Toward the Creation of an Electrophysiological Atlas for the Pre-operative Planning and Intra-operative Guidance of Deep Brain Stimulators (DBS) Implantation

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Abstract. In current practice, optimal placement of deep brain stimulators (DBSs) is an iterative procedure. A target is chosen pre-operatively based on anatomical landmarks identified on MR images. This point is used as an initial position that is refined intra-operatively using both micro-electrode recordings and macro-stimulation. We hypothesize that boundaries of nuclei and sub-nuclei not visible in the anatomic images can be resolved in atlases that include electrophysiological information, thus improving both pre- and intra-operative guidance. In this work we report on our current progress toward creating such an atlas. We also present results we have obtained in creating an atlas of optimal target points that can be used for automatic pre-operative selection of the targets. We demonstrate that initial points selected with this atlas are closer to the final points than the initial points chosen manually.

1 Introduction

Since its first FDA approval in 1998 deep-brain stimulation (DBS) has gained significant popularity in the treatment of movement disorders [1,2]. The therapy has significant applications in the treatment of tremor, rigidity, and drug induced side effects in patients with Parkinson's disease and essential tremor. This procedure, which necessitates placing electrodes within targets ranging from 4-12 mm in diameter, requires stereotactic neurosurgical methodology. Typically, the process of implantation of a DBS electrode follows a step-wise progression of a) initial estimation of target localization based on imaged anatomical landmarks, b) intraoperative microanatomical mapping of key features associated with the intended target of interest, c) adjustment of the final target of implantation by appropriate shifts in three dimensional space, and d) implantation of a quadripolar electrode with contacts located surrounding the final desired target. These steps are required because the surgical targets of interest involve deep brain

C. Barillot, D.R. Haynor, and P. Hellier (Eds.): MICCAI 2004, LNCS 3216, pp. 729–736, 2004.

nuclei or subregions within the subthalamus or globus pallidus internus. These structures are not visible in any imaging modalities, such as magnetic resonance imaging (MRI), X-ray computed tomography (CT), or Positron Emission Tomography (PET). Pre-operatively, the location of these targets can thus only be inferred approximately from the position of adjacent structures that are visible in the images. Intra-operative adjustment of the target point is based on the surgical team's (at our institution, this team involves a neurosurgeon, a neurophysiologist, and a neurologist) interpretation of electrophysiological recordings and responses to stimulations. Anecdotal evidence based on conversations with the surgical team and observations of the procedure suggests that intra-operative electrode adjustment involves (1) matching a set of input data (e.g., loss of rigidity, firing rate, severity of side effects, stimulation voltage, etc.) with electrophysiological landmarks that can be related to the target of interest and (2) planning and execution of a displacement from the current position to the desired one. For instance, as a result of test stimulations applied through a trajectory, the clinical team may observe that unacceptable double vision occurs along with mild symptomatic relief of rigidity. The interpretation of this information would be that the trajectory is too medial. The difficult anatomical question at this point is: *in this particular patient* how far lateral does the trajectory need to be moved, e.g., 1, 2, or 3mm. Because of anatomical differences between patients, this question is difficult to answer. It could, however, be more easily answered if the current position could be mapped onto an atlas, the displacement determined in the atlas, and this displacement mapped back onto the patient. Doing so requires several key ingredients: (1) accurate algorithms to register patients and atlases, (2) populating the atlases with information that permits the labeling of structures and substructures based on their electrophysiological signatures, and (3) mapping electrophysiological signals to landmarks in the atlas. Others have proposed the creation of electrophysiological atlases [3] but these were populated with labels derived from intra-operative observations such as the type of side effect or its location. To the best of our knowledge we are the first to create an electrophysiological atlas directly from from the raw digitized signals. In the rest of the paper, we first present an extension of preliminary work presented earlier [4] that demonstrates the feasibility of using automatic nonrigid registration algorithms to create these atlases and to use them for preoperative planning. Then, we discuss the techniques we have developed for the creation of electrophysiological atlases. Finally, we present results we have obtained with recordings acquired on 8 patients.

2 Methods

2.1 Patients and Pre-operative Target Selection

All patients undergoing consideration for DBS implantation of the STN are first evaluated by a movement disorders neurologist and optimized on medications. If patients reach advanced parkinsonian symptoms (rigidity, bradykinesia, tremor, dyskinesias) despite optimal medical therapy, they are considered for surgical therapy by a multi-disciplinary group involving neurology, neurosurgery, neurophysiology, neuropsychiatry specialists. Target selection is decided upon by the team if no contraindications exist. A majority of patients with the above symptoms are recommended for STN (Sub Thalamic Nucleus) targeting of DBS therapy. Pre-operative target identification is performed by the functional neurosurgeon (P.E.K.) and is based on an identification of the AC-PC (anterior and posterior commissure) location and arriving at 4mm posterior, 12mm lateral, and 4mm inferior to the mid-commissural point for STN. Small adjustments to the target points can be made based on the width of the third ventricle and other anatomical asymmetries noted on the MRI scan, but these usually only consist of less than 1mm deviations from the initial intended target location.

2.2 Intraoperative Placement and Guidance System

Traditional methodology for carrying out the stepwise target localization procedure followed for DBS implantation requires an external, rigid fixture, called a “stereotactic frame” that encompasses the patient’s head and upon which micromanipulating equipment can be mounted and maneuvered with sub-millimetric precision. Recently, a market-cleared and CE-compliant miniature stereotactic positioner called a *microTargeting Platform* became clinically available (*microTargeting Drive System for Stereotactic Positioning, incorporating STarFix guidance*, FHC Inc., Bowdoinham, ME). This device, which is used at our institution presents several advantages: 1) Separation of the phase of the procedure that includes image acquisition and target planning from the actual day of the surgery. This allows for CT and MR images to be acquired under anesthesia and thereby reduce motion artifacts on the resultant images. 2) Patients are not tethered to the bed since the platform is small enough not to require stabilization thus reducing patient discomfort during the procedure. 3) The platform permits simultaneous bilateral implantation, which is not possible with traditional frames. Accuracy studies performed on this platform have also shown a placement accuracy at least good as the accuracy achievable with larger frames [5].

2.3 Data

A set of CT and MRI volumes are acquired pre-operatively for each patient. These are acquired with the patient anesthetized and head taped to the table to minimize motion. CT images are acquired at kvp = 120V, exposure = 350ms, 512x512 voxels ranging in size from 0.49 to 0.62 mm, slice thickness = 2 mm for one patient, 1.3 mm for 2 patients, 1mm for all others; MR images are 3D SPGR volumes, TR: 12.2, TE: 2.4, dimension 256x256x124 voxels, voxels dimensions 0.85X0.85X1.3mm3 except for subject 7 for which the voxels dimensions are 1X1X1.3mm3. Nineteen patients are included in the current study: 13 bilateral STN and 6 unilateral STN. For the 8 latest patients, micro-electrical signals have been recorded intra-operatively and saved using the dual channel LeadPoint system from Medtronic Neurological. These signals were recorded along the electrode path starting 10mm above the preoperative target point and ending 5mm below. Signals were recorded every .5mm for 10sec, and sampled at 22Khz. After the procedure, the digitized signals and the position at which these signals have been acquired are downloaded from the LeadPoint system and stored on file for further processing. At the time of writing, 850 signal epochs have been recorded.

2.4 Registration Algorithms

Two types of registrations algorithms are needed to process our data: rigid and non-rigid. The rigid registration algorithm is required to register MR and CT volumes of the same patient. This is necessary because the intra-operative positions of the recording and stimulating electrodes are given in CT coordinates. The algorithm we have used for this is an independent implementation of a standard MI-based algorithm [6]. Non-rigid registration is required to register patient data to an atlas and vice-versa. In this study, non-rigid registration is always performed on MR image volumes using an algorithm we have proposed recently [7]. Briefly, this algorithm computes a deformation field that is modeled as a linear combination of radial basis functions with finite support. The similarity measure we use is the Mutual Information between the images. We also compute two transformations (one from the atlas to the subject and the other from the subject to the atlas) that are inverse of each other.

3 Results

3.1 Registration Accuracy and Creation of an Atlas of Target Points

Validation of non-rigid registration algorithms is a notoriously difficult problem because of the lack of "gold standards". Fortunately, with a few assumptions, the nature of our problem allows us to assess in an indirect way the accuracy of our algorithms and their adequacy for our long term objectives. The STN is a very small structure (on the order of a few mm). Because of this and if one assumes that (1) the surgical team is able to place the electrode within the STN in each patient, (2) our intra-operative guidance system can provide us with the accurate position of the electrode in CT coordinates, and (3) our registration algorithms are accurate, then, mapping each and every target point selected intra-operatively onto the atlas should result in tight clusters of points in this atlas. In this work, we have chosen one of the subjects as the reference, which we call the atlas, and we have registered all the other volumes to it. We have then projected every final target point onto the atlas, thus creating two clouds of points (one for the left and the other for the right STNs). Figure 1 shows the results we have obtained and it demonstrates, at least qualitatively, our ability to cluster tightly the points selected intra-operatively onto the atlas. To quantify these results, we have computed the position of the centroid of each of these two clouds of points. We have then computed the distance between each point and its corresponding centroid, which we call Dc. Table 1 reports the results we have obtained.

Table 1. Position (mean and std) of the target points in the atlas and distance from centroids in mm

	Left				Right			
	X	Y	Z	Dc	X	Y	Z	Dc
Mean	121.6	106	50.2	2.8	97.5	106	49.2	2.8
Std	1.5	1.5	2.2	1.1	1.9	1.7	1.6	0.7

Table 2. Distances (in mm) between pre-operative target position and final intra-operative position.

Pre-operative placement error				
	Left		Right	
	Auto	Man	Auto	Man
Mean	2.49	2.70	2.78	3.88
Std	1.31	1.98	0.76	2.04

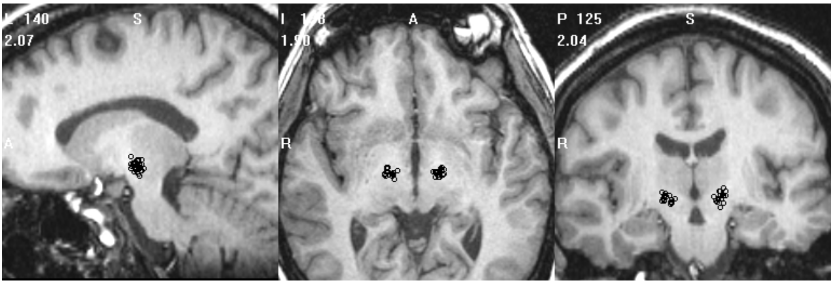

Fig. 1. DBS positions selected intra-operatively mapped onto the atlas.

3.2 Automatic Pre-operative Prediction of the Optimal Target Point

Rather than relying on a reference system based on the AC-PC line as it is done currently, the pre-operative target point could be predicted automatically by first selecting a standard target point in the atlas, registering the atlas to the patient image volume, and mapping the target point from the atlas to the patient volume. To evaluate this approach we have used the centroids introduced in the previous paragraph as our standard target points and we have mapped those onto the patient image volume to define the pre-operative position of the target point. To avoid both defining and evaluating the standard target point on the same data sets, we have used a leave-one-out strategy (i.e., the coordinates of the centroids have been computed using 17 volumes and projected on the 18th one; the process has been repeated 18 times). To compare the position of the pre-operative target point chosen manually using the current clinical procedure and the automatic technique we propose, we define the pre-operative placement error. This error is defined as the Euclidean distance between the final intra-operative position selected by the surgical team and the position chosen pre-operatively. It is thus the distance by which the surgical team adjusted the position of the electrode during the procedure. Table 2 reports both the manual and the automatic pre-operative placement errors. This table shows that the pre-operative target point selected automatically is closer to the final target point than the pre-operative target point chosen manually.

3.3 Electrophysiological Atlas Creation

An important component of our project is the development of a database that permits storage and access of all the pre-, intra-, and post-operative information pertaining to patients undergoing treatment at our institution. In this database, any spatially-dependent patient information can be related to a position in the atlas through registration. Albeit under construction, our current database already supports queries such as "return all the intra-operative recordings for patients with Parkinson we have in our database in a 5mm sphere centered at coordinates (x, y, z) in the atlas". This query returns a set of pointers to files that contain the digitized signals. These files can then be processed, features extracted, and these features associated with a point in the atlas. Intra-operative electrophysiological signals are often categorized in terms of firing rate (FR) that measures tonic activity and indices that measures phasic activity, including the burst index (BI), pause ratio (PR), pause index (PI), or interspike interval histogram (ISI) [8]. Figure 2 shows some of the results we have generated. From top to bottom the three signals are epochs that have been recorded along an electrode path. The first row corresponds to a position above the STN, the middle one is in the middle of the STN, and the bottom one below the STN. The left panels show the raw signal as well as the spikes we have extracted from these signals (black spike trains on the bottom of the left panel). The right panel show the interspike interval histogram (ISI) as well as the value for features commonly associated with these signals. Once features have been extracted, their values can be color-coded and displayed in the atlas. Figure 3 shows the mean value of the Burst Index in our current atlas. 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

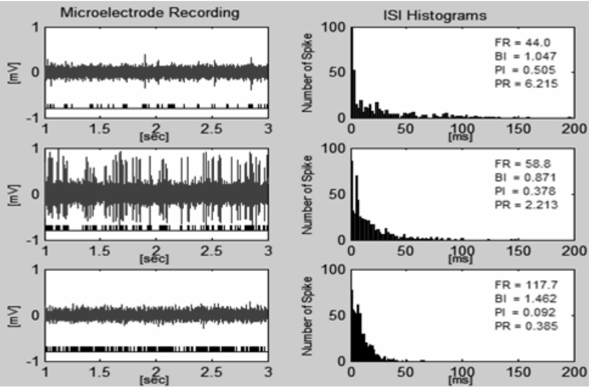

Fig. 2. Display of Electrophysiological signals and features extracted from these.

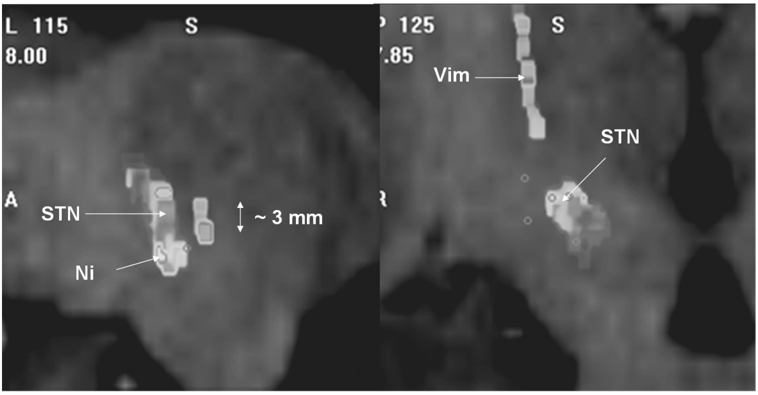

Fig. 3. Mean Burst Index in our electrophysiological atlas color-coded and superimposed on the MR images (Left, a sagital view; right a coronal view). Bright and dark pixels correspond to high and low values, respectively. Regions that correspond to various nuclei are shown with arrows.

values to structures such as the niagra and the ventralis intermedius (Vim) nucleus. Although the scarcity of data does not yet permit a precise localization of complete nuclei boundaries, the results we have obtained clearly show patterns in the data and clusters that correspond to known anatomical structures that are not visible in MR images.

4 Discussion and Conclusions

DBS placement requires selecting pre-operatively a candidate target point and adjusting this target point intra-operatively. In previously published work [4] we have demonstrated that automatic selection of the pre-operative target is not only feasible but better than the manual technique currently used. This conclusion was based on a limited data set (8 patients). Here we extend this study to 18 patients and we reach the same conclusion. With 18 patients, we have observed that the final target points, when mapped onto the atlas, form sub-clusters. This may be a discovery and an indication that the position of the optimal target point may be a function of parameters 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 than someone with arm rigidity whose ideal cluster may be more anterior and posterior. As the number of patients increases in our database, we will be able to confirm or disprove this finding. Results we have already obtained with the signals we have acquired indicate that features derived from these signals can be used to identify the STN and other nuclei, thus supporting the concept of an electrophysiological atlas that reveals the boundaries of structures and substructures not visible in current imaging modalities,which may be of value in target placement for other disorders, such as essential tremor [9]. Coupled with accurate registration algorithms, this atlas will not only permit the selection of preoperative target but also provide intra-operative guidance. This will be achieved by correlating intra-operative recordings with electrophysiological information contained in the atlas, which will permit the surgical team to identify the current location of the electrode, and plan and execute displacements from this position. The current difficulty with this concept 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. Thanks to a collaboration with FHC, Vanderbilt is the first site at which a device is used that permits recording along 5 parallel tracks on each side for a total of 10 simultaneous channels. At the time of writing one procedure has already been performed with this new device. This will allow us to rapidly expand our signal database which, in turn, will allow us to improve the localization of substructure boundaries based on electrophysiological signatures.

Acknowledgements. Pierre-François D'Haese is working towards a Ph.D. degree with awards from FRIA and FNRS (Belgian Science Foundation)(also supported by the Walloon Region by the MERCATOR grant). Supported in part by grant NIH/NCI 1R21 CA89657-01A2.

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