Application of a Population Based Electrophysiological Database to the Planning and Guidance of Deep Brain Stereotactic Neurosurgery

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Abstract. Stereotactic neurosurgery for movement disorders involves the accurate localization of functionally distinct nuclei deep within the brain. These surgical targets exist within anatomy appearing homogeneous on pre-operative magnetic resonance images (MRIs) making direct radiographic localization impossible. We have developed a visualization-oriented searchable and expandable database of functional organization representing bilaterally the sensorimotor thalamus, pallidum, internal capsule, and subthalamic nucleus. Data were obtained through microelectrode recording and stimulation mapping routinely performed during 145 functional stereotactic procedures. Electrophysiologic data were standardized using a multi-parameter coding system and annotated to their respective MRIs at the appropriate position in patient stereotactic space. We have developed an intensity-based nonlinear registration algorithm to accommodate for normal anatomical variability that rapidly warps a patient's volumetric MRI to an MRI average brain considered representative of the patient population. The annotated functional data are subsequently transformed into the average brain coordinate system using the displacement grids generated by the algorithm. When the database is searched, clustering of like inter-patient physiologic responses within target anatomy and adjacent structures is revealed. These data may in turn be registered to a preoperative MRI using a desktop computer enabling prior to surgery interactive delineation of surgical targets.

1 Introduction

1.1 Image-Guided Stereotaxy

Surgical guidance software used during image-guided neurosurgery provides surgeons with image-based information for precise targeting of specific regions or pathologies of the brain. Such precision is only possible when the target can be seen on the patient's preoperative magnetic resonance image (MRI) or computed tomographic (CT) image. When desired targets are functionally but not anatomically distinct, as in stereotactic functional procedures for movement disorders or chronic pain, the gross target structures may often be visualized (the thalamus, subthalamic nucleus, and the globus pallidus internus) but the important functional subdivisions

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they contain can not. In these cases, the exact location of the surgical target must be approximated and subsequently refined intra-operatively.

To facilitate the approximation of indiscernible targets, printed or digitized versions of atlases containing photographs of human post-mortem brain slices [1,2] may be scaled to align with visible anatomical landmarks in the preoperative image and displayed as an overlay. Integrating digitized atlases of anatomy into computer guidance for functional neurosurgery has proven to be useful in the operating room and encouraged the development of several independent and commercially available atlas-based stereotactic planning systems. The atlas-to-patient image registration is achieved using linear scaling techniques based upon the length of an imaginary line joining the anterior and posterior commissures (AC-PC line).

1.2 Drawbacks of Anatomical Atlases

Anatomical atlases are used extensively for stereotactic surgical guidance. Despite their clinical acceptance, atlases of brain anatomy are not ideal predictors of surgical targets that are identified primarily by their function rather than their morphology. For example, the Schaltenbrand Wahren [1] anatomical atlas has poor volume sampling and uneven interslice distances (1-4 mm). As a result, the surgeon must frequently select the atlas plate that most closely approximates the region of patient brain being explored because no atlas plate corresponding to this region exists. A problem inherent to any atlas of anatomy is that it contains no information about normal anatomical variability.

The inaccuracy of the target localization step can be largely attributed to normal anatomical variability in the relationships of the target nuclei with the structures used to indirectly approximate their locations [3]. These effects are made apparent by the considerable mismatch that frequently exists once an anatomical atlas has been registered to a patient image with standard anterior commissure-posterior commissure (AC-PC) linear fitting techniques.

1.3 Electrophysiologic Exploration

The electrophysiologic environment of the target structure is interrogated through the use of electrodes introduced under stereotactic conditions into the deep brain region identified by the atlas. The atlas-approximated target is refined using a surgical electrode capable of electrical stimulation or recording of neuronal action potentials through repeated insertion into the predicted target region. The patient is awake throughout this procedure. The functional organization within and adjacent to the suspected target can be mapped based on the stereotypical responses elicited by stimulation of functionally different anatomy or through noting the changes in neuronal firing patterns correlated with physical stimuli or movement of the patient's body during microelectrode recording. These electrophysiological data provide the surgeon with the necessary information to mentally construct an evolving map of function specific to that patient's brain. Comparison of these data with that provided in the literature allows the surgeon to estimate the electrode tip position relative to surrounding landmarks. However, clinical studies demonstrate that the position of the final electrophysiologically refined target can vary dramatically from its predicted location [4]. Since multiple trajectories increase the risk of inducing patient trauma, it is highly desirable to reduce the number of electrode tracks required.

1.4 Nonlinear Registration

While functional stereotactic procedures generate enormous volumes of intra-operative data that are specific to one individual's brain, it has become common practice to map these responses to a standard coordinate space using a piecewise-linear image registration approach [2]. However, registering inter-subject data to a single coordinate system using a standard 9 degree-of-freedom (translation, rotation, scale) linear technique will not compensate for normal anatomical variability and generates poor clustering of like functional data [5]. It is the goal of our research to overcome the limitations of this piecewise-linear approach. To address the normal anatomical variability found among patients, we have developed a nonlinear registration algorithm that successfully registers, or 'warps', a patient's volumetric MRI to match a standardized brain MRI while providing a quantitative measure of warp accuracy for the user [6]. The algorithm incorporates an intensity-driven, multi-resolution strategy that attempts to maximize the normalized cross-correlation of gradient magnitudes in successively less blurred images until an acceptable registration is obtained. It is unsupervised, platform independent, and multi-threaded to take advantage of multi-processor computers and cluster computing environments. This algorithm was implemented using a series of multi-threaded hierarchical transformation classes that we have contributed to the vtk code repository [7,8].

1.5 Electrophysiology Database

We present here a collection of intra-operatively recorded electroanatomic observations collected during 163 functional stereotactic procedures performed on 145 patients at two institutions. The ultimate goal of the electrophysiologic database is to provide surgical guidance using the pooled functional information collected from a human population rather than, or in tandem with, an anatomical atlas. Each patient in the database typically results in between 50 and 200 individually coded responses being entered into the database. Our nonlinear registration algorithm accommodates for normal anatomical variability by determining the best intensity-based correlation of subcortical anatomy observed between the patient images and a standardized brain MRI. We have integrated the functional atlas into ASP, the image-guidance software package developed in our lab [8], and linked it to an interactive graphical user interface (GUI) to simplify data entry and retrieval.

2 Method

2.1 Patients and Imaging

To date there are over 145 patients included in the database, representing varying degrees of parkinsonism, essential tremor, localized tremor, and chronic pain from institutions in Montreal, Quebec and London, Ontario. Excluded from the study were patients who exhibited space-occupying lesions or other pathology that could distort the functional organization of the brain or compromise the quality of the nonlinear registration. Patients with congenital anomalies or amputations were included for later analysis but not inserted into the primary database.

2.2 Functional Data Entry

2.2.1 Visualization System

For our purposes, we have extended the ASP platform to encode, store, and display electrophysiologic data as individual three-dimensional polygon-based objects. Virtual probes custom designed to match the specifications and characteristics of those used in the operating room have been integrated.

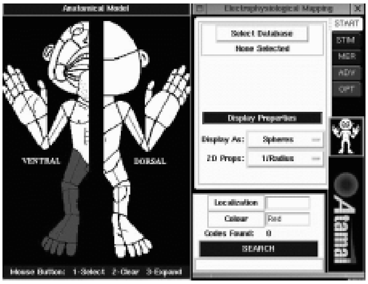

Fig. 1. Database GUI

2.2.2 Standardization of Functional Data

As outlined previously [9], we assign a six-parameter code to each data point entered using the ASP system. To facilitate this process, we designed a GUI that rapidly guides the user through code creation and prompts for information necessary to satisfy all parameters. Integrated into this interface is a subdivided clickable model of the human body. Each anatomical subdivision and groups of subdivisions contained in the model were assigned a unique identification number so that once clicked with the mouse, the number for the selected body part appears in the appropriate entry field in the GUI (figure 1).

2.2.3 Annotation in Native MRI-Space

Within the ASP system, coded functional data are plotted directly onto the patient's preoperative image along a virtual trajectory that corresponds to the position, declination, and azimuth of the operative trajectory (figure 2). A virtual electrode matching the dimensions of the physical tool determines the placement of the data point along the trajectory in millimeters from target. Each functional data-point is displayed as an individual sphere colour-coded to reflect the response type and diameter indicating the amount of current (μA) or voltage used to evoke the response. Images are automatically registered to the coordinate system defined by the stereotactic head frame using a "Frame Finder" software algorithm incorporated into the visualization platform [10].

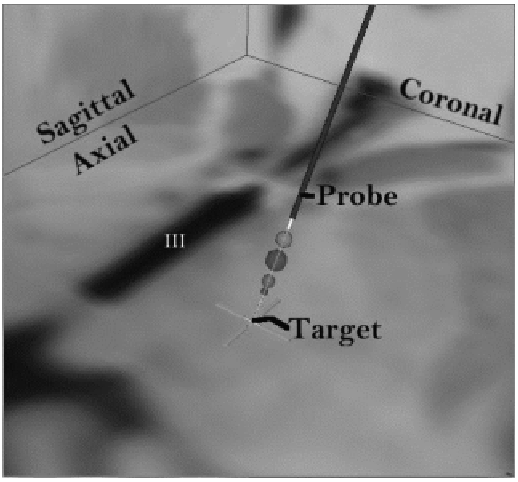

Fig. 2. Probe (purple) registered to patient MRI with crosshairs (yellow) placed at target. Spheres indicate responses obtained with stimulation. Slice plane orientations indicated. *III: 3rd ventricle*

Once tagged to their respective imaging volumes, the x, y, and z Cartesian coordinates of these data in patient image-space along with the corresponding ASP-generated codes are saved in a text file for addition to the central database. A secondary code that describes the sex, age, pathological condition, and handedness of the patient, surgical procedure and specifications of the probes used during the procedure is assigned to the header of each data file. These data need only be entered once per procedure.

2.3 Pooling Population Data

2.3.1 Nonlinear Registration Algorithm

Nonlinear registration of one image volume to another using our algorithm involves two separate steps. The first generates a global affine transformation that maximizes the normalized cross-correlation between the two volumes. The second computes a deformation grid, using the affine transformation as a starting point, to maximize the same similarity metric on successively smaller sub-volumes of the images. The output of the algorithm is a MRI-specific deformation grid that describes the transformation for every voxel in native patient MRI-space to the coordinate system of the target volume. Since we are only interested in registering the deep anatomical structures of the brain, we limit the registration to only those voxels residing within the volume of a user-specified closed polygonal surface. With the use of such a mask, we can compute a deformation grid describing the best nonlinear fit of the patient deep brain anatomy to that of the standardized brain in less than five minutes (dual 933MHz PIII, Linux).

2.3.2 Standardized Brain Volume

We use the standard brain template CJH27 [11] as the repository for the database information. Once a patient image was warped to this high-resolution volume, the functional data annotated to the source image could subsequently be re-mapped into standard brain image space. The standard image thus acts as the common coordinate system for collecting and analyzing all population electrophysiologic data. To view the population database registered to a patient's MRI image, the inverse of the MRI-specific deformation grid generated as part of this procedure is used to re-map the pooled data into patient image-space.

2.3.3 Quantifying Registration Accuracy

While visual inspection provides an assessment of registration quality, we also need to assess it qualitatively. Our nonlinear warping algorithm maximizes the normalized cross-correlation of two images by modifying a field of deformation vectors until the highest correlation value is achieved. This alignment metric is calculated in four separate domains or blurring levels (12, 8, 4, and 2mm FWHM Gaussian blurs). Computing and averaging the correlations for each domain across the entire image volume creates a three-dimensional map of cross-correlation values. When this map is simultaneously displayed with the warped target image in ASP, a visual check will rapidly pinpoint any region of poor registration.

2.4 Searching the Database

The database may be selectively searched with the same GUI used to enter the functional data. Database codes relating to a specific response and selected anatomical regions can be retrieved and displayed as clusters of spheres in 3D space or density maps on the slice-plane images (figure 3). Our software permits interactive adjustment of the properties of selected spheres, such as opacity, colour, and shading, or toggling of their presence in the virtual scene to facilitate interpretation of the search results.

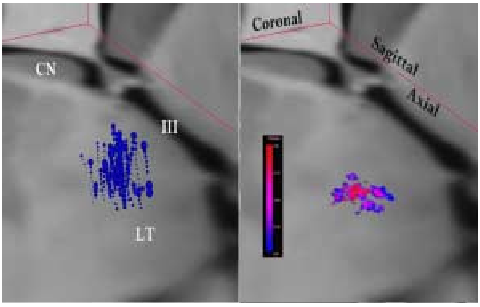

Fig. 3. Results of database search for codes indicating stimulation induced tingling sensations. Response is indicative of stimulation of ventrocaudal sensory thalamic nucleus. *Left:* Each sphere indicates a distinct response. *Right:* Density map for the same data cluster shown in left image (density colour scale also shown). *CN: caudate nucleus, III: third ventricle, LT: left thalamus.*

3 Results

3.1 Clustering of Population Data

Following nonlinear registration of patient electrophysiologic data to the database mapped to the standard brain MRI, we can demonstrate meaningful clustering of like physiologic responses within surgical targets.

3.1.1 Thalamus

In thalamotomy for tremor-dominant movement disorders, the placement of the therapeutic lesion is determined by the location of neurons that fire in synchrony with physical tremor, or tremor cells, located within the Ventralis intermedius (Vim) nucleus. We show in figure 4 the bilateral clustering of 350 tremor cell codes found within the left and right thalami as detected by microelectrode recording during 39 thalamotomies. These data provide a probabilistic localization of the Vim nuclei and the regions of highest probability for locating tremor synchronous neurons. The greater number of tremor cells in the left thalamus (n=224) verses the right (n=126) is representative of the greater number of left-sided procedures currently in the database.

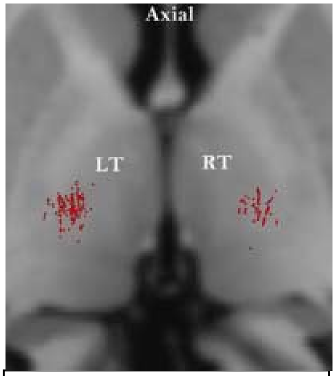

Fig. 4. Bilateral clustering of tremor cells. *LT/RT:* Left and right thalamus.

3.1.2 Globus Pallidus

We have gathered electrophysiological data bilaterally for the internal globus pallidus (GPi). During pallidotomy, surgeons locate the optic tract positioned just inferior to the apex of the anatomy by evoking visual phenomena with electrical stimulation. The optic tract acts not only as an anatomical landmark for probe placement but also signifies a region of brain that must be avoided while lesioning the GPi or implanting a chronic stimulator within it. Figure 5 (left) demonstrates a clustering of 115 stimulation spheres around and within a segmentation of the left optic tract where 29 patients reported seeing flashing lights correlated with stimulation. Sphere size indicates relative stimulation intensity and as one would expect, the further from the optic tract the responses were evoked the larger the diameter of the spheres.

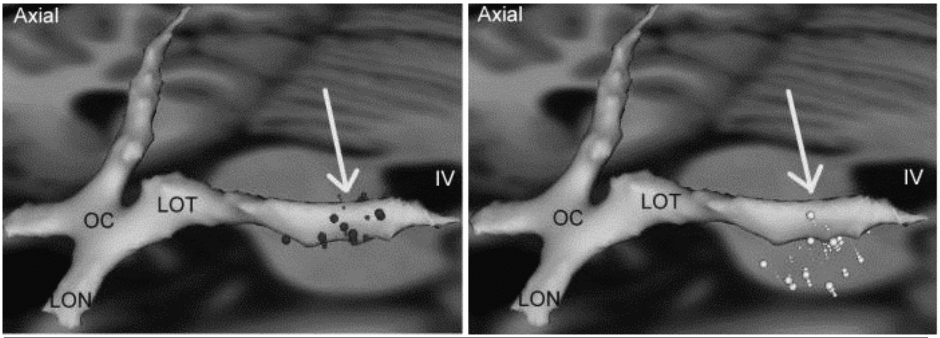

Fig. 5. Left: Nonlinearly registered spheres (red) representing visual phenomena evoked through stimulation of optic tract. Right: Same data as left registered using a 9DOF linear fit. Note poor clustering around surface rendered optic tract (yellow). *LON: Left optic nerve, OC: Optic chiasm, LOT: Left optic tract, IV: Fourth ventricle.*

3.2 Nonlinear Versus Linear Registration

In figure 5 (right) we demonstrate the efficacy of our nonlinear approach by registering the same optic tract related data described in 3.1.2 to the standardized brain using linear registration. The linear procedure is a 9 DOF registration technique, similar to that commonly used to register anatomical atlases to the anatomy of patient MRIs. Responses of the type presented here can only be evoked by stimulation when the probe tip is within the optic tract or in very close proximity (<1mm) to its surface. Not only are the clustering of population data visibly tighter with nonlinear registration, 82% of the spheres are contained within the limits described above compared with only 22% achieved with linear registration.

4 Discussion

4.1 Technological Advances

We have described a method and presented encouraging results for the first truly three-dimensional collection of subcortical electrophysiology capable of nonlinearly registering to an MRI volume. Nonlinear registration was used in all cases to accommodate for nonlinear anatomical variability. Incorporating nonlinear registration into the pooling and analyses of population electrophysiology produces tighter clustering than standard linear registration techniques. Our rapid algorithm allows nonlinear registration to be achieved in a clinically acceptable timeframe (3-12 minutes depending on hardware configuration and number of processors) for a typical 3D MRI volume.

When database contents are selectively displayed in our visualization program, delineation of functional borders within homogeneous appearing anatomy is possible and high probability tremor areas can be identified. A digital probabilistic atlas of this nature that utilizes population data will improve in accuracy over time and achieve better statistics with the addition of more data.

Our interactive GUI makes generic or detailed searches possible. Using the interface, the surgeon can extract and display only those data most closely approximating a patient's age, sex, handedness, and diagnosis, or conversely choose to view only data representative of a larger cross section of the database population. The interactive GUI facilitates rapid, detailed coding of patient data that, in our experience, does not impede the normal flow of the surgical procedure when used intra-operatively.

Acknowledgements

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