation results, which may be due to several reasons: (i) failure to capture control of the group of neurons, (ii) stimulation of non-desirable areas resulting in unpleasant stimulation, or (iii) necessity for higher stimulus intensities to produce the desired effect resulting in reduced battery life of the implantation, or an any combination of these or other reasons. At least for these reasons, targeting the specific neurons of interest for the DBS therapy requires millimetric precision and allowance for variability among patients. Therefore, the process of implantation of a DBS electrode lead requires stereotactic neurosurgical methodology, i.e., the use of a common reference coordinate system to target structures within the brain of a target of interest. Typically, the process of implantation of a DBS electrode follows a step-wise progression of (i) initial estimation of target localization based on imaged anatomical landmarks, (ii) intra-operative microanatomical mapping of key features associated with the intended target or target position of the brain of a target of interest, (iii) adjustment of the final target of implantation by appropriate shifts in three dimensional space, and (iv) implantation of a quadripolar electrode with contacts located surrounding the final desired target or target position of the brain of the target of interest.

[0007] Because of the invisibility of deep brain targets or target positions of interest in any current imaging modalities, such as MRI, CT, or PET, the location of these targets can only be inferred approximately from the position of adjacent structures that are visible in the images. To augment the information that these images provide, printed anatomic atlases or electronic versions of these have been used. Anatomic atlases, such as the Schaltenbrand-Wahren atlas [14], involve a series of unevenly spaced brain sections that have been histologically stained to reveal the structures and substructures of interest. When digitized, these atlases can be superimposed on the pre-operative images using landmarks visible both in the atlas and in the image volumes. Although it represents a partial solution to the target identification problem, this approach seems to suffer from a number of shortcomings [15]. First, available anatomic atlases have been created from one single brain [16] or from several hemispheres pertaining to different individuals [14]. When a single brain is used, information is limited to one sectioning plane per hemisphere. When several brains are used, these atlases show non-contiguous anatomy in intersecting orthogonal slices. Registration (i.e. spatial alignment) of these atlases to the image volumes also raises a number of issues. The standard procedure is to register atlas and image volumes using the inter commisural anterior commissure (hereinafter "AC")-posterior commissure (hereinafter "PC") reference system. This method is one in which the AC and PC points are manually selected in the image volumes. The image volumes are first translated to align the AC points. They are then rotated to align the AC-PC line and the midsagittal planes. Unfortunately, this technique results in substantial misregistration errors. A better approach proposed by St-Jean et al. [17] involves digitizing the Schaltenbrand-Wahren atlas, stacking individual slices, and creating three-dimensional (hereinafter "3D") structures from these slices through interpolation. These 3D structures are then registered to one magnetic resonance (hereinafter "MR") image volume by identifying homologous landmarks, thus creating an MR image volume on which labels from the atlas can be projected. But, this procedure only guarantees that the landmarks are registered to each other. In a later publication [15], the authors acknowledge that this limitation plus the fact that the creation of the 3D structures involves interpolating two-dimensional (hereinafter "2D") atlas slices that can be between 0.5 mm and 3 mm apart limit the accuracy and therefore the clinical usefulness of this approach.

[0008] In current clinical practice, the initial target localization is manually selected on MR images based on AC-PC coordinates. The initial target localization is refined by intra-operatively probing a surrounding region of the initial target with a recording and/or a stimulating electrode. First a recording electrode is placed into the initial target localization to characterize neuronal firing patterns, which are in turn used to infer locations of deep brain nuclei relevant to the targeted region. A stimulating electrode is then placed into the inferred location to elicit responses in an awake patient. Both of these sources of information allow neurosurgeons, neurologists, and neurophysiologists to establish functional borders and to mentally reconstruct a somatotopic organization of the structures of interest so as to identify a final target location at which a deep brain stimulator is to be placed. It can be a lengthy process (sometimes extending for hours in the awake patient) and it requires expertise in neurosurgery, neurophysiology, and clinical neurology [18, 19]. This combined expertise is available only at a limited

number of sites, which limits access to the procedure to about 3000 patients per year despite the estimated 180,000 patients per year who would benefit from it in the United States alone. Great clinical relevance would be gained if electrophysiological information could be captured from a large population, processed, and represented in a way that would make it usable for guidance purposes.

[0009] Therefore, a heretofore unaddressed need exists in the art to address the aforementioned deficiencies and inadequacies.

SUMMARY OF THE INVENTION

[0010] In one aspect, the present invention relates to a system for creating an atlas for optimal placement of a deep brain stimulator in a brain of a target of interest. In one embodiment, the system includes a data storage device, an image acquisition device for acquiring a brain image volume from the brain of the target of interest, and a data acquisition device for acquiring electrophysiological information from the brain of the target of interest.

[0011] Furthermore, the system includes a data processing device operably coupled to the data storage device, the image acquisition device and the data acquisition device, respectively. The data processing device is adapted for, among other things, performing the steps of relating the acquired electrophysiological information to spatial coordinates in the acquired brain image volume of the target of interest, and registering the acquired brain image volume of the target of interest to a common image volume of reference so as to create an atlas in which spatial coordinates of the brain of the target of interest are related to atlas coordinates such that the acquired electrophysiological information associated with the related spatial coordinates in the acquired brain image volume of the target of interest can be related to atlas coordinates in the atlas, and vice versa. The data processing device is adapted for further performing the step of storing the atlas in a digitized format of files in the data storage device.

[0012] Moreover, the system includes a user interface in communication with the atlas, which has an architecture to be accessible over a network. The user interface is used for populating the atlas with new electrophysiological information acquired from a target of interest, accessing the electrophysiological information from the atlas, and obtaining the electrophysiological information from in the atlas in one of a text format, an image format and a mixture thereof, respectively. In one embodiment, the obtained electrophysiological information includes an initial optimal target position for at least one deep brain stimulator to be placed in a brain of a target of interest.

[0013] In one embodiment, the data storage device includes a memory. The image acquisition device is arranged, in use, to acquire a computerized tomographical image and/or a magnetic resonance image for a target of interest. In one embodiment, the data acquisition device includes at least one microelectrode, and/or at least one stimulation electrode placed in a brain of a target of interest for acquiring intra-operative information for the target of interest. The data acquisition device further includes at least one deep brain stimulator placed in the brain of the target of interest for acquiring post-operative information.

[0014] The electrophysiological information to be acquired includes pre-operative information, intra-operative information and post-operative information for a target of interest, respectively. In one embodiment, the pre-operative information includes at least one piece of information associated with presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof. The symptoms have at least one of upper extremity rigidity, lower extremity rigidity, upper extremity dystonia and lower extremity dystonia. The unified Parkinson's disease rating scale scores are a rating tool for evaluating mentation, behavior and mood, activities of daily living, motor activity, and complication of therapy for a target of interest undergoing treatment.

[0015] The intra-operative information includes at least one piece of information associated with at least one microelectrode, where the information includes microelectrode recordings, a position of the microelectrode recordings, a label of a structure in which the microelectrode recordings is located, and any mixture thereof. The microelectrode recordings are characterized by a firing rate that measures tonic activity and indices that measures phasic activity, where the indices include a burst index, a pause ratio, a pause index, and an interspike interval histogram. Other characteristic features may also be extracted from the microelectrode recordings and can also be utilized. The intra-operative information may also include at least one piece of information associated with at least one stimulation electrode, where the information includes voltages applied to the at least one stimulation electrode, a response of a target of interest undergoing treatment to the stimulation, differences in voltage between disappearance of symptoms and appearance of side effects, a position of the at least one stimulation electrode, a final intra-operative target position of a deep brain stimulator to be placed, and any mixture thereof. The response of the target of interest undergoing treatment to the stimulation includes loss of rigidity, location where the loss of rigidity is observed, appearance of side effects, and/or location affected by these side effects.

[0016] The post-operative information comprises at least one piece of information associated with at least one deep brain stimulator, where the information includes a position of the at least one deep brain stimulator in post-operative computerized tomographical images, optimal setting of the at least one deep brain stimulator, overall assessment of a target of interest after placement of the at least one deep brain stimulator, and any mixture thereof.

[0017] In another aspect, the present invention relates to a method of creating an atlas. The atlas contains electrophysiological information related to at least one of a plurality of living subjects, where any portion of interest of a brain of one of the plurality of living subjects and corresponding image volume may be identified by a set of corresponding spatial coordinates.

[0018] In one embodiment, among other things, the method includes the step of choosing a brain image volume as a common image volume of reference from a plurality of brain image volumes, each of the plurality of brain image volumes being acquired pre-operatively from a brain of one of the plurality of the living subjects.

[0019] The method further includes the steps of acquiring electrophysiological information for one of the plurality of living subjects, and relating the acquired electrophysiological information to spatial coordinates in the brain image volume of the corresponding living subject. Furthermore, the method includes the step of registering the brain image volume of the corresponding living subject to the common image volume of reference so as to create an atlas in which any spatial coordinates of the brain of the corresponding living subject are related to atlas coordinates in the atlas such that the acquired electrophysiological information associated with the related spatial coordinates in the brain image volume of the corresponding living subject can be related to atlas coordinates in the atlas, and vice versa. Moreover, the method includes the step of storing the atlas in a digitized format of files. The atlas has an architecture to be accessible over a network.

[0020] Additionally, the method includes the steps of populating the atlas with new electrophysiological information acquired from a target of interest, accessing the electrophysiological information from the atlas, and obtaining the electrophysiological information from the atlas in one of a text format, an image format and a mixture thereof, respectively. In one embodiment, the obtained electrophysiological information includes an initial optimal target position for at least one deep brain stimulator to be placed in a brain of a target of interest.

[0021] In yet another aspect, the present invention relates to a system that contains electrophysiological information related to at least one of a plurality of living subjects, where any portion of interest in the brain of one of the plurality of living subjects and corresponding brain image volume may be identified by a set of corresponding spatial coordinates.

[0022] In one embodiment, the system includes a data storage device, and an atlas stored in the data storage device for containing the electrophysiological information. The atlas is created such that when a brain image volume is registered to the atlas, any spatial coordinates of the brain image volume are related to corresponding atlas coordinates in the atlas, and vice versa. The atlas has an architecture to be accessible over a network and is in communication with a user interface. The user interface, in one embodiment, is used for populating the system with new electrophysiological information acquired from a target of interest, accessing the electrophysiological information from the system, and obtaining the electrophysiological information from the system in one of a text format, an image format and a mixture thereof, respectively. The system further includes a controller in communication with the data storage device. The data storage device has a memory.

[0023] In a further aspect, the present invention relates to a computer readable medium or media. In one embodiment, the computer readable medium or media includes a data structure and a user interface in communication with the data structure. The data structure relates to an atlas that contains electrophysiological information related to at least one of a plurality of living subjects, where any portion of interest for the brain of the at least one of the plurality of living subjects and corresponding image volume may be identified by a set of corresponding spatial coordinates.

[0024] In one embodiment, the atlas is created such that when a brain image volume of a living subject is registered to the atlas, any spatial coordinates in the brain image volume of the living subject are related to corresponding atlas coordinates in the atlas, and vice versa. Therefore, the electrophysiological information associated with spatial coordinates from which the electrophysiological information is acquired in the brain of the living subject can be related to atlas coordinates in the atlas, and vice versa. The atlas is stored in a digitized format of files.

[0025] The data structure, in one embodiment, includes a plurality of transformations and corresponding inverses of the plurality of transformations. Each of a plurality of transformations registers a brain image volume to the atlas, where the brain image volume is acquired from one of the plurality of living subjects.

[0026] In yet a further aspect, the present invention relates to a method for optimal placement of a deep brain stimulator in a brain of a target of interest. In one embodiment, the method includes the step of acquiring from the target of interest pre-operatively at least one piece of information associated with a state of brain condition of the target of interest. The state of brain condition is related to a type of a disease, and/or a degree of the disease. The information associated with the state of brain condition of the target of interest includes presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof of the target of interest.

[0027] Furthermore, the method includes the steps of accessing remotely an atlas that contains electrophysiological information related to a plurality of living subjects, where any portion of the brain of one of the plurality of living subjects and corresponding brain image volume may be identified by a set of corresponding spatial coordinates, entering the acquired information from the target of interest to the atlas to find a match between the acquired information and the electrophysiological information contained in the atlas, and automatically obtaining an optimal position in the brain of the target of interest for placing a deep brain stimulator from the matched information. In one embodiment, the atlas is stored in a memory device associated with a central host computer. The accessing step includes the step of accessing the atlas over a network from a client computer. The central host computer and client computer are coupled to and in communication with the network, respectively. The network, in one embodiment, has at least one of a public network, a dedicated network, a local network, and any combination of them. The public network, in one embodiment, comprises the Internet.

[0028] Moreover, the method includes the steps of acquiring electrophysiological information intra-operatively from the brain of the target of interest and adjusting the optimal position in the brain of the target of interest for placing a deep brain stimulator accordingly. Additionally, the method includes the steps of finding a final optimal position in the brain of the target of interest for placing a deep brain stimulator from the adjusted optimal position and placing a deep brain stimulator in the brain of the target of interest.

Also, in one embodiment, the method includes the steps of downloading information related to the optimal position in the brain of the target of interest for placing a deep brain stimulator from the matched information to a local computer and adjusting the optimal position in the brain of the target of interest for placing a deep brain stimulator from the downloaded information. The method further includes the step of updating the atlas from information related to the target of interest.

[0029] In another aspect, the present invention relates to a method for optimal placement of a deep brain stimulator in a brain of a target of interest. In one embodiment, the method includes the step of acquiring from the target of interest pre-operatively at least one piece of information associated with a state of brain condition of the target of interest. Furthermore, the method includes the steps of accessing remotely an atlas that contains electrophysiological information related to a plurality of living subjects, wherein the atlas is formed with a plurality of clusters, each cluster being related to a state of brain condition and having a plurality of optimal positions for a deep brain stimulator distributed therein, entering the acquired information from the target of interest to the atlas to find a match between the acquired information and the electrophysiological information contained in the atlas, and automatically obtaining an optimal position in the brain of the target of interest for placing a deep brain stimulator from one of the plurality of optimal positions for a deep brain stimulator distributed in the plurality of clusters.

[0030] These and other aspects of the present invention will become apparent from the following description of the preferred embodiment taken in conjunction with the following drawings, although variations and modifications therein may be affected without departing from the spirit and scope of the novel concepts of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] FIG. 1 schematically shows one example of a quadripolar deep brain stimulator that can be utilized to practice the present invention.

[0032] FIG. 2 schematically shows a platform that can be utilized to practice the present invention: (a) a perspective view of the platform, and (b) a perspective view of the platform with a guiding member in place.

[0033] FIG. 3 schematically shows a system that can be utilized to practice the present invention.

[0034] FIG. 4 shows a post-operative CT image of a patient after the bilateral DBS implantation according to one embodiment of the present invention.

[0035] FIG. 5 shows images of the final DBS positions acquired intra-operatively from a group of 8 patients with corresponding atlas coordinates visually shown according to one embodiment of the present invention: (a) a sagittal view of the left side subthalamic nucleus (hereinafter "STN") targets, (b) a transverse view of the left side STN targets, (c) a coronal view of the left side STN targets, (d) a sagittal view of the right side STN targets, (e) a transverse view of the right side STN targets, and (f) a coronal view of the right side STN targets.

[0036] FIG. 6 shows images of the final DBS positions acquired post-operatively from a group of 8 patients with corresponding atlas coordinates visually shown according to one embodiment of the present invention: (a) a sagittal view of the left side STN targets, (b) a transverse view of the left side STN targets, (c) a coronal view of the left side STN targets, (d) a sagittal view of the right side STN targets, (e) a transverse view of the right side STN targets, and (f) a coronal view of the right side STN targets.

[0037] FIG. 7 shows images of the final DBS positions acquired intra-operatively from a group of 18 patients with corresponding atlas coordinates visually shown according to one embodiment of the present invention: (a) a sagittal view of the left side and right side STN targets, (b) a transverse view of the left side and right side STN targets, and (c) a coronal view of the left side and right side STN targets.

[0038] FIG. 8 is a flowchart showing a method for creating an atlas containing electrophysiological information related to at least one living subject according to one embodiment of the present invention.

[0039] FIG. 9 is a flowchart showing a method for optimal placement of a deep brain stimulator in a brain of a target of interest according to one embodiment of the present invention.

[0040] FIG. 10 shows microelectrode recording (hereinafter “MER”) signals acquired from a target of interest and features extracted from the MER signals according to one embodiment of the present invention: (a) the MER signals at a position above the STN, (c) the MER signals at the middle of the STN, and (e) the MER signals at a position below the STN; and (b), (d), and (f), each showing an interspike interval (hereinafter “ISI”) histogram and feature values corresponding to the MER signals of (a), (c), and (e), respectively.

[0041] FIG. 11 shows mean burst index (hereinafter “BI”) color-coded and superimposed on MR images according to one embodiment of the present invention: (a) a sagittal view of the mean BI, and (b) a coronal view of the mean BI.

DETAILED DESCRIPTION OF THE INVENTION

[0042] The present invention is more particularly described in the following examples that are intended as illustrative only since numerous modifications and variations therein will be apparent to those skilled in the art. Various embodiments of the invention are now described in detail. Referring to the drawings, like numbers indicate like parts throughout the views. As used in the description herein and throughout the claims that follow, the meaning of “a,” “an,” and “the” includes plural reference unless the context clearly dictates otherwise. Also, as used in the description herein and throughout the claims that follow, the meaning of “in” includes “in” and “on” unless the context clearly dictates otherwise. Moreover, titles or subtitles may be used in the specification for the convenience of a reader, which has no influence on the scope of the invention. Additionally, some terms used in this specification are more specifically defined below.

DEFINITIONS

[0043] The terms used in this specification generally have their ordinary meanings in the art, within the context of the invention, and in the specific context where each term is used.

[0044] Certain terms that are used to describe the invention are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing various embodiments of the invention and how to practice the invention. For convenience, certain terms may be highlighted, for example using italics and/or quotation marks. The use of highlighting has no influence on the scope and meaning of a term; the scope and meaning of a term is the same, in the same context, whether or not it is highlighted. It will be appreciated that the same thing can be said in more than one way. Consequently, alternative language and synonyms may be used for any one or more of the terms discussed herein, nor is any special significance to be placed upon whether or not a term is elaborated or discussed herein. Synonyms for certain terms are provided. A recital of one or more synonyms does not exclude the use of other synonyms. The use of examples anywhere in this specification, including examples of any terms discussed herein, is illustrative only, and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to various embodiments given in this specification.

[0045] As used herein, “around,” “about” or “approximately” shall generally mean within 20 percent, preferably within 10 percent, and more preferably within 5 percent of a given value or range. Numerical quantities given herein are approximate, meaning that the term “around,” “about” or “approximately” can be inferred if not expressly stated.

[0046] As used herein, the term “living subject” refers to a human being such as a patient, or an animal such as a lab testing monkey.

[0047] As used herein, the term “target of interest” refers to a living subject under treatment or test.

[0048] As used herein, “target,” “position of interest,” and “target region” are synonyms in the specification and refer to an object of stimulation in a deep brain of a living subject for treatment of a brain-controlled disorder.

[0049] As used herein, “stimulation” refers to increase temporarily the activity of a body organ or part thereof responsive to an input signal to the body organ or part.

[0050] The terms “project,” “map,” and “transform,” as used herein, are synonyms in the specification and refer to a transformation of a point of interest from a source image volume to a target image volume, and vice versa.

[0051] The terms “place,” “implant,” and “insert,” as used herein, are synonyms in the specification and refer to put or embed a device, such as a microelectrode recording lead, macrostimulation lead, and/or a deep brain stimulator, into a target region of a brain of a living subject.

OVERVIEW OF THE INVENTION

[0052] Optimal placement of a deep brain stimulator comprises an iterative procedure and associated means for performing the task. A target region of a brain of a target of

interest is chosen pre-operatively based on anatomical landmarks identified on MR images. This target region or position is used as an initial position that is refined intra-operatively using information at least from one of micro-electrode recordings and macrostimulation. For example, first a microelectrode recording lead is placed into the initial position to characterize neuronal firing patterns, which are, in turn, used to infer locations of deep brain nuclei relevant to the target region. A unipolar macrostimulation lead is then placed into the inferred location to elicit responses in an awake patient. Both of these sources of electrophysiological information allow neurosurgeons, neurologists, and neurophysiologists to establish functional boundaries and to reconstruct a somatotopic organization of the structures of interest so as to identify a final target position at which a deep brain stimulator is to be placed. Because the length of the procedure increases with the time it takes to adjust the DBS to its final position, a good initial position is critical. On the other hand, creation of an atlas that contains electrophysiological information captured during the procedure for visualization of these functional boundaries so as to identify target positions of interest would gain great clinic relevance and facilitate the process to find an optimal initial position for placement of a DBS for a target of interest.

[0053] The present invention, in one aspect, relates to a method of creating an atlas that contains electrophysiological information related to at least one of a plurality of living subjects, where any portion of the brain of one of the plurality of living subjects and corresponding brain image volume may be identified by a set of corresponding spatial coordinates.

[0054] Referring to FIG. 8, a representative flowchart 800 of the method according to one embodiment of the present invention is shown. At step 801, a brain image volume is chosen as a common image volume of reference from a plurality of brain image volumes, where each of the plurality of brain image volumes is acquired pre-operatively from the brain of one of the plurality of the living subjects. At step 803, electrophysiological information for one of the plurality of living subjects is acquired. At step 805, the acquired electrophysiological information is related to spatial coordinates in the brain image volume of the corresponding living subject. At step 807, the brain image volume of the corresponding living subject is registered to the common image volume of reference so as to create an atlas in which any spatial coordinates of the brain of the corresponding living subject are related to atlas coordinates in the atlas such that the acquired electrophysiological information associated with the related spatial coordinates in the brain image volume of the corresponding living subject can be related to atlas coordinates in the atlas, and vice versa. The atlas has an architecture to be accessible over a network.

[0055] Furthermore, the method includes the step of storing the atlas in a digitized format of files. Additionally, the method includes the steps of populating the atlas with new electrophysiological information acquired from a target of interest, accessing the electrophysiological information from the atlas, and obtaining the electrophysiological information from the atlas in one of a text format, an image format and a mixture thereof, respectively.

[0056] In another aspect, the present invention relates to a method of optimal placement of a deep brain stimulator in a brain of a target of interest by using an atlas that contains electrophysiological information related to a plurality of living subjects.

[0057] Referring to FIG. 9, a representative flowchart 900 of the method according to one embodiment of the present invention is shown. At step 902, at least one piece of information associated with a state of brain condition of the target of interest is acquired from the target of interest pre-operatively. The state of brain condition is related to a type of a disease, and/or a degree of the disease. At step 904, an atlas that contains electrophysiological information related to a plurality of living subjects is accessed remotely. The atlas is formed with a plurality of clusters, where each cluster is related to a state of brain condition and have a plurality of optimal positions for a deep brain stimulator distributed therein. At step 906, the acquired information from the target of interest is entered into the atlas to find a match between the acquired information and the electrophysiological information contained in the atlas. And at step 908, an optimal position in the brain of the target of interest for placing a deep brain stimulator is automatically obtained from one of the plurality of optimal positions for a deep brain stimulator distributed in the plurality of clusters.

[0058] These and other aspects of the present invention are more specifically described below.

METHODS, IMPLEMENTATIONS AND EXAMPLES OF THE INVENTION

[0059] Patients and Data and Image Acquisitions

[0060] In one embodiment of the present invention, a group of 8 patients who undergo deep brain stimulator implantation at a target of the STN is chosen to gather a set of data for evaluating the invented method. The group of patients and the number of patients are employed merely as an example to acquire a set of data for practicing the present invention, and the use of the group of patients and the number of patients should not limit the scope of the present invention. Each patient, was assigned a number from S1 to S8 as his or her identification. The data was collected after obtaining an Independent Research Board (hereinafter "IRB") approval at Vanderbilt University.

[0061] The set of data related to electrophysiological information to be acquired for each patient is categorized in terms of pre-operative information, intra-operative information and post-operative information, respectively.

[0062] The pre-operative information in general includes at least one piece of information associated with a state of brain condition of a target of interest that is related to a type of a disease, and a degree of the disease. Other information may also be acquired. In one embodiment, the information associated with the state of brain condition generally includes presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof. The symptoms have at least one of upper extremity rigidity, lower extremity rigidity, upper

extremity dystonia and lower extremity dystonia. The unified Parkinson's disease rating scale scores are a rating tool for evaluating mentation, behavior and mood, activities of daily living, motor activity, and complication of therapy for the patient undergoing treatment.

[0063] The intra-operative information in general includes at least one piece of information associated with at least one microelectrode, where the information includes microelectrode recordings, a position of the microelectrode recordings, a label of a structure in which the microelectrode recordings is located, and any mixture thereof. Other information may also be acquired. The microelectrode recordings are characterized by a firing rate (hereinafter "FR") that measures tonic activity and indices that measures phasic activity, where the indices include a BI, a pause ratio (hereinafter "PR"), a pause index (hereinafter "PI), and an ISI histogram. The intra-operative information also includes at least one piece of information associated with at least one stimulation electrode, where the information includes voltages applied to the at least one stimulation electrode, a response of the patient undergoing treatment to the stimulation, differences in voltage between disappearance of symptoms and appearance of side effects, a position of the at least one stimulation electrode, a final intra-operative target position of a deep brain stimulator to be placed, and any mixture thereof. Other information may also be acquired. The response of the patient undergoing treatment to the stimulation includes loss of rigidity, location where the loss of rigidity is observed, appearance of side effects, and/or location affected by these side effects.

[0064] The post-operative information in general comprises at least one piece of information associated with at least one deep brain stimulator, where the information includes a position of the at least one deep brain stimulator in post-operative computerized tomographical images, optimal setting of the at least one deep brain stimulator, overall assessment of the patient after placement of the at least one deep brain stimulator, and any mixture thereof. Other information may also be acquired.

[0065] At each stage of the deep brain stimulator implantation for a patient undergoing treatment, the electrophysiological information related to the patient is acquired either by devices such as an image acquisition device and a data acquisition device, and/or by a surgical team who is in charge of the treatment of the patient. The image acquisition device is arranged, in use, to acquire a CT image and/or a MR image for the patient. Any types of clinic available CT imaging systems and MR imaging systems can be used for patient image acquisition to practice the present invention. In one embodiment, the data acquisition device has at least one microelectrode and/or at least one stimulation electrode placed in predetermined target positions of the brain of the patient, for acquiring intra-operative information. The at least one stimulation electrode, in one embodiment, includes a unipolar macrostimulation lead. The data acquisition device further has at least one deep brain stimulator placed in the final target position of the brain of the patient for acquiring post-operative information. Additionally, the data acquisition device has a micropositioning drive for recording positions of the at least one microelectrode, the at least one stimulation electrode and the final target position for the at least one deep brain stimulator to be placed, respectively. Implantation procedures of the at least one deep brain

stimulator for the patient and corresponding data acquisitions according to one embodiment of the present invention are detailed in the following sections.

[0066] All patients undergoing consideration for a DBS implantation at the target of the STN are first evaluated by a neurologist specializing in movement disorders, and their medications are adjusted to optimize their condition. If patients reach advanced Parkinsonian symptoms, such as rigidity, bradykinesia, tremor, and dyskinesia, despite optimal medical therapy, they are considered for the surgical therapy by a multi-disciplinary group involving neurology, neurosurgery, neurophysiology, and neuropsychiatry specialists. Target selection is decided upon by the surgical team if no contraindications exist. A majority of patients with the above symptoms are recommended for STN targeting of DBS therapy.

[0067] Pre-operative target identification is performed by the functional neurosurgeon and is based on an identification of the AC-PC location seen on MR image (3D SPGR volumes, TR: 12.2 msec, TE: 2.4 msec, voxel dimensions $0.85 \times 0.85 \times 1.3 \text{ mm}^3$) pre-operatively. For the STN target, a preliminary point is chosen at 4 mm posterior, 12 mm lateral, and 4 mm inferior to the mid-commissural point. The adjustments for the initial intended target are made based on the width of the third ventricle and anatomical asymmetries noted on the MR image scan, but these adjustments usually have less than 1 mm deviations from the initial intended target location.

[0068] In general, a target position of treatment for a target of interest is selected by a surgical team, based on pre-operatively acquired information that is associated with a state of brain condition of the target of interest. The information associated with the state of brain condition of the target of interest comprises presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof of the target of interest.

[0069] Traditional methodology for carrying out this stepwise target localization and implantation procedure has been based on an externally fixed, rigid fixture, called a stereotactic frame that encompasses the patient's head and upon which the micro-manipulating equipment can be mounted and maneuvered with sub-millimetric precision. These various stereotactic frames have been optimized to obtain accurate images used to create the initial target trajectory and plan and then to reduce erroneous movement associated with passage of the test electrodes and the final implantation [5]. These frames typically require mounting the day of surgery, subsequent imaging with either CT and/or MR image axial slices, and target planning prior to starting the actual procedure of intra-operative mapping and ultimate placement of the electrode implantation into the final target.

[0070] Recently, a FDA approved miniature stereotactic frame, called a Starfix platform (FHC Corporation, Bowdoinham, Me.), has become clinically available. This device, also referred as a platform hereafter, as shown in **FIGS. 2A and 2B**, allows for more versatility with elective stereotactic procedures, such as DBS implantation, and can be utilized to

practice the present invention. Other platforms including other stereotactic frames in clinical use can also be used to practice the present invention. The Starfix platform or frame is used in this particular embodiment to relate spatial coordinates in the OR to spatial coordinates in the images. The construction and/or use of the atlas do not depend on the specific frame being used. The platform **200** has a platform body **210**, an adjustor **220** attached to the platform body **210** and a plurality of legs **230** outwardly and equal-angularly extending from the platform body **210**. Each of the plurality of legs **230** has a hole **280** at an end portion for receiving a corresponding fiducial marker post **240** implanted into the outer table of the skull of a patient so as to secure the platform **210**. The platform **210** also has a guiding member **250**. The guiding member **250** has a plurality of guiding tubes **260** including a center guiding tube **270**. The positions of the guiding tubes **260** including the central tube **270** can be adjusted by the adjustor **220**. The platform **210** is currently manufactured as a customized tripod that can be mounted onto bone-based fiducial marker posts **240**. Each platform is uniquely manufactured based on a stereotactically planned trajectory using software designed to mathematically relate the location of such bone markers with respect to brain structures [6]. The bone-based fiducial marker having a fluid-filled cylinder that is visible on both CT and MR images is detachably attached to a post that is implanted into the outer table of the skull. These images can then be used in the stereotactic software to designate a trajectory in relation to the bone-based marker posts. The plan is sent to the manufacturer who then translates the stereotactic plan into a customized platform for a given trajectory through a rapid prototyping facility. The resultant platform is shipped to the hospital within a certain time frame and is used for mounting the same types of micro-manipulators that are used on traditional stereotactic frames. The remaining portion of the procedure is the same with respect to intra-operative localization of the final target of implantation with the patient awake.

[0071] Each patient undergoing surgery receives either one (for unilateral DBS implantation) or two (for bilateral DBS implantation) platforms. Each leg of the platform is attached to a corresponding bone-implanted post. For each patient, the acquisition of data proceeds in three stages. First, under anesthesia, the fiducial marker posts are implanted onto predetermined positions on the skull of the patient, fiducial markers such as Acustar™ fiducial markers (Z-Kat, Inc., Hollywood, Fla.) are attached to the posts. The use of this marker and post in open craniotomies has been reported on earlier [6]. Other fiducial markers and posts can also be used to practice the present invention. CT and MR image volumes are acquired by the image acquisition device with the patient anesthetized and head taped to the table to minimize motion. For examples, CT images acquired at kvp=120 V, exposure=350 mas, 512×512 pixels ranging in size from 0.49 to 0.62 mm, slice thickness=2 mm for one patient, 1.3 mm for 2 patients, 1 mm for all others. MR images are 3D SPGR volumes, TR: 12.2, TE: 2.4, voxel dimensions 0.85×0.85×1.3 mm³ except for patient S7 for which the voxel dimensions are 1×1×1.3 mm³. After image acquisition, the fiducial markers are removed. With the help of MR-CT registration software, for instance, VoXimo (FHC Corporation, Bowdoinham, Me.), the surgeon selects the initial target points based on AC-PC coordinates and associated entry points on the surface of the skull. In addition,

the centroids of the markers and the directions of their posts are determined from the acquired images. These data are sent electronically to a fabrication plant where a customized platform is manufactured to fit the posts and provide an opening positioned over the entry point and oriented toward the target. These data are also saved in a data storage device such as a memory to form a database. In one embodiment, the data saved in the data storage device forms a relational database. The data saved in the data storage device, in another embodiment, forms an object oriented database, or a mixed object oriented database. The database can be implemented in Microsoft Access (Microsoft Corporation, Richmond, Wash.). The database can also be implemented in other software, such as Oracle (Oracle Corporation, Redwood Shores, Calif.), Microsoft SQL (Microsoft Corporation, Richmond, Wash.) and IBM DB2 (IBM Corporation, Armonk, N.Y.).

[0072] Second, surgery begins with drilling a burr hole, for instance, having 14 mm in diameter. Referring to FIG. 3, an adaptor (not shown here) is attached to each post **352**, the platform **350** is attached to the adaptor, and a micropositioning drive **310** is attached to the platform **350**. In one embodiment, a microTargeting® device (FHC Corporation, Bowdoinham, Me.) is employed as the micropositioning drive, also referred as a microdrive hereafter. A microelectrode recording lead is placed into the patient at the selected initial target position through the central tube of the guide member attached to the platform. The position of the microelectrode recording lead is adjusted so as to find a new position where resting firing frequencies are noted or detected. The adjustment involves three-dimensional adjustment. In addition to changes in depth, it is possible to re-insert a probe **320** along parallel tracks distributed within a 10 mm circle around the initial track. The microelectrode lead is removed and an unipolar macrostimulation lead is inserted to the new position as determined by the microelectrode recordings. With the patient awake, response to stimulation generated from the macrostimulation lead is monitored as the position of the macrostimulation lead is further adjusted until optimal stimulation to the deep brain target is detected. When the final positions are selected, the macrostimulation lead is removed and a deep brain stimulator lead is inserted at the final position. Medtronic #3387 and #3389 quadripolar lead®, as shown in FIG. 1 and described above can be used as DBS lead to practice the present invention. Other types of DBS lead can also be utilized to practice the present invention. A DBS lead **100** is inserted to a depth such that the centroid **160** of the four electrodes **110-140** of the DBS lead **100** is coincident with the final position of the electrode on the unipolar macrostimulation lead. The proximal end of the DBS lead is then anchored to the skull and buried beneath the scalp. The platform is then removed. Within twenty-four hours of surgery, the imaging markers are re-attached to the posts and a post-operative CT scan is acquired. If no complications occur, the patient is discharged home within a day of the surgery. During the entire procedure coordinates are read on the microdrive. These physical coordinates are transformed into pre-operative CT coordinates using the software used for pre-operative planning. The CT image is then registered to the corresponding MR image by the MR-CT registration software, for instance, VoXim®. The MR image is then registered to an atlas as described infra.

[0073] Third, within about two weeks or other time periods deemed properly by the surgeon the patient is brought back to the operating room and the DBS lead is attached to an internal pulse generator, for example, a Soletra generator (Medtronic, Inc., Minneapolis, Minn.), under general anesthesia. This is usually done as an outpatient procedure. Programming of the generators is performed typically as an outpatient procedure one month later by a neurologist.

[0074] To assess the final position of the DBS in the post-operative CT scans, the centroid of the DBS contact-electrodes needs to be detected in the CT images. Referring back to FIG. 1, the DBS lead 100 includes four exposed platinum/iridium contact-electrodes 110, 120, 130 and 140. The centroid 160 of the DBS contact-electrodes is at mid-way between the inner two contact-electrodes 120 and 130, which is the target point to which the surgeon attempts to deliver stimulation. Referring to FIG. 4, a post-operative CT image 400 of a patient after the bilateral DBS implantation having two DBS leads 410 is shown. The wire leads 420 are running under skin from the DBS leads 410 to the internal pulse generator (not shown).

[0075] For each patient, the MER signals are recorded intra-operatively and saved using a recording device such as dual channel LeadPoint system from Medtronic Neurological, Inc., Minneapolis, Minn. These signals are recorded along a microelectrode path starting 10 mm above the pre-operative target point and ending 5 mm below. Signals are recorded every 0.5 mm for 10 sec, and sampled at 22 KHz. After the procedure, the digitized signals and corresponding positions are downloaded from the LeadPoint system and stored on file in the data storage device for use. For this particular example, 850 signal epochs have been recorded.

[0076] For each patient, each piece of electrophysiological information is related to spatial coordinates of the brain of the patient from which the piece of electrophysiological information is acquired. The acquired electrophysiological information is stored in the data storage device for use as described above.

REGISTRATION ALGORITHMS AND ATLAS CREATION

[0077] An atlas is a common volume of reference in which any spatial coordinates of a brain of a target of interest are related to atlas coordinates in the atlas. Therefore, the acquired electrophysiological information associated with the spatial coordinates in the brain image volume of the target of interest can be related to atlas coordinates in the atlas, and vice versa. Creation of the atlas requires registering individual image volumes to the common volume of reference, which corresponds to the spatial normalization of each individual brain image. Two types of registrations algorithms are needed to proceed with the creation of the atlas: rigid and nonrigid registrations. The rigid registration algorithm is employed to register a CT image volume to a MR image volume of the same patient, while the non-rigid registration algorithm is used to register the MR image to the common volume of reference, and vice versa. This is needed because the intra-operative positions of the recording and stimulating electrodes are given in CT coordinates in a corresponding pre-operative CT image. The registration between CT and MR image volumes of the same patient can

be implemented using a standard mutual-information based algorithm as proposed by Maes et al. [12]. In one embodiment, the CT image is registered to the corresponding MR image by MR-CT registration software, for instance, VoXim®. Two nonrigid registration algorithms developed at Vanderbilt University are utilized hereto to register the MR image volume to the common volume of reference. Other algorithms may also be utilized to practice the present invention.

[0078] The first one is called a demon algorithm proposed by Thirion [8]. The demons algorithm computes a transformation that minimizes the voxel-by-voxel intensity difference between the source image volume and the target image volume. This method is itself derived from an instantaneous optical flow equation proposed by Horn and Schunck [20] for motion tracking in image sequences (in the present invention, the two image volumes to be registered are viewed as two frames in a sequence). The basic assumption on which this equation is based is that the image intensity value of a point in the anatomy does not change as it is displaced. This permits the computation of a velocity vector (or in the invention a displacement vector) at each voxel that obeys the following equation:

$$\frac{\partial i}{\partial x} \frac{\partial x}{\partial t} + \frac{\partial i}{\partial y} \frac{\partial y}{\partial t} + \frac{\partial i}{\partial z} \frac{\partial z}{\partial t} = - \frac{\partial i}{\partial t}$$

[0079] in which i is the intensity value in the image at the point with coordinates (x, y, z) . This equation is under-constrained and regularization techniques are used to smooth the displacement field. Thirion proposes to decouple the computation of the displacement field and its regularization as opposed to casting the problem as one single optimization problem. The displacement at each point in the image is first computed by solving the equation. The displacement field is then regularized by filtering it with a Gaussian filter. The larger the standard deviation of this filter is, the smoother the displacement field is. The algorithm is iteratively applied in a multi-scale way. The matching is first computed on coarse downsampled images then successively to images with a finer spatial resolution. This strategy has several advantages: it speeds up the computations, improves the convergence properties of the algorithm, and uses the fact that, for human anatomy, macroscopic features are, in general, more stable than microscopic features. In one embodiment of the present invention, two image pyramids are derived from the images to be registered, up to a predetermined scale. A number of iterations of the algorithm are applied to the images at the coarsest scale and the results obtained at this scale serve as initial conditions for the next one until the finer scale is reached. Furthermore, an additional mechanism such as a bijectivity constraint is used to ensure a one-to-one correspondence between the two images to be matched. Following the approach proposed by Burr [21] this is done by computing both a direct and a reverse deformation field which are maintained compatible such that $T_{1 \rightarrow 2} \otimes T_{2 \rightarrow 1} = I$, with $T_{1 \rightarrow 2}$ the deformation field from image 1 to image 2, $T_{2 \rightarrow 1}$ the deformation field from image 2 to image 1, \otimes indicating composition, and I the identity transformation.

[0080] This greatly increases the robustness of the algorithm, and it has the advantage of insuring that both the forward, i.e., from the reference volume to the individual volumes, and reverse, i.e., from the individual volumes to the reference volumes, transformations are one-to-one.

[0081] In one embodiment of the present invention, another nonrigid algorithm called an Adaptive Basis Algorithm (hereinafter "ABA") [9] is developed, which operates on a quite different principle. Rather than trying to minimize the intensity differences at every voxel, this algorithm computes a transformation that maximizes the Mutual Information (hereinafter "MI") between the images. In this technique, inspired by the work of Rueckert et al. [10] and Meyer et al [11], the deformation that registers one image (a source image) onto the other (a target image) is modeled with a linear combination of radial basis functions with finite support. The similarity measure that drives the registration process is the mutual information between the source image and the target image. In this algorithm, several improvements over existing mutual information-based non-rigid registration algorithm are implemented. These include working on an irregular grid, adapting the compliance of the transformation locally, decoupling a very large optimization problem into several smaller ones, and deriving schemes to guarantee the topological correctness of the transformations.

[0082] More specifically, the adaptive base algorithm includes the following steps: at first, a source image and a target image are defined to be one of the remaining N-1 image volumes and the atlas, respectively. Second, an image pyramid for each of the source image and the target image is created, respectively. Each image pyramid has M levels. Each level of the image pyramid has a resolution and is segmented with a corresponding scale so as to form a grid. Each image pyramid is formed such that level i of the pyramid has lower resolution and larger scale than level (i-1), where $i=1, \dots, M$, and M is an integer greater than 1. Then, a deformation field, $v(x)$, x being a position vector, which registers the source image volume to the target image volume, is defined, and the deformation field is further initialized as $v(x)=v_M(x)$. In one embodiment, the deformation field is initially set to be zero. Furthermore, the deformation field, $v_i(x)$, is computed at level i of the image pyramids, where the deformation field $v_i(x)$ at level i is a sum of the deformation field at level (i+1) and a linear combination of a set of radial basis functions spaced on the grid of level i, so as to register the source image volume to the target image volume at level i and where the computing starts at level (M-1). Moreover, regions of misregistration are identified, which is resulted from the step of computing the deformation field $v_i(x)$ at level i. Additionally each of the regions of misregistration are optimized independently from each other by modifying the region of support and radial basis functions corresponding to the region in the deformation field $v_i(x)$. Furthermore, the computing step, the identifying step and the optimal step are iterated at level (i-1) of the image pyramids till level 1 is reached so as to incrementally construct a final deformation field in the form of

$$v(x)=v_1(x)+\dots+v_M(x).$$

[0083] The adaptive base algorithm further includes the step of optimizing a constraint scheme for enforcing a Jacobian matrix of the deformation field to remain uniformly invertible throughout a domain of the source image volume and a corresponding domain of the target image volume so as to generate topologically correct transformations between the source image volume and the target image volume.

[0084] To create an atlas, a MR image volume of a living subject is chosen as a common image volume of reference. Registering MR image volumes acquired from a target of interest to the common image volume of reference will create an atlas. The image registration can be utilized by a nonrigid registration algorithm, such as the demon algorithm, the ABA algorithm, and others. Once the transformation between one image volume and the atlas is computed, any spatial coordinates in this volume, such as spatial coordinates relating to the acquired electrophysiological information and the spatial coordinates of DBS, can be transformed into corresponding atlas coordinates in the atlas. In this example, a MR image volume acquired from one of the group of 8 patients is chosen to serve as the common volume of reference, where each of the group of 8 patients has at least one DBS implanted in the brain. Image volumes acquired from the remaining 7 patients of the group of 8 patients are respectively registered to the common image volume of reference by a demon algorithm and/or the ABA algorithm so as to create the atlas. Thus, there are at least 7 DBS atlas points (coordinators) in the atlas, each is projected by the spatial point (coordinators) of the at least one DBS in each of the image volumes for the remaining 7 patients. The optimal DBS position in the atlas is computed as the centroid of all the DBS positions after their projection onto the atlas.

[0085] Predicting the initial optimal DBS position for each patient is the inverse of the operation described above. It includes projecting the optimal DBS position from the atlas to each individual image volume. This does not require another registration step because the transformation from the patient to the atlas and from the atlas to the patient are computed simultaneously. The nonrigid registration algorithms impose constraints on these transformations to keep them almost inverse of each other to produce bijective transformations. For instance, to predict an initial optimal position in an image volume of a patient that the deep brain stimulator is to be implanted using the atlas and nonrigid registration algorithm, the image volume of the patient needs being registered to the atlas by the nonrigid registration algorithm so as to find a registration transformation of the image volume to the atlas. Application of an inverse of the transformation will project the optimal target position of the deep brain stimulator in the atlas to the image volume so as to identify the initial optimal position of the deep brain stimulator in the targeted region of the brain of the patient.

VISUAL EVALUATION OF THE REGISTRATION RESULTS

[0086] Two examples of obtaining the DBS coordinates according to the present invention are presented. The first one relies on coordinates provided intra-operatively by a STarFix guidance system during surgery. This system translates the physical coordinates of the DBS electrode into pre-operative CT coordinates. The second one relies on an algorithm to get the centroid of the deep brain stimulator in the post-operative CT scans [22]. One can expect differences between these coordinates, the causes of which are several. First, the STarFix system is not perfectly accurate. Second, the intra-operative target point is arrived at with a micro-stimulating electrode. This electrode is then replaced by the permanent DBS stimulator, which introduces the surgical placement error. Third, the brain may shift during surgery because of swelling and/or loss of cerebrospinal fluid. After surgery, the brain returns to its normal state, which also causes the electrode to move.

[0087] Referring now to FIGS. 5 and 6, first to FIG. 5, several circles forms a cluster 510 and each circle in the cluster 510 corresponds to an atlas position of a final DBS target projected onto the atlas 500. These final DBS targets, or more specifically, spatial coordinators of each corresponding final DBS target, are acquired intra-operatively by a STarFix guidance system. FIGS. 5(a), 5(b), and 5(c) show a sagittal view, a transverse view, and a coronal view of the left side DBS targets projected onto the atlas, respectively, while FIGS. 5(d), 5(e), and 5(f) respectively show a sagittal view, a transverse view, and a coronal view of the right side DBS targets projected onto the atlas. The results shown here are obtained with the ABA algorithm. The results are qualitatively similar with the demons algorithm. All spatial coordinates of the individual deep brain stimulators in association with FIG. 5 have been acquired intra-operatively by a STarFix guidance system.

[0088] Similar to FIG. 5 but with the spatial coordinates of the DBS targets acquired with post-operative CT scans, FIG. 6 represents images of the final DBS spatial coordinates acquired post-operatively from the group of 8 patients with corresponding atlas coordinates visually shown according to one embodiment of the present invention. In FIG. 6, several circles forms a cluster 610 and each circle in the cluster 610 corresponds to the atlas position of a final DBS target projected onto the atlas 600. FIGS. 6(a), 6(b), and 6(c) show a sagittal view, a transverse view, and a coronal view of the left side DBS targets projected onto the atlas, respectively, while FIGS. 6(d), 6(e), and 6(f) respectively show a sagittal view, a transverse view, and a coronal view of the right side DBS targets projected onto the atlas.

[0089] Still referring to FIGS. 5 and 6, according to the present invention, the positions of final DBS targets form a cluster in the atlas (cluster 510 in FIG. 5 and cluster 610 in FIG. 6, respectively) and it indicates that the atlas coordinates projected from the spatial coordinates of the DBS positions acquired intra-operatively form a tight cluster 510 than the cluster 610 formed by the atlas coordinates projected from the spatial coordinates of the DBS positions acquired post-operatively.

[0090] According to another embodiment of the present invention, images of atlas coordinates 700 that are transformed from the final DBS positions acquired intra-operatively from a group of 18 patients are shown in FIG. 7. FIGS. 7(a), 7(b), and 7(c) respectively show a sagittal view, a transverse view, and a coronal view of both the left side and the right side DBS targets. FIG. 7 clearly shows that the atlas coordinates projected from the spatial coordinates of the DBS positions acquired intra-operatively from the group of 18 patients also form a cluster 710 in each side of the brain. Thus, according to the present invention, the position of the optimal target may be a function of parameter related to a state of brain condition of a patient such as disease type or state. For example, patients who have prominent leg rigidity may benefit from an implant centered in a cluster more posterior and inferior in the STN target than someone with arm rigidity whose ideal cluster may be more anterior and superior.

ATLAS-GUIDED INITIAL TARGET POSITIONS

[0091] Table 1 shows the atlas coordinates transformed from the spatial coordinates of the final DBS positions for the eight bilateral STN patients by using the ABA algorithms. The DBS coordinates are acquired intra-operatively. Each patient, is assigned a number from S1 to S8 in column

Subject as his or her identification. Columns Left and Right represent locations of the bilateral DBS, that is, column Left corresponds to the left side implantation of the DBS, while column Right corresponds to the right side implantation of the DBS. Sub-columns X, Y and Z are atlas coordinates of a DBS placed in a specific target region (left side or right side) for a specific patient, which corresponds to an individual point in the atlas, represented by a corresponding circle 510 in FIG. 5. Rows S1 to S8 represent a set of atlas coordinates of a bilateral DBS of patients S1 to S8, respectively. For instance, Row S3 of Table 1 represents patient S3 having a bilateral DBS implantation, where the atlas coordinates of the left side DBS are (X, Y, Z)=(122.47, 107.80, 51.18) in unit of mm, and the atlas coordinates of the right side DBS are (X, Y, Z)=(96.86, 107.02, 50.24) in unit of mm. The centroid of the atlas coordinates of the DBS positions of the eight bilateral STN patients is computed for the left side implantation and the right side implantation, respectively, which are presented in Row Mean. Row STD represents a standard deviation (hereinafter "STD") the atlas coordinates relative to the centroid. Row SEM is a standard error of the mean (hereinafter "SEM"). The Euclidean distance between each point in the atlas and its corresponding centroid is represented in the Dc column.

[0092] Similar to Table 1, Table 2 shows the atlas coordinates transformed from the spatial coordinates of the final DBS positions for the eight bilateral STN patients by using the demons algorithms. The DBS coordinates are acquired intra-operatively.

TABLE 1

Atlas coordinates transformed from spatial coordinates of the final DBS positions that are acquired intra-operatively using the ABA algorithms. Atlas Coordinates Transformed by the Adaptive Basis Algorithm (in unit of mm)								
Sub- ject	Left				Right			
	X	Y	Z	Dc	X	Y	Z	Dc
S1	124.28	106.39	53.98	2.58	95.47	106.20	53.20	3.52
S2	121.88	106.30	53.44	1.44	N/A	N/A	N/A	N/A
S3	122.47	107.80	51.18	1.43	96.86	107.02	50.24	2.12
S4	119.79	106.27	51.78	2.74	101.38	104.91	50.23	3.40
S5	123.42	107.41	51.40	1.42	99.10	105.99	50.19	1.35
S6	123.42	107.99	53.21	1.82	96.68	104.69	52.96	2.57
S7	122.48	105.80	51.90	1.07	97.54	104.98	50.51	0.92
S8	121.70	106.60	50.91	1.52	99.85	104.69	49.63	2.34
Mean	122.43	106.82	52.22	1.75	98.12	105.49	51.00	2.32
STD	1.37	0.81	1.16	0.60	2.07	0.91	1.45	0.97
SEM	0.49	0.28	0.41	0.21	0.73	0.32	0.51	0.34

[0093]

TABLE 2

Atlas coordinates transformed from spatial coordinates of the final DBS positions that are acquired intra-operatively using the demons algorithm. Atlas Coordinates Transformed by the Demons Algorithm (in unit of mm)								
Subject	Left				Right			
	X	Y	Z	Dc	X	Y	Z	Dc
S1	124.28	106.39	53.98	2.29	95.47	106.20	53.20	2.90
S2	121.60	104.24	54.43	1.94	N/A	N/A	N/A	N/A
S3	122.03	106.52	53.04	0.88	95.92	105.95	51.87	2.14
S4	120.31	106.73	51.97	2.54	99.78	105.72	51.23	2.21
S5	123.11	106.00	52.77	1.08	98.85	104.68	51.94	1.08

TABLE 2-continued

Atlas coordinates transformed from spatial coordinates of the final DBS positions that are acquired intra-operatively using the demons algorithm.
Atlas Coordinates Transformed by the Demons Algorithm (in unit of mm)

Subject	Left				Right			
	X	Y	Z	Dc	X	Y	Z	Dc
S6	122.42	105.63	54.60	1.32	97.01	103.79	53.97	2.44
S7	121.86	104.44	53.44	1.32	97.89	104.19	52.34	0.89
S8	122.07	105.63	52.16	1.15	99.92	104.58	49.61	3.22
Mean	122.21	105.70	53.30	1.56	97.83	105.01	52.02	2.12
STD	1.15	0.93	0.99	0.61	1.78	0.94	1.40	0.87
SEM	0.41	0.33	0.35	0.22	0.63	0.33	0.5	0.31

[0094] As shown in Tables 1 and 2, when the spatial coordinates of the final DBS positions acquired intra-operatively are transformed into the atlas coordinates by the ABA and Demons algorithms, respectively, the STD and the SEM of the atlas coordinates have small values, which indicate that the final positions of the DBSs transformed into the atlas coordinates result in tight clusters. It is also worth noting that even though these two algorithms are based on very different similarity measures, they lead to essentially identical results, suggesting that the accuracy-limiting factor is not the registration algorithm used but either the spatial resolution of the MR images, the accuracy of the DBS positioning system, a bias introduced by the spatial normalization scheme, normal inter-subject variation, suboptimal intra-operative selection of the target, or a combination of these.

[0095] Tables 3 and 4 show the same information as Tables 1 and 2 but with spatial coordinates of the deep brain stimulators that are acquired from the post-operative CT scans. A comparison of Tables 1 and 2 with Tables 3 and 4 shows clearly that atlas coordinates of the DBS positions do not cluster as well when the coordinates are acquired post-operatively as when the coordinates are acquired intra-operatively. For instance, the STD value for the left side DBS in Table 1 is 0.60 mm, while the corresponding STD value in Table 3 is 0.99 mm, which is 65% more than the STD value when the coordinates are acquired intra-operatively. Similarly, the STD value for the right side DBS in Table 1 is 0.97 mm, while the corresponding STD value in Table 3 is 0.158 mm, which is 63% more than the STD value when the coordinates are acquired intra-operatively. The results shown in FIGS. 5 and 6 also indicate the same trend, where the spatial coordinates of the DBS positions are acquired intra-operatively in FIG. 5, and the spatial coordinates of the DBS positions in FIG. 6 are acquired post-operatively. The projected atlas coordinates of the DBS positions form a tighter cluster 510 than the cluster 610 formed by the projected atlas coordinates of the DBS positions accordingly.

[0096] The distance between an individual atlas point projected from a corresponding DBS position and the centroid of atlas coordinates projected from DBS positions of eight patients is significantly smaller for the intra-operative coordinates than that for the post-operative CT coordinates. Statistical significances for one-sided t-tests are as follows: ABA algorithm for a left side STN target with $P < 0.03$, Demons algorithm for a left side STN target with $P < 0.01$, ABA algorithm for a right side STN target with $P < 0.01$,

Demons algorithm for a right side STN target with $P < 0.01$, where P , with a value ranging from zero to one, corresponds to a probability value of a statistical hypothesis test as known to people skilled in the art.

TABLE 3

Atlas coordinates transformed from spatial coordinates of the final DBS positions that are acquired with post-operative CT scans using the ABA algorithm.
Atlas Coordinates Transformed by the Adaptive Basis Algorithm (in unit of mm)

Sub-ject	Left				Right			
	X	Y	Z	Dc	X	Y	Z	Dc
S1	123.01	107.65	53.81	1.69	95.38	107.6	54.73	4.11
S2	121.44	107.14	55.25	2.87	N/A	N/A	N/A	N/A
S3	123.88	108.15	49.84	3.3	97.59	110.55	48.76	4.95
S4	117.64	107.39	52.37	4.36	102.89	106.25	52.65	4.67
S5	123.18	107.35	53.14	1.38	99.18	106.72	51.3	1.09
S6	121.27	108.85	53.14	1.64	93.86	105.6	55.34	5.72
S7	123.48	105.57	51.9	2.53	97.13	105.16	50.5	2.5
S8	122	108.18	50.29	2.27	102.1	105.89	50.35	4.22
Mean	121.99	107.54	52.47	2.5	98.3	106.82	51.95	3.9
STD	2	0.97	1.79	0.99	3.33	1.83	2.41	1.58
SEM	0.71	0.34	0.63	0.35	1.18	0.65	0.85	0.56

[0097]

TABLE 4

Atlas coordinates transformed from spatial coordinates of the final DBS positions that are acquired with post-operative CT scans using demons algorithm.
Atlas Coordinates Transformed by the Demons Algorithm (in unit of mm)

Sub-ject	Left				Right			
	X	Y	Z	Dc	X	Y	Z	Dc
S1	123.01	107.65	53.81	1.74	95.38	107.6	54.73	3.4
S2	121.44	104.86	55.42	2.65	N/A	N/A	N/A	N/A
S3	123.34	107.13	51.63	2.37	96.98	108.94	50.04	4.02
S4	118.54	108.08	52.62	3.76	100.79	107.41	53.52	3.08
S5	122.76	106	54.46	1.51	98.97	105.68	52.97	1.19
S6	120.59	106.68	53.91	1.4	94.08	104.35	56.14	5.41
S7	122.9	104.15	53.56	2.54	97.5	104.37	52.36	2.09
S8	122.2	107.04	51.3	2.15	102.08	105.93	50.75	4.67
Mean	121.85	106.45	53.34	2.26	97.97	106.33	52.93	3.41
STD	1.62	1.36	1.4	0.76	2.86	1.73	2.13	1.46
SEM	0.57	0.48	0.5	0.27	1.01	0.61	0.75	0.52

[0098] The tighter the cluster of the projected atlas points of the DBS positions in the atlas is, the better the results are. Therefore, using the intra-operative coordinates according to the present invention to predict an initial target position may lead better results than using the post-operative CT coordinates. Nevertheless, as described above, both the intra-operative DBS coordinates and the post-operative DBS coordinates can be utilized to practice the present invention. One explanation for this discovery is that the spread of the clusters in the atlas increases if measurement noise in the DBS positions used to create this atlas also increases. The sources of error associated with the post-operative DBS coordinates involve the centroid detection algorithm and the errors associated with registering pre-operative and post-operative CT images. The difference is the surgical placement error, i.e., the distance between the target point chosen intra-operatively and the position of the permanent DBS.

TABLE 5

Distances between the initial target positions selected manually and the final DBS positions acquired intra-operatively and distance between the initial target positions selected automatically and the final DBS positions acquired intra-operatively (the atlas used herein has been generated with the intra-operative DBS coordinates). Target Prediction Errors intra-operative Atlas (in unit of mm)						
Subject	Left			Right		
	Automatic			Automatic		
	Manual	ABA	Demons	Manual	ABA	Demons
S1	5.95	2.58	2.4	6.94	3.52	2.94
S2	5.72	1.78	3.39	N/A	N/A	N/A
S3	2.53	2.41	1.5	4.49	2.45	2.23
S4	5.3	2.46	2.8	1.99	3.24	2.36
S5	2.31	2.17	1	3.64	1.6	1.51
S6	5.95	2.36	2.85	7.31	3.39	3.84
S7	2	1.64	2.37	2.01	1.75	1.68
S8	1.71	1.75	0.7	1.67	2.94	3.67
Mean	3.93	2.14	2.13	4.01	2.7	2.6
STD	1.94	0.37	0.96	2.36	0.78	0.91
SEM	0.69	0.13	0.34	0.83	0.28	0.32

[0099] Thus, according to the present invention, when projected onto a common reference volume, optimal DBS positions result in tight clusters if these positions can be determined accurately in each individual patient. These results also show, albeit in an indirect way, that the coordinates acquired intra-operatively are more accurate than the coordinates acquired post-operatively, and suggest a high accuracy for use of a platform from which intro-operative coordinates of the final DBS are acquired.

[0100] Tables 5 exhibits the Euclidean distances between the manually selected initial target positions and the final DBS positions and the Euclidean distances between the automatically selected initial target positions and the final DBS positions, respectively, for each patient. The final DBS positions are acquired intra-operatively. The atlas used in this case has been generated with the intro-operative DBS coordinates. The Euclidean distance between an initial target position and a final DBS position represent a target prediction error.

[0101] Specifically, column Subject of Table 5 in represents the group of 8 patients with each patient having a number from S1 to S8 assigned as his or her identification. Columns Left and Right of Table 5 represent locations of the bilateral DBS, that is, column Left corresponds to the left side implantation of the DBS, while column Right corresponds to the right side implantation of the DBS. Sub-column Manual of Table 5 represents the Euclidean distance between the manually selected initial target position and the final DBS position in a specific side implantation of the DBS. For example, sub-column Manual of column Left corresponds to the Euclidean distance in the left side implantation of the DBS, while sub-column Manual of column Right corresponds to the Euclidean distance in the right side implantation of the DBS. And sub-column Automatic of Table 5 having sub sub-columns ABA and Demons represents the Euclidean distance between the automatically selected initial target position and the final DBS position in a specific side implantation of the DBS. The automatically selected initial target position is computed based on the ABA algorithm for sub sub-column ABA, while it is computed

based on the Demons algorithm for sub sub-column Demons. Rows S1 to S8 of Table 5 represent a set of the Euclidean distances (or target prediction errors) of patients S1 to S8, respectively. For instance, Row S3 of Table 5 represents patient S3 having a bilateral DBS implantation, where the target prediction errors for the left side DBS implantation are 2.53 mm for manually selected initial target position, 2.41 mm for automatically selected initial target position with the ABA algorithm, and 1.5 mm for automatically selected initial target position with the Demons algorithm, respectively, and the target prediction errors for the right side DBS implantation are 4.49 mm for manually selected initial target position, 2.45 mm for automatically selected initial target position with the ABA algorithm, and 2.23 mm for automatically selected initial target position with the Demons algorithm, respectively. Row Mean represents a mean value of the target prediction errors. Row STD represents a standard deviation of the target prediction errors relative to the mean value of the target prediction errors. And row SEM is a standard error of the mean.

[0102] Similar to Table 5 but with the atlas generated with the post-operative DBS coordinates, Table 6 represents the Euclidean distances between the initial target positions selected manually and the final DBS positions acquired intra-operatively and the Euclidean distances between the initial target positions selected automatically and the final DBS positions acquired intra-operatively, respectively, for each patient.

TABLE 6

Distances between the initial target positions selected manually and the final DBS positions acquired intra-operatively and distances between the initial target positions selected automatically and the final DBS positions acquired intra-operatively (the atlas used herein has been generated with the post-operative DBS coordinates). Target Prediction Errors Post-operative Atlas (in unit of mm)						
Subject	Left			Right		
	Automatic			Automatic		
	Manual	ABA	Demons	Manual	ABA	Demons
S1	5.95	1.69	1.74	6.94	4.11	3.4
S2	5.72	2.87	3.69	N/A	N/A	N/A
S3	2.53	5.05	3.64	4.49	5.67	5.23
S4	5.3	3.71	4.16	1.99	3.55	2.54
S5	2.31	2.02	2.05	3.64	1.31	1.42
S6	5.95	2.41	2.2	7.31	6.56	6.27
S7	2	4.12	4.07	2.01	4.22	3.7
S8	1.71	2.89	2.74	1.67	4.46	5.45
Mean	3.93	3.09	3.04	4.01	4.27	4
STD	1.94	1.13	0.97	2.36	1.66	1.73
SEM	0.69	0.4	0.34	0.83	0.59	0.61

[0103] Table 5 demonstrates that for the data sets obtained and used as described herein, an atlas-guided placement of DBS is not only feasible but also is better than the technique in current clinical use. With both ABA and demons registration algorithms, the initial target points are substantially closer to the final ones than the initial target point chosen manually. It is shown that the average distance between an initial position selected with the automatic method of the present invention and a final position of a DBS is 45% smaller on the left side and 30% on the right, respectively, than the one between an initial position selected manually and a final position of a DBS. For the group of 8 patients, for

example, in Table 5, the mean distances between the initial targets and final positions are 2.14 mm (ABA algorithm) and 2.70 mm (ABA algorithm) on the left and right sides, respectively, for the atlas-based automatic method, as compared with 3.93 mm and 4.01 mm for the manual method.

[0104] Despite the small size of the data sets employed in the study, the distance between the initial target points and the final target points is significantly smaller ($P < 0.01$, one sided paired t-test) than the distance between the initial target points chosen manually and the final target points for both ABA and demons algorithms on the left side. On the right side, the significance is only slightly smaller ($P < 0.07$) and ($P < 0.06$) for the ABA and demons algorithms, respectively. A comparison of Tables 5 and 6 also reveals that when using the post-operative CT coordinates to create the atlas, atlas-guided placement of DBS does not do much better than the current manual approach. This is consistent with what is described above in connection with Tables 1 to 4 that tighter clusters are formed with the intra-operative coordinates than that formed with the post-operative CT coordinates.

TABLE 7

Distances between the initial target positions selected manually and the final DBS positions acquired intro-operatively and distance between the initial target positions selected automatically and the final DBS positions acquired intro-operatively (the atlas used herein has been generated with the intro-operative DBS coordinates acquired from a group of 18 patients).
Target Prediction Errors ultra-operative Atlas (in unit of mm)

Subject	Left		Right	
	Manual	Automatic	Manual	Automatic
P1	2.53	2.36	4.49	3.17
P2	1.61	2.75	5.03	4.31
P3	5.45	0.83	N/A	N/A
P4	5.12	2.54	N/A	N/A
P5	0	0.97	5.8	2.9
P6	1.71	1.67	1.67	1.63
P7	3.14	3.19	0.48	1.91
P8	1	1.13	2.08	2.56
P9	3.48	2.92	3.27	2.93
P10	1.99	3.34	1.99	3.52
P11	2.31	2.24	3.64	2.16
P12	0	0.71	2	2.34
P13	1.5	2.93	N/A	N/A
P14	1.51	4.72	N/A	N/A
P15	5.95	3.75	7.31	2.18
P16	5.95	2.37	6.94	2.98
P17	2.01	1.38	3	2.54
P18	5.85	5.22	5.38	4.18
Mean	2.7	2.5	3.88	2.79
STD	1.98	1.32	2.04	0.77

[0105] Similar to Table 5 but for a group of 18 patients, Table 7 presents the Euclidean distances between the manually selected initial target positions and the final DBS positions acquired intro-operatively and the Euclidean distances between the automatically selected initial target positions and the final DBS positions acquired intro-operatively, respectively. The atlas used in this case is generated with the intro-operative DBS coordinates. In Tables 7, each patient is assigned a number from P1 to P18 in column Subject as his or her identification.

[0106] For the group of 18 patients, Table 7 again displays that the atlas-projected initial target point is substantially closer to the final ones than the initial target point chosen manually for a target of interest, that is, the atlas-based

automatic target localization approach is better than the manual one. For example, the mean distances between the initial targets and final positions are 2.50 mm and 2.79 mm on the left and right side, respectively, for the atlas-based automatic method, as compared with 2.7 mm and 3.88 mm for the manual method.

[0107] By comparing Table 5 with Table 7, one notes that the mean distances between the atlas-predicted initial targets and final DBS positions, and the standard deviation of the error are different. For example, the mean distances and the standard deviation for the group of 18 patients are about 2.5 mm and 1.32 mm for the left side DBS implementation, and 2.79 mm and 0.77 mm for the right side DBS implementation, respectively. However, for the group of 8 patients, the mean distances and the standard deviation are about 2.14 mm and 0.37 mm for the left side DBS implementation, and 2.7 mm and 0.78 mm for the right side DBS implementation, respectively.

DATA POPULATING AND REPRESENTING

[0108] In the exemplary embodiment as described supra, the method of creating an electrophysiological atlas is illustrated with a group of 8 patients undergoing treatment. The method is further extended to a large group having 18 patients. According to the present invention, the atlas is created with an architecture such that new electrophysiological information acquired can be populated into the atlas and electrophysiological information contained in the atlas can be accessed via a user interface. For instance, after a set of image volumes (pre-operative MR and CT volumes) of a target of interest has been acquired, the CT volume is registered to the MR image, which is then registered to the atlas. The corresponding computed transformations are saved on files in a memory device and used to project patient coordinates onto atlas coordinates, and vice versa. The memory device can be associated with a central host computer which itself can be in communication with a local and/or a public network such as the Internet.

[0109] Based on pre-operatively acquired information associated with a state of brain condition of the target of interest, the surgical team makes a pre-operative surgical plan. The state of brain condition is related to a type of a disease, and/or a degree of the disease. The information associated with the state of brain condition of the target of interest generally includes presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof of the target of interest.

[0110] From a client (or local) computer, in communication with the central host computer, the surgical team accesses remotely or locally the atlas stored in the central host computer, and enters the acquired information from the target of interest to the atlas to find a match between the acquired information and the electrophysiological information contained in the atlas. Then an optimal position in the brain of the target of interest for placing a deep brain stimulator from the matched information is automatically selected from the atlas. In one embodiment, the automati-

cally selected optimal position is given in terms of an electrode path for a single DBS implantation (or two electrode paths for a bilateral DBS implantation). A cylindrical region around the electrode path is defined in the atlas accordingly.

[0111] The entire database (atlas) is queried, and smaller databases that contain selected information about the points within these cylinders are created. In one embodiment, the entire database including the smaller databases is accessed by the surgical team over a network from a client computer during the intra-operative DBS implantation. The network can be one of a public network such as the Internet, a dedicated network, a local network, and any combination of them. The public network includes the Internet. In another embodiment, these smaller databases are downloaded to a client (or local) computer together with the corresponding transformations for the target of interest for the surgical use of the intra-operative DBS implantation. This approach is favored over accessing the entire database across the network to avoid potential problems with network connections during the surgery and to permit real-time searches on the local computer that can be brought into the operating room. In an alternative embodiment, the entire database including the smaller databases is written into a computer readable medium or media, such as, compact discs (CD), floppy disks, hard drivers, and the likes, for the use of the intra-operative DBS implantation in an operating room where the network may not be available.

[0112] In one embodiment, the intra-operative positions of the electrodes, for example, a microelectrode recording lead and a macrostimulation lead, placed in the brain of the target of interest are acquired by a microdrive, such as a micro-Targeting® device. The microdrive is in communications with the local computer in the operating room, and/or the central host computer through the network for uploading the intra-operative positions of the electrodes. The acquired positions are automatically transformed into atlas coordinates via a pre-computed registration. This approach permits intra-operative queries such as "show me all the points in the atlas with a mean firing frequency within a given range and within 5 mm of the current position of the electrode". This query returns a list of records, each of which is a pointer to a file that contains a series of positions that are then color-coded and displayed on the patient image volume. This approach can be used, for instance, to assess whether the firing rate which the surgical team is measuring is a likely value at the current electrode position, and whether the measured firing rate is observed at a distance away from the current position, which would, in turn, indicate whether the electrode is at the anatomic position.

[0113] Referring now to FIG. 10, MER signals are acquired along an electrode path at different positions from a patient, and features associated with the MER signals, including a FR, a BI, a PI, a PR, and an ISI histogram, are extracted. As shown in FIGS. 10a, 10c and 10e, signals 1010, 1012 and 1014 are raw MER signals acquired at a position above the STN, at the middle of the STN and at a position below the STN, respectively. Spike trains 1011, 1013 and 1015 are respectively extracted from raw MER signals 1010, 1012 and 1014. ISI histograms 1020, 1022 and 1024 associated with the corresponding raw MER signals 1010, 1012 and 1014 are respectively shown in FIGS. 10b, 10d and 10f. For each of raw MER signals 1010, 1012 and

1014, the FR, the BI, the PI, and the PR are also extracted. For example, for raw MER signals 1010, FR=44.0, BI=1.047, PI=0.505, PR=6.215, as shown in FIG. 10b, for raw MER signals 1012, FR=58.8, BI=0.871, PI=0.378, PR=2.213, as shown in FIG. 10d, and for raw MER signals 1014, FR=117.7, BI=1.462, PI=0.092, PR=0.385, as shown in FIG. 10f.

[0114] Once these features have been extracted, their values can be color-coded and displayed in the atlas. FIG. 11 shows the mean value of the BI in the electrophysiological atlas for a patient undergoing treatment, which is color-coded. Bright and dark pixels correspond to high and low values of the BI, respectively. One can distinguish several regions with low, medium, and high values for this feature. Low values correspond to white matter, medium values to the STN, and high values to structures such as the niagra (hereinafter "Ni") and the Vim (another nucleus). For instance, as shown in FIG. 11, region 1110 is the STN, region 1120 is the Ni, and region 1130 represents the Vim, respectively. Although the scarcity of data does not yet permit a precise localization of complete nuclei boundaries, the results obtained according to the present invention clearly show patterns in the data and clusters that correspond to known anatomical structures that are invisible in MR images.

FURTHER OBSERVATIONS AND DISCUSSIONS

[0115] In the present invention, among other things, a method for creating an atlas containing electrophysiological information related to at least one living subject is disclosed, which can be used for automatic selection of the pre-operative target for DBS placement and identification of boundaries of structures and substructures which are not visible in current imaging modalities for intra-operative guidance. This is achieved by correlating intra-operative recordings with electrophysiological information contained in the atlas, which permits the surgical team to identify the current location of the electrode, and plan and execute displacements from this position. The current difficulty is the intra-operative acquisition of signals that cover a region around the various targets of interest. Recording equipment used in current clinical practice only permit recording of one channel at a time. Very recently, a 10 channel recording device developed by FHC Corporation, Bowdoinham, Me., has been clinically available. This device permits recording along 5 parallel tracks on each side for a total of 10 simultaneous channels. This may allow the signal database of the present invention to be rapidly expanded which, in turn, may improve the localization of substructure boundaries based on electrophysiological signatures.

[0116] Additional improvements may be made. Because the number of patients for gathering the necessary data is limited, the method has been evaluated on the set of data used to create the atlas. This may bias the results in the favor of the method. As the number of data sets increase, a separation of the image volumes into training and testing set may address this issue. Other approach may be to use a synthesized average image as the atlas. Additionally, all the image volumes are employed in the study regardless of clinical outcome. An alternative approach may be to select only cases for which the clinical outcome is excellent to build the atlas. However, none of these issues affect the utilization of the present invention.

[0117] While there has been shown several and alternate embodiments of the present invention, it is to be understood that certain changes can be made as would be known to one skilled in the art without departing from the underlying scope of the invention as is discussed and set forth above and below. Furthermore, the embodiments described above are only intended to illustrate the principles of the present invention and are not intended to limit the scope of the invention to the disclosed elements.

[0118] List of References

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What is claimed is:

1. A system for creating an atlas for optimal placement of a deep brain stimulator in a brain of a target of interest, comprising:

- a. a data storage device;
- b. an image acquisition device for acquiring a brain image volume from the brain of the target of interest;
- c. a data acquisition device for acquiring electrophysiological information from the brain of the target of interest; and

- d. a data processing device operably coupled to the data storage device, the image acquisition device and the data acquisition device, respectively, and performing the steps of:
 - (a). relating the acquired electrophysiological information to spatial coordinates in the acquired brain image volume of the target of interest; and
 - (b). registering the acquired brain image volume of the target of interest to a common image volume of reference so as to create an atlas in which spatial coordinates of the brain of the target of interest are related to atlas coordinates such that the acquired electrophysiological information associated with the related spatial coordinates in the acquired brain image volume of the target of interest can be related to atlas coordinates in the atlas, and vice versa.
- 2. The system of claim 1, wherein the data processing device further performs the step of storing the atlas in a digitized format in the data storage device.
- 3. The system of claim 1, wherein the atlas has an architecture to be accessible over a network.
- 4. The system of claim 3, further comprising a user interface in communication with the atlas.
- 5. The system of claim 4, wherein the user interface is used for populating the atlas with new electrophysiological information acquired from a target of interest.
- 6. The system of claim 4, wherein the user interface is used for accessing the electrophysiological information from the atlas.
- 7. The system of claim 6, wherein the user interface is used for obtaining the electrophysiological information from the atlas in one of a text format, an image format and a mixture thereof.
- 8. The system of claim 7, wherein the obtained electrophysiological information includes an initial optimal position for at least one deep brain stimulator to be, placed in a brain of a target of interest.
- 9. The system of claim 1, wherein the data storage device comprises a memory.
- 10. The system of claim 1, wherein the image acquisition device is arranged, in use, to acquire a computerized tomographical image and/or a magnetic resonance image for a target of interest.
- 11. The system of claim 1, wherein the data acquisition device comprises at least one microelectrode placed in a brain of a target of interest.
- 12. The system of claim 1, wherein the data acquisition device comprises at least one stimulation electrode placed in a brain of a target of interest.
- 13. The system of claim 1, wherein the data acquisition device comprises at least one deep brain stimulator placed in a brain of a target of interest.
- 14. The system of claim 1, wherein the electrophysiological information comprises pre-operative information, intra-operative information and post-operative information for a target of interest, respectively.
- 15. The system of claim 14, wherein the pre-operative information comprises at least one piece of information associated with presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status

examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof.

16. The system of claim 15, wherein the symptoms comprise at least one of upper extremity rigidity, lower extremity rigidity, upper extremity dystonia and lower extremity dystonia.

17. The system of claim 15, wherein the unified Parkinson's disease rating scale scores are a rating tool for evaluating mentation, behavior and mood, activities of daily living, motor activity, and complication of therapy for a target of interest undergoing treatment.

18. The system of claim 14, wherein the intra-operative information comprises at least one piece of information associated with at least one microelectrode, wherein the information includes microelectrode recordings, a position of the microelectrode recordings, a label of a structure in which the microelectrode recordings is located, and any mixture thereof.

19. The system of claim 18, wherein the microelectrode recordings are characterized by a firing rate that measures tonic activity and indices that measures phasic activity, wherein the indices include a burst index, a pause ratio, a pause index, and an interspike interval histogram.

20. The system of claim 14, wherein the intra-operative information comprises at least one piece of information associated with at least one stimulation electrode, wherein the information includes voltages applied to the at least one stimulation electrode, a response of a target of interest undergoing treatment to the stimulation, differences in voltage between disappearance of symptoms and appearance of side effects, a position of the at least one stimulation electrode, a final intra-operative target position of a deep brain stimulator to be placed, and any mixture thereof.

21. The system of claim 20, wherein the response of the target of interest undergoing treatment to the stimulation includes loss of rigidity, location where the loss of rigidity is observed, appearance of side effects, and/or location affected by these side effects.

22. The system of claim 14, wherein the post-operative information comprises at least one piece of information associated with at least one deep brain stimulator, wherein the information includes a position of the at least one deep brain stimulator in post-operative computerized tomographical images, optimal setting of the at least one deep brain stimulator, overall assessment of a target of interest after placement of the at least one deep brain stimulator, and any mixture thereof.

23. A method of creating an atlas that contains electrophysiological information related to at least one of a plurality of living subjects, wherein any portion of a brain of one of the plurality of living subjects and corresponding brain image volume may be identified by a set of corresponding spatial coordinates, comprising the steps of:

- a. choosing a brain image volume as a common image volume of reference from a plurality of brain image volumes, each of the plurality of brain image volumes being acquired pre-operatively from a brain of one of the plurality of the living subjects;
- b. acquiring electrophysiological information for one of the plurality of living subjects;

- c. relating the acquired electrophysiological information to spatial coordinates in the brain image volume of the corresponding living subject; and
 - d. registering the brain image volume of the corresponding living subject to the common image volume of reference so as to create an atlas in which any spatial coordinates of the brain of the corresponding living subject are related to atlas coordinates in the atlas such that the acquired electrophysiological information associated with the related spatial coordinates in the brain image volume of the corresponding living subject can be related to atlas coordinates in the atlas, and vice versa.
- 24.** The method of claim 23, further comprising the step of storing the atlas in a digitized format.
- 25.** The method of claim 23, wherein the atlas has an architecture to be accessible over a network.
- 26.** The method of claim 25, further comprising the step of populating the atlas with new electrophysiological information acquired from a target of interest.
- 27.** The method of claim 25, further comprising the step of accessing the electrophysiological information from the atlas.
- 28.** The method of claim 27, further comprising the step of obtaining the electrophysiological information from the atlas in one of a text format, an image format and a mixture thereof.
- 29.** The method of claim 28, wherein the obtained electrophysiological information includes an initial optimal target position for at least one deep brain stimulator to be placed in a brain of a target of interest.
- 30.** The method of claim 23, wherein the electrophysiological information comprises pre-operative information, intra-operative information and post-operative information for each of the plurality of living subjects, respectively.
- 31.** The method of claim 30, wherein the pre-operative information comprises at least one piece of information associated with presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof.
- 32.** The method of claim 31, wherein the symptoms comprise at least one of upper extremity rigidity, lower extremity rigidity, upper extremity dystonia and lower extremity dystonia.
- 33.** The method of claim 31, wherein the unified Parkinson's disease rating scale scores are a rating tool for evaluating mentation, behavior and mood, activities of daily living, motor activity, and complication of therapy for a target of interest undergoing treatment.
- 34.** The method of claim 30, wherein the intra-operative information comprises at least one piece of information associated with at least one microelectrode, wherein the information includes microelectrode recordings, a position of the microelectrode recordings, a label of a structure in which the microelectrode recordings is located, and any mixture thereof.
- 35.** The method of claim 34, wherein the microelectrode recordings are characterized by a firing rate that measures tonic activity and indices that measures phasic activity,

wherein the indices include a burst index, a pause ratio, a pause index, and an interspike interval histogram.

36. The method of claim 30, wherein the intra-operative information comprises at least one piece of information associated with at least one stimulation electrode, wherein the information includes voltages applied to the at least one stimulation electrode, a response of a target of interest undergoing treatment to the stimulation, differences in voltage between disappearance of symptoms and appearance of side effects, a position of the at least one stimulation electrode, a final intra-operative target position of a deep brain stimulator to be placed, and any mixture thereof.

37. The method of claim 36, wherein the response of the target of interest undergoing treatment to the stimulation includes loss of rigidity, location where the loss of rigidity is observed, appearance of side effects, and/or location affected by these side effects.

38. The method of claim 30, wherein the post-operative information comprises at least one piece of information associated with at least one deep brain stimulator, wherein the information includes a position of the at least one deep brain stimulator in post-operative computerized tomographical images, optimal setting of the at least one deep brain stimulator, overall assessment of a target of interest after placement of the at least one deep brain stimulator, and any mixture thereof.

39. A system that contains electrophysiological information related to at least one of a plurality of living subjects, wherein any portion of interest in the brain of one of the plurality of living subjects and corresponding brain image volume may be identified by a set of corresponding spatial coordinates, comprising:

- a. a data storage device; and
 - b. an atlas stored in the data storage device for containing the electrophysiological information, the atlas being created such that when a brain image volume is registered to the atlas, any spatial coordinates of the brain image volume are related to corresponding atlas coordinates in the atlas, and vice versa.
- 40.** The system of claim 39, wherein the atlas has an architecture to be accessible over a network.
- 41.** The system of claim 40, wherein the atlas can be in communication with a user interface.
- 42.** The system of claim 41, wherein the user interface is used for populating the system with new electrophysiological information acquired from a target of interest.
- 43.** The system of claim 41, wherein the user interface is used for accessing the electrophysiological information from the atlas.
- 44.** The system of claim 39, wherein the electrophysiological information comprises pre-operative information, intra-operative information and post-operative information for each of the plurality of living subjects, respectively.
- 45.** The system of claim 44, wherein the pre-operative information comprises at least one piece of information associated with presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof.

46. The system of claim 45, wherein the symptoms comprise at least one of upper extremity rigidity, lower extremity rigidity, upper extremity dystonia and lower extremity dystonia.

47. The system of claim 46, wherein the unified Parkinson's disease rating scale scores are a rating tool for evaluating mentation, behavior and mood, activities of daily living, motor activity, and complication of therapy for a target of interest undergoing treatment.

48. The system of claim 44, wherein the intra-operative information comprises at least one piece of information associated with at least one microelectrode, wherein the information includes microelectrode recordings, a position of the microelectrode recordings, a label of a structure in which the microelectrode recordings is located, and any mixture thereof.

49. The system of claim 48, wherein the microelectrode recordings are characterized by a firing rate that measures tonic activity and indices that measures phasic activity, wherein the indices include a burst index, a pause ratio, a pause index, and an interspike interval histogram.

50. The system of claim 44, wherein the intra-operative information comprises at least one piece of information associated with at least one stimulation electrode, wherein the information includes voltages applied to the at least one stimulation electrode, a response of a target of interest undergoing treatment to the stimulation, differences in voltage between disappearance of symptoms and appearance of side effects, a position of the at least one stimulation electrode, a final intra-operative target position of a deep brain stimulator to be placed, and any mixture thereof.

51. The system of claim 50, wherein the response of the target of interest undergoing treatment to the stimulation includes loss of rigidity, location where the loss of rigidity is observed, appearance of side effects, and/or location affected by these side effects.

52. The system of claim 44, wherein the post-operative information comprises at least one piece of information associated with at least one deep brain stimulator, wherein the information includes a position of the at least one deep brain stimulator in post-operative computerized tomographical images, optimal setting of the at least one deep brain stimulator, overall assessment of a target of interest after placement of the at least one deep brain stimulator, and any mixture thereof.

53. The system of claim 39, wherein the data storage device comprises a memory.

54. The system of claim 39, further comprising a controller in communication with the data storage device.

55. A computer readable medium or media, comprising:

- a. a data structure relating to an atlas that contains electrophysiological information related to at least one of a plurality of living subjects, wherein any portion of interest for the brain of at least one of the plurality of living subjects and corresponding image volume may be identified by a set of corresponding spatial coordinates; and
- b. a user interface in communication with the data structure.

56. The computer readable medium or media of claim 55, wherein the data structure comprises a plurality of transformations and corresponding inverses of the plurality of transformations.

57. The computer readable medium or media of claim 56, wherein each of a plurality of transformations registers a brain image volume to the atlas, wherein the brain image volume is acquired from one of the plurality of living subjects.

58. The computer readable medium or media of claim 57, wherein the atlas is created such that when a brain image volume of a living subject is registered to the atlas, any spatial coordinates in the brain image volume of the living subject are related to corresponding atlas coordinates in the atlas, and vice versa.

59. The computer readable medium or media of claim 58, wherein the electrophysiological information associated with spatial coordinates from which the electrophysiological information is acquired in the brain of the living subject can be related to atlas coordinates in the atlas, and vice versa.

60. The computer readable medium or media of claim 59, wherein the user interface is used for populating the atlas with new electrophysiological information acquired from a target of interest.

61. The computer readable medium or media of claim 59, wherein the user interface is used for accessing the electrophysiological information from the atlas.

62. The computer readable medium or media of claim 61, wherein the user interface is used for obtaining the electrophysiological information from in the atlas in one of a text format, an image format and a mixture thereof.

63. The computer readable medium or media of claim 62, wherein the obtained electrophysiological information includes an initial optimal target position for at least one deep brain stimulator to be placed in a brain of a target of interest.

64. The computer readable medium or media of claim 57, wherein the atlas is stored in a digitized format of files.

65. The computer readable medium or media of claim 57, wherein the electrophysiological information comprises pre-operative information, intra-operative information and post-operative information for each of the plurality of living subjects, respectively.

66. A method for optimal placement of a deep brain stimulator in a brain of a target of interest, comprising the steps of:

- a. acquiring from the target of interest pre-operatively at least one piece of information associated with a state of brain condition of the target of interest;
- b. accessing remotely an atlas that contains electrophysiological information related to a plurality of living subjects, wherein any portion of the brain of one of the plurality of living subjects and corresponding brain image volume may be identified by a set of corresponding spatial coordinates;
- c. entering the acquired information from the target of interest to the atlas to find a match between the acquired information and the electrophysiological information contained in the atlas; and
- d. automatically obtaining an optimal position in the brain of the target of interest for placing a deep brain stimulator from the matched information.

67. The method of claim 66, wherein the atlas is stored in a memory device associated with a central host computer.

68. The method of claim 67, wherein the accessing step comprises the step of accessing the atlas over a network

from a client computer, and wherein the central host computer and client computer are coupled to and in communication with the network, respectively.

69. The method of claim 68, wherein the network comprises at least one of a public network, a dedicated network, a local network, and any combination of them.

70. The method of claim 69, wherein the public network comprises the Internet.

71. The method of claim 66, further comprising the steps of acquiring electrophysiological information intra-operatively from the brain of the target of interest and adjusting the optimal position in the brain of the target of interest for placing a deep brain stimulator accordingly.

72. The method of claim 71, further comprising the steps of finding a final optimal position in the brain of the target of interest for placing a deep brain stimulator from the adjusted optimal position and placing a deep brain stimulator in the brain of the target of interest.

73. The method of claim 71, further comprising the steps of downloading information related to the optimal position in the brain of the target of interest for placing a deep brain stimulator from the matched information to a local computer and adjusting the optimal position in the brain of the target of interest for placing a deep brain stimulator from the downloaded information.

74. The method of claim 66, further comprising the step of updating the atlas from information related to the target of interest.

75. The method of claim 66, wherein the information associated with the state of brain condition of the target of interest comprises presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof of the target of interest.

76. The method of claim 66, wherein the state of brain condition is related to a type of a disease.

77. The method of claim 76, wherein the state of brain condition is related to a degree of a disease.

78. A method for optimal placement of a deep brain stimulator in a brain of a target of interest, comprising the steps of:

- a. acquiring from the target of interest pre-operatively at least one piece of information associated with a state of brain condition of the target of interest;
- b. accessing remotely an atlas that contains electrophysiological information related to a plurality of living subjects, wherein the atlas is formed with a plurality of clusters, each cluster being related to a state of brain condition and having a plurality of optimal positions for a deep brain stimulator distributed therein;
- c. entering the acquired information from the target of interest to the atlas to find a match between the acquired information and the electrophysiological information contained in the atlas; and
- d. automatically obtaining an optimal position in the brain of the target of interest for placing a deep brain stimulator from one of the plurality of optimal positions for a deep brain stimulator distributed in the plurality of clusters.

79. The method of claim 78, wherein the state of brain condition is related to a type of a disease.

80. The method of claim 79, wherein the state of brain condition is related to a degree of a disease.

81. The method of claim 78, wherein the information associated with the state of brain condition of the target of interest comprises presenting complaints, locations of symptoms related to one or more diseases, type and degree of the one or more diseases, unified Parkinson's disease rating scale scores both on and off medications, mini-mental status examination, medications and dosages, cognitive performance, gait performance, pre-operative target positions, and any mixture thereof of the target of interest.

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