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CranialVault and its CRAVE tools: a clinical computer assistance system for Deep Brain Stimulation (DBS) therapy

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Abstract

A number of methods have been developed to assist surgeons at various stages of deep brain stimulation (DBS) therapy. These include construction of anatomical atlases, functional databases, and electrophysiological atlases and maps. But, a complete system that can be integrated into the clinical workflow has not been developed. In this paper we present a system designed to assist physicians in pre-operative target planning, intra-operative target refinement and implantation, and post-operative DBS lead programming. The purpose of this system is to centralize the data acquired at the various stages of the procedure, reduce the amount of time needed at each stage of the therapy, and maximize the efficiency of the entire process. The system consists of a central repository (CranialVault), of a suite of software modules called CRAVE (CRAnialVault Explorer) that permit data entry and data visualization at each stage of the therapy, and of a series of algorithms that permit the automatic processing of the data. The central repository contains image data for more than 400 patients with the related pre-operative plans and position of the final implants and about 10,550 electrophysiological data points (micro-electrode recordings or responses to stimulations) recorded from 222 of these patients. The system has reached the stage of a clinical prototype that is being evaluated clinically at our institution. A preliminary quantitative validation of the planning component of the system performed on 80 patients who underwent the procedure between January 2009 and December 2009 shows that the system provides both timely and valuable information.

Keywords

Deep brain stimulation; centralized data repository; computer-based assistance; visualization

1. Background

Movement disorders such as Parkinson's disease (PD), essential tremor (ET) and dystonia affect approximately 1 million, 1.5 million, and 250,000 people respectively in the United States. Direct health-related expenses, indirect disability expenses and lost productivity in the United States for PD alone amount to \$25 billion annually (Medtronic 2009). Since its first FDA (Federal Drug Agency) approval in 1998, high frequency deep brain stimulation

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BMD and RL receive a portion of the royalties paid by FHC, Inc. to Vanderbilt for the license of the planning module.

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(DBS) has become a contemporary treatment of these diseases as well as of an emerging number of other focal neurological disorders (Schrader et al. 2002, Thompson et al. 1997, Starr 2002).

DBS therapy involves three stages: pre-operative target localization, intra-operative electrode placement, and post-operative programming. First, the surgeon pre-operatively selects a target that is expected to provide maximum therapeutic benefit to the patient. Most common targets for movement disorders are the sub-thalamic nucleus (STN), the ventral intermediate thalamic nucleus (VIM) and the globus pallidus internus (GPi). These are found in patient's imaging data either directly with or without the help of an atlas, or indirectly by using internal landmarks such as the anterior and posterior commissures (AC-PC) or the red nucleus boundaries. Second, the position of the target is refined during the intra-operative stage to compensate for patient's anatomical variability and brain shift. Intra-operative brain shift happens due to loss of cerebrospinal fluid and air invasion into the skull (pneumocephalus) through the burr hole, gravitational force, see for instance (Rohlfing et al. 2003), change in pressure due to skull opening during the surgery and forces due to insertion of the DBS lead. Target refinement is typically done using two types of intra-operative observations: micro-electrode recordings (MERs) and stimulation response. Intra-operative data are acquired using exploratory electrodes that are generally inserted and guided using an external rigid fixture called a stereotactic frame. During MER, a recording electrode is used to characterize the neuronal firing patterns, which are then used to infer the location of deep brain nuclei relevant to the targeted region. The neurosurgeon, often with the help of a neurophysiologist, then establishes functional borders of the structures of interest that will be stimulated to find an optimal location for the implant. During the stimulation phase, mild electrical currents are applied using stimulating electrodes to elicit responses in the patient. Relevant stimulation data consist of the position at which the patient has been stimulated, the voltage/current that has been used, and the response that has been observed (i.e., symptom reduction and/or appearance of adverse effects). When a satisfactory position is found, the exploratory electrodes are removed and the DBS implants are inserted. Additionally, an implantable pulse generator (IPG) is placed under the patient's skin near the collarbone and connected to the final implants for stimulation. About a month after the surgical procedure, the neurologist adjusts the parameters of the IPG by identifying the contact(s) and stimulation parameters including voltage, pulse width, and frequency that produce the most therapeutic benefit. Each of the 4 contacts lead is separately evaluated (monopolar configuration) for adverse effects as well as for symptom reduction. Once identified, the optimal contact is activated. Programming is typically performed with neither the benefit of information on the anatomical location of the implant, nor knowledge of the electrophysiological data acquired during the procedure. The programming process can take considerable time (30–60 minutes) or even more if the implantation is bilateral. It can be particularly uncomfortable for the patients since they are required to stop their medications a day or so prior to the session.

A number of methods have been developed to assist physicians at the different steps of the DBS procedure. Some of these approaches (Yelnik et al. 2007, Bardinet et al. 2009; Chakravarty et al. 2006a, Chakravarty et al. 2006b) involve the reconstruction of a 3D histological atlas from thin contiguous slices and registration to the MR image volume of the same subject. Using such an atlas, structures like the STN, substantia nigra (SNr) and the red nucleus can be segmented in a patient's MR and used as internal landmarks to assist the surgeon in target planning. However, there is a lack of consensus on the exact anatomical location at which stimulation can provide the best therapeutic benefit for a given disease (Plaha et al. 2006, Maks et al. 2009, Andrade-Souza et al. 2008). Motor, psychiatric and cognitive effects following the procedure are also variable. (Burn and Troster 2004, Hershey et al. 2003, Houeto et al. 2002). Videen et al. (2008) hypothesize that this is due to

variability in the placement of the electrodes. Thus, accurate physiological atlases of data acquired during DBS are needed to provide valuable insight to DBS planning, placement, and programming and complement anatomical information provided by histological data. These physiological atlases can contain (1) information acquired intra-operatively such as MER, response to stimulation and the locations of implanted electrodes, (2) post-operative programming data (clinically selected optimal contact and the stimulator settings), (3) clinical information acquired over time to allow assessment of the procedure's long term effects. Several attempts have been made at developing such physiological atlases. Nowinski et al. (2003, 2005, 2007) put forth the concept of a probabilistic functional atlas (PFA). The PFA provides the spatial distribution of the clinically most effective contacts normalized to a common space. The authors showed that surgical target planning based on their PFA was better than that based on anatomical atlases alone. Building on the work of Finnis et al. (2003), Guo et al. (2005) describe a functional database used to capture and normalize information acquired intra-operatively and compare different techniques to target the STN (Guo et al. 2006). The data were normalized spatially by registering the MR volume of each patient to one reference volume with a combination of rigid and non-rigid registrations. Our group (D'Haese et al. 2004, 2005a, 2005b) has described techniques by which a computer system can be used to predict the position of the pre-operative target and proposed methods to build accurate electrophysiological atlases and maps (Pallavaram et al. 2008b, 2009a, 2009d). Castro et al. (2006a, 2006b) have also shown that atlas-based targeting is feasible with an accuracy comparable to manual selection of targets.

Only a few techniques have been developed to assist the surgeons intra-operatively. Gironell et al. (2005) have presented the benefits of an intra-operative neurophysiological navigator computerized system in helping a surgical team select the optimal target. Miocinovic et al. (2007) developed a software tool (Human Cicerone) that enables interactive 3D visualization of co-registered patient images, 3D brain atlases, MER data and volume of tissue activated for use during the surgery. Luis Luján et al. (2009) recently presented an automated method for optimally fitting a 3-dimensional brain atlas to intra-operative MER that could aid in the surgical decision-making process by providing a visual guide for target identification. One of our recent study also suggests that brain shift can be detected by comparing electrophysiological atlases and intra-operative patient's data (Pallavaram et al. 2009b). In 2006, we introduced the concept of using deformable statistical atlases to assist neurologist during post-operative programming (D'Haese et al. 2006). Butson et al. (2007, 2008) have also presented results on models for patient-specific volume of tissue activation that can be used for selecting stimulator parameters during post-operative programming.

Thus, numerous attempts have been made at developing systems and techniques, which could assist physicians at the various stages of DBS procedures. However, a fully integrated system that addresses the issue of connectivity and data transfer between the various stages of the therapy or one that permits easy access to historical data pertaining to a patient or to population data has not yet been developed. In this article, we present such a system. We discuss its architecture, detail its components, and report on its state of development, implementation, and clinical utilization.

2. Materials and Methods

2.1 Design philosophy

DBS therapy requires collaboration between neurosurgeons, neurologists, psychiatrists, engineers, electrophysiologists, physical therapists and administrative staff. Analyzing the requirements for a centralized system that allows multiple groups or sites to access and contribute to a common resource simultaneously from different locations and at different stages of the therapy, and that can be integrated into the clinical flow to permit data

acquisition and assistance through a full DBS procedure led to the following key design criteria:

- Access to meaningful data at each step of the procedure: the quantity of data available to the physician is often enormous and can be irrelevant if not filtered or processed appropriately. The system should be built such that appropriate data filters and processing methods are in place at the various stages.
- Easy access to the data pertaining to a patient or to population data from external DBS sites: in order to gather and share experience from surgeons at different locations, it is critical to be able to transfer data easily to and from any external site.
- Simplicity of use, and reliable and quick access to data and information: the interfaces should be built with tools and features that are intuitive to the physicians, and the database and communication systems should permit fast and reliable access to the data.
- Rapid prototyping: the system should be extensible to meet new requirements or permit substituting processing algorithms. For instance, it must be possible to easily extend the system to accommodate different types of stereotactic frames or to communicate with a variety of intra- or post-operative systems and devices. As will be discussed later, a number of registration and segmentation algorithms are used to process the images. The system must (a) permit updating or changing these algorithms as new techniques are developed and (b) reprocess the data contained in the database with these new algorithms.
- Security: The system must be HIPAA (Health Insurance Portability and Accountability Act) compliant to protect patient confidentiality
- Scalability: the system should easily scale up and be portable to a computer cluster.

Based on these requirements, we have developed a database that contains data for over 400 patients and we have a system in place in which two synchronized Oracle databases are running, thus guaranteeing availability of data 24/7. A suite of software has been developed to permit data entry and visualization during the pre-, intra- and post-operative phases of the process. We call this secure data repository along with the associated processing algorithms “CranialVault”, and the software suite which permits access to this database as well as visualization tools CRAVE (CRANialVault Explorer). Communication with the database happens via the internet affording the users the flexibility to download and use the data from any computer anywhere. A potential disadvantage of this solution could be speed due to network communication delays. However, the only large data sets to be transferred are the patient’s images. Our system allows downloading these images remotely via the internet as well as using locally stored images when the internet is unavailable. Other kinds of data including stimulation response and micro-electrode recordings stored in the database do not require high speed connectivity. Additionally, these can also be stored locally in a small customized database that can be used in the absence of network connectivity. This local database can be synchronized and updated the next time the system gets online. In order to ensure patient confidentiality and HIPAA compliance, we use fine-grained access control, row-level security and virtual database concepts to restrict data access to the users with the right credentials. We implemented several levels of security. First, each user has access to information depending on his/her role and needs (e.g. a surgeon will have full access to the patients information while a member of the engineering team will have read only access to de-identified data). Each user has access to patients who have been registered to his/her surgical group. This is controlled by database security policies directly bound to the table that they handle. In logical terms, a security policy is a function that dynamically strips away unwanted data when a database table is referenced by a particular user. When information

travels to and from Cranialvault, data are encrypted using the AES256 encryption standard and sent over Secure Sockets Layers (SSL) encryption. In addition, we use Oracle Advanced Security to protect the integrity of information, making sure the message has not been modified since it left the source.

2.2 Status of the database

The database we have designed, implemented, and are currently maintaining contains all or part of the following information for every DBS patient treated at Vanderbilt or at external sites with IRB (Institutional Review Board) approval who collaborate with us. (1) Pre-operative data include CT images, MR images (typically T1-weighted (MRT1) without contrast agent, T1-weighted with contrast agent (MRT1+C), and T2-weighted (MRT2)) as well as planned targets. (2) Intra-operative data acquired during the procedure include somatotopic data (correspondence between the position of a receptor in part of the body and the corresponding area of the cerebral cortex that is activated by it), response to stimulation, micro-electrode recordings and the location of electrode implantation. (3) Post-operative data include CT images acquired immediately after the procedure, CT images acquired about a month after the procedure and programming data consisting of the clinically selected contact as well as stimulation parameters. The complete set of data is not acquired for all patients but a patient is not entered in the database if we do not have a least a T1-weighted image and either the final implant position or some intra-operative data. The database also contains what we refer to as atlases. These are MR image volumes (currently we use four), which are used to normalize spatially all the information we acquire in individual patients by mapping them from patient image space to the atlas space using registration techniques. All rigid registrations are performed with an in-house implementation of a mutual information-based algorithm. All non-rigid registrations are performed with the Adaptive Bases Algorithm we have developed (Rohde et al. 2003). We use multiple atlases because there is evidence in the medical imaging literature (Rohlfing and Maurer 2004) that using multiple atlases leads to segmentation results that are more reliable than those obtained with a single atlas and that these can be used to choose atlases that register better with a patient than others. All the transformations (currently in excess of 6500) are stored in the database. This includes the intra-patient rigid registrations that aligns all the patient's sequences onto the reference sequence (usually the pre-operative CT); and the combination of the affine and non rigid registrations of the patient's MRT1 to each of the atlases. All data are stored in the native patient space (in both the stereotactic frame and the pre-operative CT (or MR when CT is not used) coordinates and then projected onto the atlas space using registration. Doing so allows us to easily modify registration algorithms or change the atlases. When either of these is done, we only have to re-compute the registration between the patient and the atlas to project the data onto the atlas space. Each of the four atlases is built using the same number of patients. Patients used for atlas creation are selected based on image quality, small intra-operative shift measured by the amount of air in the intracranial cavity observed in the post-operative CTs, or outcome data (see Pallavaram 2009d). We also store manual segmentations of structures such as the thalamus, putamen, STN, SNr, GPi, ventricles, and red nucleus in the four MR image atlas volumes as well as the location of landmarks like the AC and PC. These can then be used to segment structures and localize points of interest in particular patients as discussed in the next section.

2.3 A website for easy interface to the database

In addition to the data repository, we host a website synchronized with the database. The purpose of this website is to provide both the surgical team and the administrative staff working on the project with an interface to the database. Through this website, staff can enter patient scheduling information, transfer patient images as well as enter patient data such as UPDRS (Unified Parkinson's Disease Rating Scale) scores. These scores are

acquired before and after the surgery to permit assessing the effect of the procedure. The website also serves as a one-stop destination for the neurosurgeons to request pre-operative target predictions as well as for neurologists to request post-operative programming assistance. These will be discussed in section 2.5.

2.4 Information produced by the database

Using the data acquired for individual patients and the four MR atlas volumes, our system can be used to (1) localize automatically the AC and the PC, (2) predict the optimal position of the implant, (3) segment anatomical structures, and (4) produce electrophysiological maps in a new patient volume.

2.4.1 Automatic AC and PC prediction—The AC and PC points are predicted by registering the atlases to a patient volume, projecting the AC and PC points from the four atlases onto this volume, and combining them using a method based on the STAPLE algorithm put forth by Warfield et al. (2004). In brief, this technique evaluates the performance of the mapping between each atlas and the patient's volume using segmented structures that surround the region of interest and weighs the contribution of each atlas to the results (D'Haese et al. 2005b). We have published a validation study (Pallavaram et al. 2009c) on this approach performed retrospectively, which shows that our method can predict the AC and PC points automatically more accurately than expert clinicians can do clinically. In section 3.1 we report on recent results we have obtained clinically.

2.4.2 Automatic prediction of the target points and segmentation of structures—For each target, a cluster of final implant positions is stored in the atlases as a result of projecting this information from individual patients onto the atlases. Using the method described in section 2.4.1, we project the centroid of such a cluster from each atlas onto a new patient and combine these projections to produce an optimal target prediction. Similarly, structures segmented in the atlases can be projected from the atlases onto the patient volumes. In 2005, we published a study in which we compared retrospectively the automatic and manual selections of the target points by comparing them to the position of the implant chosen intra-operatively by the surgeon (D'Haese et al. 2005b). We reported an average Euclidian error of 1.7 mm for the automatic method compared to 2.4 mm when manual prediction was done without any assistance. Since then, we compared the pre-operative target points suggested by our system in routine use and the points chosen by the surgeons. Results of this study are presented in section 3.1.

2.4.3 Creation of electrophysiological maps—As introduced in the background section, the surgical team stimulates different locations of the patient's brain with mild electrical currents and records the voltages that produce efficacy and onset of adverse effects. Once these data are gathered in our central repository, and projected onto our atlases, they are used to create statistical maps, which show the zone(s) of efficacy as well as of various adverse effects (for example, maps of contraction or double vision). To build these maps, we follow the method we have described in (Pallavaram et al. 2008b). Briefly, we assume that responsive neurons are localized somewhere on a 3D spherical shell centered on the stimulation point. To study a patient's response to stimulation at a given location, stimulation voltage is applied in steps (typically 0.5–1.0 V) until a response is observed. If a response occurs at stimulation voltage V and not at the previous step $V-\epsilon$, we assume that the responsive neurons were activated between $V-\epsilon$ and V where ϵ is a positive real number. Thus, we assume that the responsive neurons lie on this spherical shell. We associate a uniform probability density function with the neurons in the spherical shell. This is illustrated in 2D for simplicity in Figure 1. In this figure, three measurement points are shown (P1, P2, P3). A uniform probability density function within an annulus is associated

with each point (gray annulus). Summing over a number of such stimulation points and normalizing them yields a probability map of responsive stimulation regions. Our voltage to radius relationship (R) is based on the data published by Butson et al. (2007, 2008) for mono-polar stimulation using a DBS electrode in an isotropic medium and with standard stimulator settings.

Figure 2 shows a typical STN efficacy map created with this method superimposed on an MR image. To create somatotopy maps, we place truncated Gaussian kernels of finite support (typically 1 mm) at each somatotopy point. Overlapping regions of the kernels are added and normalized to produce a smooth map that serves as a probabilistic map of somatotopy.

2.5 Data flow and computer aided assistance

Figure 3 illustrates the data and process flows used for every patient undergoing DBS surgery at Vanderbilt or at external sites collaborating with us on the project. The centralized repository and associated processing algorithms (CranialVault) are connected to each of the visualization modules of CRAVE as will be discussed in sub-sections 2.5.1 through 2.5.3.

2.5.1 Pre-operative assistance—We call this module the *Planner*. Routine clinical planning for DBS at Vanderbilt and some external sites is now performed as follows. Once acquired, pre-operative CT and MRI are transferred from the scanners to our server and added to CranialVault. Arrival of new images triggers a series of automatic image processing algorithms: 1) CT and MR images are aligned with a rigid body mutual-information (MI) based algorithm; 2) the patient's MRT1 sequence is then registered non-rigidly to the atlases using our non rigid intensity-based algorithm (Rohde et al. 2003), and results are stored in the database. 3) Next, our system automatically generates a computer-based pre-operative plan. This plan is created based on the request submitted by the neurosurgeon through the CranialVault website in which (s)he chooses the targets to be predicted (the most commonly used being STN, Vim, or GPi) and the desired date and time of delivery of the predictions (section 2.3). The computer-assisted plan generated by our system consists of the following: (a) pre-computed transformations to align all the images pertaining to the patient (i.e., CT, MRT1, MRT2, etc.), (b) prediction of the anterior (AC) and posterior commissures (PC) (section 2.4.1), (c–d) prediction of the target points and segmentation of relevant anatomical structures (section 2.4.2), and (e) statistical maps showing probability of high implant efficacy or side effects regions, as well as maps of somatotopic arrangement (section 2.4.3). A trajectory is defined by the predicted target and a pre-defined approach angle. Once the plan is generated (within 10–15 minutes after the arrival of the images), surgeons are notified automatically via an email generated by the system. The neurosurgeon then starts the planner and connects to the CranialVault using his/her username and password. A list of available automatically generated plans is displayed and the plan of interest is selected. The plan is then reviewed, edited if necessary, and finalized. Because the registrations are precomputed, it saves the neurosurgeon time that would otherwise be spent registering the various pre-operative images. Also, the availability of pre-computed selections for anatomical landmarks and targets as well as the statistical maps and segmentations of structures provide the surgeon with apriori information to finalize the plan. We use at our institution a patient customized frame; the StarFix microTargeting Platform® (501(K), Number K003776, Feb. 23, 2001, FHC, INC, Bowdoin, ME) manufactured by FHC instead of traditional frames such as the Leksell G-frame (Elekta AB, Stockholm, Sweden) or the CRW frame (Radionics, Burlington, MA, USA). For this reason, once the plan is finalized, a platform file is generated and sent automatically to FHC for manufacturing. Figure 4 shows the interface of the planning module. Segmented

structures (see section 2.4.2) as well as automatic trajectory predictions generated by our system are also shown in the figure.

Plan verification and finalization is done with the planning module of the CRAVE suite which has been validated by FHC, Inc. as per FDA requirements. It is thus being used clinically for the creation of the frames.

2.5.2 Intra-operative assistance—Once the surgeon connects to CranialVault intra-operatively, the pre-operative plan is loaded and can be visualized in the intra-operative module of CRAVE. The planned trajectories, statistical electrophysiological maps and automatically segmented structures, as well as guide tubes to be used for MER and stimulation during the procedure are also displayed as shown in figure 5(a). The module is then used for recording intra-operative data via a user-friendly interface.

First, during MER, neuronal activity is analyzed using features such as the neuronal firing frequency. Signals from different nuclei have different signatures. For instance, in a common approach, the neuronal firing frequency presents a marked increase as the recording electrode enters the STN and shows a marked decrease as it exits the STN before increasing even more while entering the SNr. It is difficult for the surgeons to mentally create a picture of the encountered nuclei using data acquired with up to 10 probes at once. This information is processed and shown to the surgeon as 3D histograms along each track that is used as shown in figure 5(b). The 3D representation helps the surgical team to better visualize changes in firing frequency and find electrophysiological patterns to identify an approximate region to start the stimulation testing. The team often then labels the segments of interest as shown on the figure 5(b). In the example shown in this figure, it is easy to identify the STN as the widest region of the histogram on the center and medial tracks. The team can also see that the STN was missed by the lateral track and then limit the zone to be stimulated on the medial and center tracks. Once this is done, the surgical team can choose to turn-off the 3D histograms to avoid cluttering the display.

Next, responses to stimulations are manually recorded in the module as they are observed using the graphical interface of the intra-operative module. As introduced earlier, a response to stimulation consists of percentage of efficacy (if any), current producing this efficacy, side effects (e.g. muscle contraction, double vision, paraesthesia, nausea ...) (if any) and the current causing them. This information is combined and visualized as a color-coded sphere for each stimulation response observation. The radius of each sphere is proportional to the therapeutic window at that location (the difference between the currents producing side effect and efficacy), the opacity is proportional to the percentage of efficacy and the color of the sphere is dependent on the presence or not of side effects (red on one end of the color scale when side effects are serious and minimal efficacy is observed to green on the other end when side effects are minimal and substantial efficacy is observed). Thus, at one glance, the surgical team can visualize which locations produce the best stimulation response. This way it can easily identify the optimal location for final implant placement. On figure 5.b) the team found several good locations on the center track while finding some points producing unacceptable side effect on the medial one. They then decided to place the final lead on the center track.

Because the intra-operative module is connected to the database, direct and immediate transfer of all data (electrophysiological as well as position of final implant) recorded during the surgery is possible. Graphical user interfaces and device interfaces are currently under development and evaluation to permit real-time transfer of electrode location as well as MER and stimulation data directly from the system used for recordings and stimulations.

2.5.3 Post-operative assistance using CranialVault and CRAVE—Post-operatively, two CT scans are acquired at our institution, the first immediately after the procedure and the second a month later. We call the latter the stable CT where the brain is expected to have recovered from brain shift, the implant stabilized and pneumocephalus resolved. Both these scans are transferred to our database. This triggers their rigid registration to the pre-operative CT scan as well as automatic extraction of the implant from these images. A post-operative pack is created. This pack contains the implant extracted from the stable CT overlaid on the pre-operative MR images, segmentations of structures of interest, electrophysiological data recorded for the patient intra-operatively, and statistical electrophysiological maps. Once the pack is verified, the neurologist is alerted via an email automatically sent by the system. The post-operative pack can then be loaded by the neurologists in the post-operative module of the CRAVE suite on their laptops or work computers as shown in figure 6. The neurologists can visualize the location of the implant with respect to the anatomy as well as patient-specific and atlas-based electrophysiological data to make an informed decision on the selection of the optimal contact. In the example shown in figure 6, the neurologist visualizes the implant and the position of each contact relative to the statistical information shown as 3D meshes. Based on the displayed information, the second contact from the bottom would be chosen instead of the first one. Stimulation with both contacts is predicted by the system as having a good probability to get an efficacious stimulation; however, the bottom contact is a lot closer to a region that, if stimulated, will generate a side effect (diplopia for instance). Our system can be used in conjunction with the activation fields proposed by Butson et al. (2007) to facilitate setting up programming parameters such as the voltage, pulse width and frequency. The final clinically selected contact(s) and programming settings are then sent back to the database to update the atlas that will be used for future patients.

3. Preliminary evaluation of the system

Various components of the system have reached different stages of development and evaluation. The pre-operative component is mature and is used routinely at Vanderbilt and at collaborating sites. The intra-operative component is operational but not used systematically because the interfaces we are developing are still evolving and the post-operative component has been used on isolated cases, mainly cases with which the clinical team experienced programming difficulties. For these cases, the information provided by the system, i.e., the position of the implant with respect to the anatomy or with respect to the electrophysiology was found to be useful. The next section describes a preliminary study we have conducted on the usefulness of the automatic planning component of the system.

3.1 Pre-operative assistance using CranialVault and CRAVE

The usefulness of pre-operative assistance was studied for 80 patients who underwent a DBS procedure between January 1st 2009 and December 20th 2009 for a total of 144 implants (82 STN, 29 GPI and 33 VIM). For each patient, a surgical plan was created by our system prior to the surgery and was made available to the surgeon at the time of planning as described in section 2.5.1.

We use three criteria to evaluate the system: 1) quality of the automatic registrations: how many times the automatic registrations between the MRI sequences and the CT were used or modified; if modified, by how much and how did it affect the position of the targets; 2) accuracy of the automatic AC and the PC selections: we measure how many times the automatic points were modified and the distance between their automatic and manual selections; and 3) accuracy of the automatic target prediction; we compute the distance between the automatic and manual target positions.

On a total of 80 patients, 67 plans were generated in time and used for computer assisted planning. The remaining 13 plans were not used either because the images were not transferred in time to our server or because the plans could not be created on time due to limited processing resources.

Out of 134 registrations, counting both MRT1 and MRT2 to CT, 128 were used without any modifications; for the 6 remaining registrations, the surgeon decided to modify them manually or semi-automatically with the registration algorithm available in the planner. Table 1 reports the difference in translation $\Delta(x,ty,tz)$ and rotation $\Delta(rx,ry,rz)$ between the pre-computed registrations and the registrations validated by the surgeons. The related error in mm on the AC, PC and target points due to the mis-registration is reported in Table 2. Table 3 details the statistics of the modifications made to the computer selected stereotactic and target points. Figure 7 plots both the frequency and the cumulative frequency of the differences between the computer assisted and the final selections of the AC and the PC.

4. Discussion and future work

As discussed in the Introduction section, repositories such as CranialVault could have a substantial impact on patient care. They would permit aggregating data from large populations, correlating outcome with electrode placement or other parameters such a demographic information or disease state, or accessing both population-based and patient-specific information at the point and time of care, thus potentially facilitating all phases of the procedure. Yet, creating this type of repository is difficult because it involves a range of disparate data as well as several medical specialties with different needs and perspectives. Accurate medical data entry is also a notoriously difficult problem in clinical practice in general and in the operating room in particular. Asking physicians to enter data for research purposes can be done on a limited scale but is hard to implement on a routine basis. In our view, the best approach to follow to build such repositories is to progressively develop a complete system that can be integrated in the clinical flow and used in the daily delivery of care, i.e., we are aiming at building simultaneously the repository and the tools that will permit exploiting the information it contains. Following this approach provides the user with an incentive to enter the data.

As discussed in this article, we have made great strides toward the development and fielding of such a system. We started with the planning phase of the procedure. We have generated 76 plans in 2007, 66 in 2008, and 80 in 2009. It is now mature and plans are generated for every patient at Vanderbilt. The quantitative results we have obtained on the clinical use of our computer assistance system for planning DBS procedures has shown that pre-computed registrations of the patient's MRIs to the pre-operative CT were used without modification in 95% of the cases while 5% of the registrations did not satisfy the surgeon and were manually modified. For the cases successfully aligned, our results show that the AC and PC automatic selections were modified in average respectively by 0.83 ± 0.57 mm and 0.83 ± 0.60 mm. 15% of the computer selections of the AC and PC were used without modifications, 63% where modified by less than 1 mm and 90% by less than 1.5 mm. For comparison, the inter-surgeons variability for the selection of the AC and PC was estimated at respectively 1.53 ± 1.44 mm and 1.45 ± 1.24 mm by Pallavaram et al. in [2008b]. Finally, our results show that the automatic selections of the targets have been modified in average by 1.04 ± 0.96 mm, 2.56 ± 1.07 mm and 3.47 ± 2.38 mm, respectively, for the STN, GPI and VIM cases. The adjustment for the STN is thus on the order of one voxel, which we consider to be good. Furthermore, in none of the cases included in this study have we observed catastrophic failure, which indicates the robustness of our system. The larger modifications we have observed for the other targets could have several explanations. Automatic targeting is based on statistics computed from the final intra-operative position of implants from prior

surgeries but the pre-operative target chosen by the surgeon may be different. For instance, surgeons may select a target that has a clear electrophysiological signature and then move the electrode by a fixed offset intra-operatively. One example is targeting for the ventralis caudalis (VC) borders for VIM cases because sensory effects can be observed intra-operatively in this structure. The final DBS lead is then placed more anterior. We are currently investigating this issue to determine if we need to modify the target point selected at the time of planning to reflect surgeon's preference.

The intra-operative module of the system is also mature and it is being clinically evaluated. Clearly, there is a large amount of information to be acquired and displayed in the operating room and, again, the success or failure of the system will depend on its perceived utility, i.e., does the information provided by the system offset the cost of entering the data? Through a tight collaboration between the engineering and the medical teams, the system went through several iterations. The intra-operative module has been used regularly since Jan-2009. It was used for 100% of the cases performed by one surgeon at our institution and about 40% of the cases performed by the other. We have observed that data entry during the surgery, even if eased by the graphical interfaces we have developed, remains taxing. Alternatives to the current GUIs will likely need to be developed. Another potential use of the intra-operative module is estimation of brain shift. By comparing predicted and measured information (e.g., the location of side effects predicted by our maps and the position at which these side effects are observed) algorithms may be developed to estimate the direction and magnitude of brain shift and suggest target adjustment. The recent work of Luis Luján et al. (2009) suggests that it is possible. In this work, performed retrospectively, the authors propose a method for optimally fitting a 3-dimensional anatomical brain atlas to intra-operative structure labels derived from MERs.

Although the post-operative module is operational and we have anecdotal evidence of its value for the neurologists, it is not yet integrated into the clinical flow. Post-operative packs are being generated on-demand but not systematically. We have generated around 35 postoperative assistance packs over the last 2 years for patients for which programming was difficult. Generating these packs for every patient at Vanderbilt, working with the neurologists to make these available at the time of programming, and evaluating the usefulness of the information provided by the system to neurologists is the next important phase in our project.

The processing pipeline, which permits the creation of the plans is stable but still requires the intervention of the engineering team to move the data from scanners to our repository and also to verify that results are reasonable. Verifying the results consists in loading the case on our server, verify the automatic prediction of the AC and the PC, and verify the segmentations which can easily be done visually. Verifying the targets is a more difficult than verifying the AC-PC or the segmentations as it requires expert knowledge. However, the engineering team can check if the predictions of the targets are in a range of possible values for the chosen target. Our goal is to reach a point at which the engineering team does not need to be involved in every case. To reach this objective, we are working on developing error-detection methods that would alert the engineering team only when attention is required. When this is achieved, we will move from a model in which data are centrally processed to a model in which data are processed locally, i.e., at every site. Currently, the sites with which we collaborate send us their images, we generate the plans, and they retrieve the plans from the database. While possible for a limited number of sites, this will be difficult to maintain for many sites and image transfer will become a bottleneck. Our goal is to have an instance of the system at remote sites, which will be synchronized with the central database. Routine processing will be done locally and transfer of data between the local and central data base will be done episodically.

Finally, we are currently working on expanding the functionality of our planning system to make it useable with other stereotactic frames such as the Leksell G-frame or the CRW frame. Because all the cases performed at Vanderbilt are done with the StarFix platform, it was logical for us to develop the planning module based on this platform. While nothing prevents the use of our system to predict the targets, the AC-PC, or to segment structures when a case is done with these other frames, our planner does not yet permit to transform image coordinates into frame coordinates. When this functionality will have been added, we will initiate collaborations with institutions, which use these frames, to evaluate the value of our system at these sites.

Clearly, developing and fielding a system as the one described in this article requires a very tight collaboration between engineers, computer scientists, and clinicians. In our opinion, co-location is critical and it is a long term effort that can only succeed if teams remain stable. The core team (PFD, BMD, PEK, RL) has remained fully engaged with the project since 2003 when the main clinical collaborator (PEK) became interested in the potential usefulness of computer assistance following the study in which it was shown that automatically selected targets were at least as good as manually selected targets (D'Haese 2005). A substantial development effort was then initiated to expand this work and predict targets routinely. When the project started, the surgical team was using another proprietary system to generate the stereotactic platforms. Because automatically produced points could not be easily imported into this proprietary product, it was decided to re-develop a complete planning software. For a period of time, plans were generated both with the clinical proprietary product and with our own research planning module. This rapidly became impractical because of the extra load required from the surgical team. Contacts were established with the frame manufacturer (FHC, Inc.), who validated the planning software for clinical use. FHC also licensed the planning module and is now distributing it under the name Way Point planner. This planning module has been used at more than 14 sites for more than 400 cases. Having full access to the planner accelerated progress because any new information provided by the system could be immediately provided to the users. Transitioning a system from the laboratory to the clinic also requires a system that is operational 24/7. In our case, this was made possible by a large development effort centered on the database and processing algorithms operating on the data stored in this database. Several years of development and testing were required to reach a point at which the system could produce the information reliably in a timely manner. A substantial amount of work remains to be done but the infrastructure we have put in place should allow us to build on what is already in place and incrementally add new features. For instance, we are now integrating new algorithms to segment additional structures (vasculature, optic tracts, and cortical surfaces). We are also expanding imaging modalities to Diffusion Tensor Images (DTI). Our plan is to have, in the next two years, a system that will be completely integrated in the clinical flow, from planning to programming. Although the scientific interest related to a central repository for DBS procedures is clear, the long term financial sustainability of the project has not been assessed. So far, the work has been made possible through research grants. When and if clinical usefulness of an integrated approach as described in this article will be demonstrated, ways to pay both for the system and for the services the system will provide will need to be determined.

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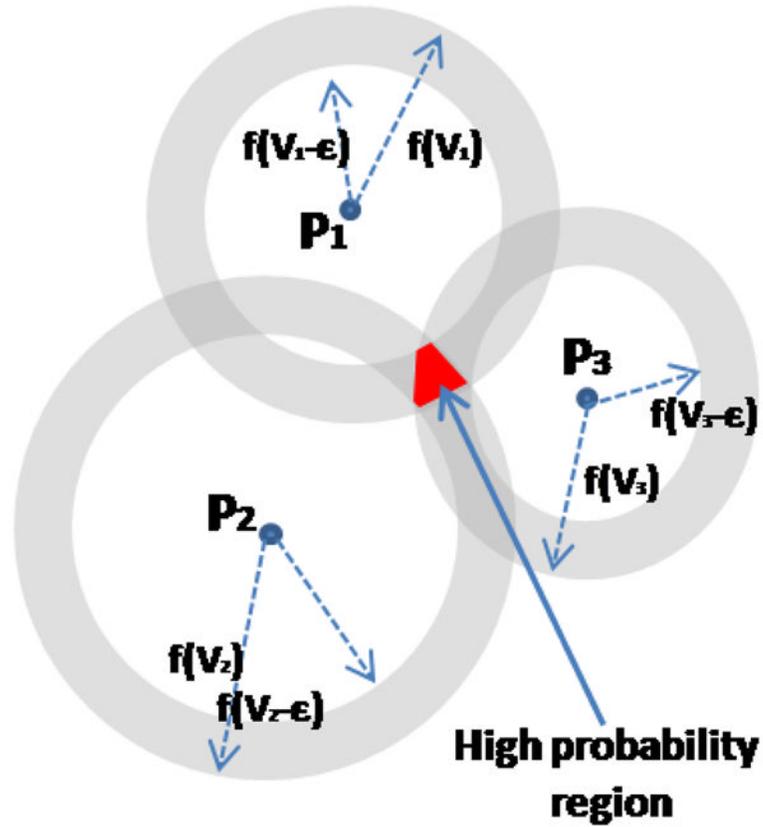


Figure 1.

Demonstration of how maps can be built in 2D using the annulus kernel. P_1 , P_2 and P_3 are three stimulation points producing responses at V_1 , V_2 and V_3 volts respectively. The region of maximum overlap between the kernels is shown in red as the high probability region. $f()$ is a function that relates voltage to radius of the kernel and ϵ is a positive real number.

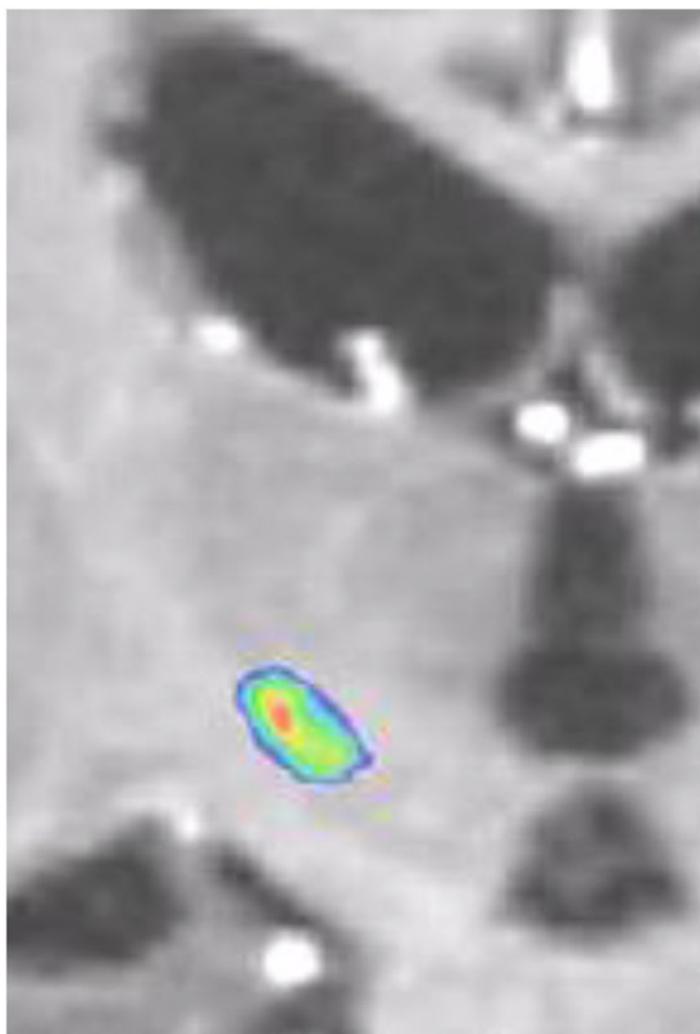


Figure 2.
Probabilistic STN efficacy map superimposed on an MRI atlas.

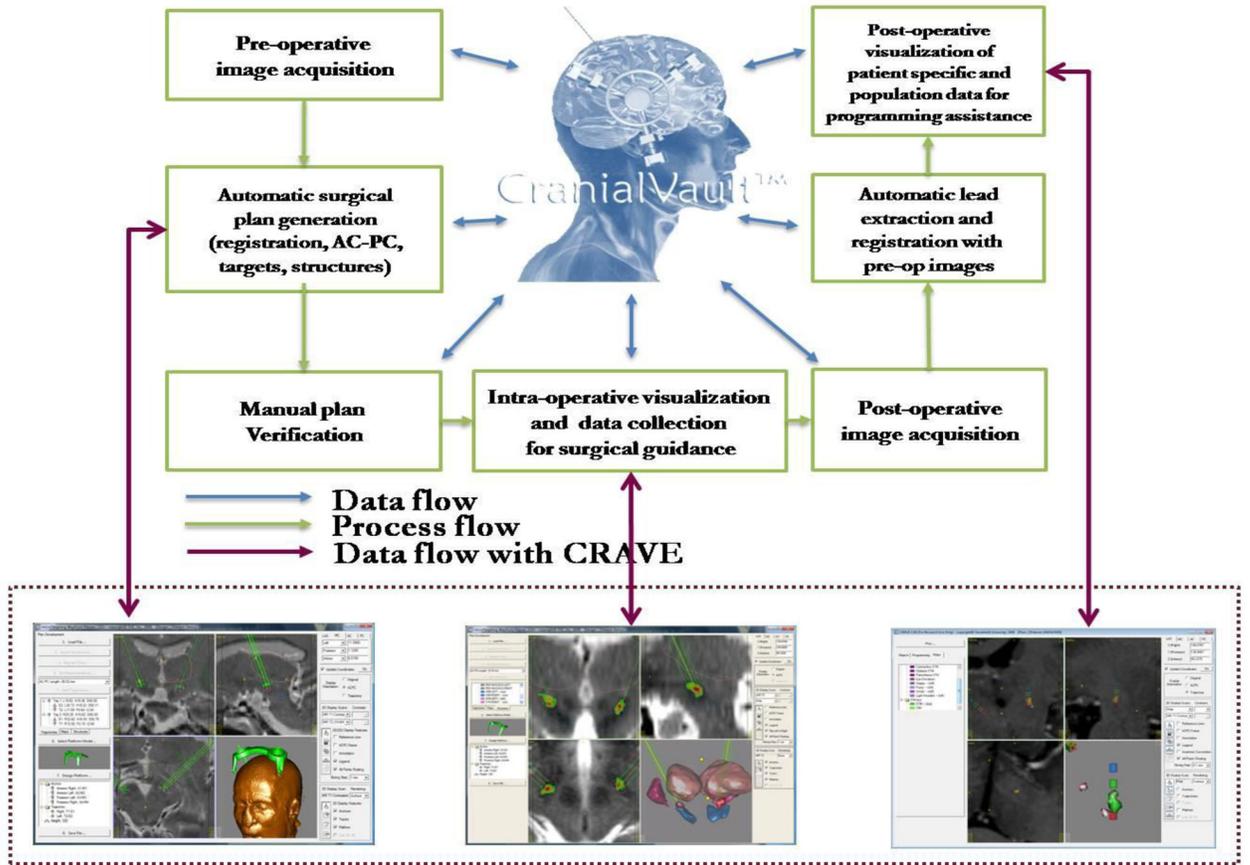


Figure 3.
Data and process flow for DBS therapy at Vanderbilt using CranialVault and CRAVE.

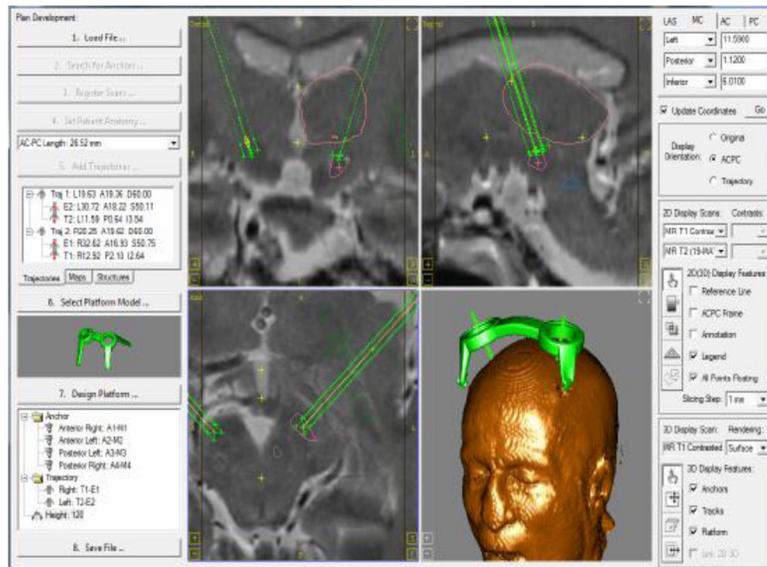


Figure 4. Planning module. Segmented structures as well as automatic trajectory predictions and statistical maps generated by our system are shown. The final design of the STARFix platform is also shown in the 3D view.

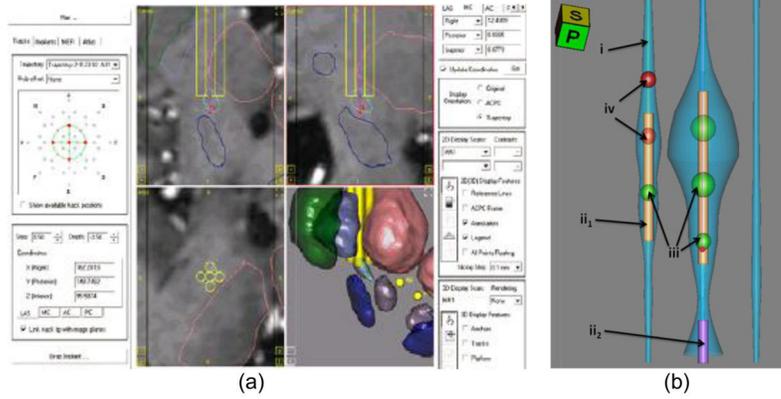


Figure 5. Intra-operative module showing (a) the planned trajectories, guide tubes for MER and stimulation as well as segmented structures generated by our system, (b) intra-operative neuronal firing frequency 3D histograms on medial, center and lateral tracks (i), labeled STN (i_1) and SNr (i_2) and stimulation response observations (good (iii) and bad (iv) responses).

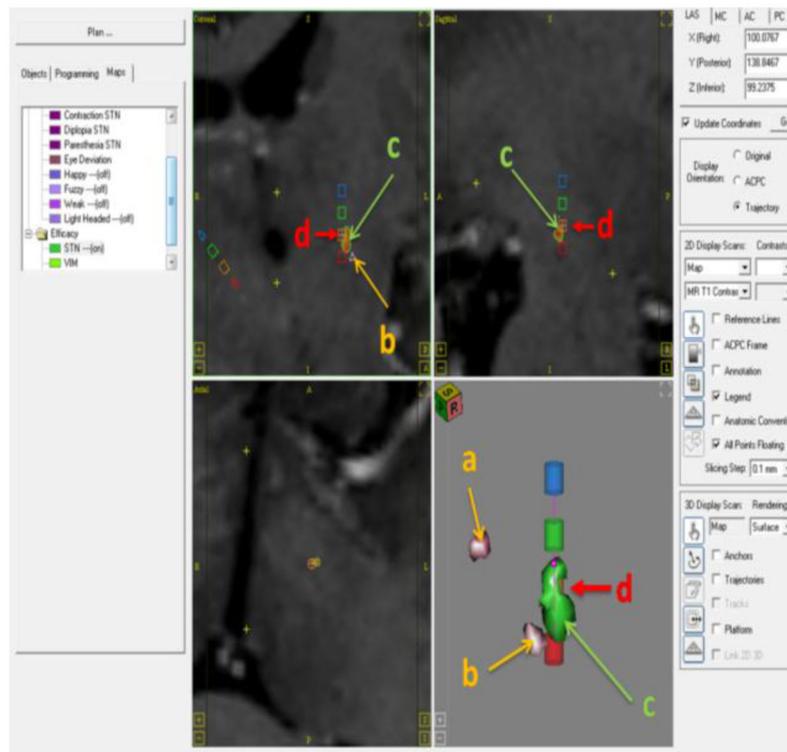


Figure 6.

Post-operative module showing the implant extracted from the post-operative stable CT and overlaid on the pre-operative MRI of an STN patient. Patient-customized statistical maps are used to assist the surgeon in finding the optimal programming parameters. For instance, maps in this figure show the 85% probability zone for the patient of getting paresthesia (a), diplopia (b) and efficacy (c). Based on this information, contact 1 (d) would be chosen by the neurologist to maximize efficacy while avoiding side effects.

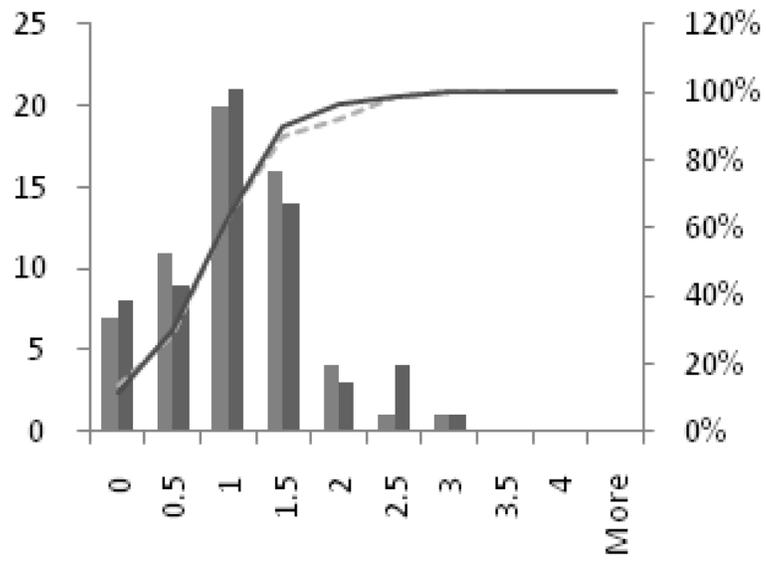


Figure 7. Frequency and the cumulative frequency of the adjustment of the computer assisted selections of the AC (light gray/line) and the PC and PC (dark gray/dotted line).

Table 1

Average difference between translations (Tx, Ty, Tz in mm) and rotations (Rx, Ry, Rz in degrees) components of computer assisted registrations modified registrations by the surgeons.

	Tx	Ty	Tz	Rx	Ry	Rz
T1->CT Avg	0.03	0.13	0.36	0.24	0.06	0.02
T1->CT Stdev	0.39	0.26	1.19	0.76	0.67	0.43
T2->CT Avg	0.05	0.01	0.47	0.18	0.04	0.17
T2->CT Stdev	0.03	0.24	0.69	0.69	0.22	0.23

Table 2

Median impacts of the mis-registration on the AC, PC, left and right targets (in mm).

	ACe	PCe	LTe	RTe
T1->CT	1.02	0.61	0.30	0.77
T2->CT	0.77	0.52	4.51	4.38

Table 3

Modifications made to the pre-selected stereotactic and targets points (in mm).

	Stereotactic points			Targets		
	AC	PC	ALL	STN	GPI	VIM
Avg.	0.83	0.83	1.94	1.04	2.56	3.47
StdDev.	0.57	0.60	1.79	0.96	1.07	2.38