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## Fully automated targeting using non-rigid image registration matches accuracy and exceeds precision of best manual approaches to Subthalamic Deep Brain Stimulation targeting in Parkinson's disease

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### Abstract

**Background**—Finding the optimal location for the implantation of the electrode in Deep Brain Stimulation (DBS) surgery is crucial for maximizing therapeutic benefit to the patient. Such targeting is challenging for several reasons including anatomical variability between patients as well as lack of consensus about the location of the optimal target.

**Objective**—To compare the performance of popular manual targeting methods against a fully automatic non-rigid image registration based approach.

**Methods**—In 71 Parkinson's disease STN-DBS implantations, an experienced functional neurosurgeon selected the target manually using three different approaches; indirect targeting using standard stereotactic coordinates, direct targeting based on the patient MRI, and indirect targeting relative to the red nucleus. Targets were also automatically predicted using a leave-one-out approach to populate the CranialVault atlas using non-rigid image registration. The different targeting methods were compared against the location of the final active contact, determined through iterative clinical programming in each individual patient.

**Results**—Targeting using standard stereotactic coordinates corresponding to the center of the motor territory of the STN had the largest targeting error (3.69 mm), followed by direct targeting (3.44 mm), average stereotactic coordinates of active contacts from this study (3.02 mm), red nucleus based targeting (2.75 mm), and non-rigid image registration based automatic predictions using the CranialVault atlas (2.70 mm). The CranialVault atlas method had statistically smaller variance than all manual approaches.

**Conclusions**—Fully automatic targeting based on non-rigid image registration using the CranialVault atlas is as accurate and more precise than popular manual methods for STN-DBS.

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**Conflict of Interest:** P-F. D'Haese, P.E. Konrad, and B.M. Dawant are founding members and stock holders, and S. Pallavaram is a stockholder in Neurotargeting, LLC that licenses the software suite from Vanderbilt University that was used in this study for data collection. P.E. Konrad is also a Consultant for Medtronic Neuromodulation.

## Keywords

automatic targeting; deep brain stimulation; non-linear image registration; electrophysiological atlases; Parkinson's disease; subthalamic nucleus

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## Introduction

Deep brain stimulation (DBS) is a therapy used to alleviate symptoms related to movement disorders such as Parkinson's disease by stimulating deep brain nuclei. Because of the small size of the nuclei, and a relatively narrow therapeutic window of stimulation therapy, such functional neurosurgical procedures require precise targeting so that the final implant can be placed in an optimal location to achieve therapeutic benefit without causing side effects. Traditionally, this requires modification of an initial approximate target location (selected pre-operatively by a neurosurgeon) using exploratory electrodes to map the electrophysiology of the brain and stimulate the regions around the planned target. Although this process compensates for initial inaccuracies in pre-operative targeting and allows adjustment for the anatomical and physiological variability across patients, it is time consuming, invasive and may increase operative risk when multiple penetrations are required <sup>1, 2</sup>.

Given the importance of accurate localization of the optimal target <sup>3-8</sup> there has been much effort over the last few decades towards the use of different approaches including indirect targeting based on anatomical landmarks and direct targeting using various imaging modalities <sup>9, 1011-1819, 2021, 2214, 23-25</sup>. Pallavaram et al. showed that there is significant inter-surgeon variability in the selection of ACPC-based stereotactic reference system and that this has a substantial effect on the localization of targets <sup>26</sup>. Moreover, there has been a lack of consensus on the ideal anatomical location for maximum therapeutic relief in PD <sup>5, 21, 27-33</sup>. Therefore, several functional atlases have also been developed based on intra- and post-operatively acquired electrophysiological data mapped using non-linear image registration techniques <sup>34-41</sup>. Castro et al. compared the accuracy of ACPC-based targeting of the STN against several image registration techniques <sup>42, 43</sup>. They found non-linear image registration to produce the highest accuracy in predicting the anatomical target inside the STN. The ground truth used in their study was direct-targeting based on selection of STN by two experts on high resolution MRI T2 scans. Chakravarty et al. <sup>44, 45</sup> took a similar approach to validate their method for segmentation of basal ganglia structures and showed that non-linear techniques perform statistically better than linear and piece-wise linear techniques. Yelnik and Bardin et al. <sup>46, 47</sup> showed how a histological and deformable 3D atlas based on non-linear image registration could be used to accurately project segmentations of structures onto patients for anatomical targeting of the STN. The ground truth for validating STN segmentations using their methods were intra-operative electrophysiological recordings and post-operative therapeutic contacts. D'Haese et al. recently showed that maps produced using nonlinear techniques correlate with their expected anatomic positions <sup>48</sup>.

In this study, we compare a fully automatic method for predicting the optimal functional target for STN-DBS in Parkinson's disease patients using non-rigid image registration and three popular manual targeting methods: direct targeting of the center of the STN based on MRI images, indirect targeting with respect to the location of the red nucleus, and indirect targeting based on stereotactic coordinates, against the clinically active contacts as the ground truth.

## Data and Method

In this study we retrospectively examined 71 STN-DBS implantations in 37 PD patients. With IRB approval each patient had pre-operative MRI (T1 and T2) and CT acquisitions of the brain as well as a delayed post-operative CT acquired approximately one month after surgery. Typical CT images were acquired at kVp = 120 V, exposure 350 mAs and 512×512 pixels. In-plane resolution and slice thickness were approximately 0.5 mm and 0.75 mm, respectively. MRI T1 (TR 7.9 ms, TE 3.8 ms, 256 × 256 × 170 voxels, with typical voxel resolution of 1 × 1 × 1 mm<sup>3</sup>) were acquired using the SENSE parallel imaging technique (T1W/3D/TFE) from Philips on a 3T scanner. MRI T2 (TR 3000 ms, TE 80 ms, 512 × 512 × 45 voxels, with typical voxel resolution of 0.47 × 0.47 × 2 mm<sup>3</sup>) were acquired using the SENSE parallel imaging technique (T2W/TSE) from Philips on a 3T scanner.

Planning was subsequently performed using the FDA approved clinical version of the *CranialVault Explorer* software suite<sup>49</sup> called **WayPoint Navigator** (distributed by FHC, Inc. Bowdoin, ME, USA) shown in figure 1. This involved the importation of pre-operative MRI and CT, identification of anatomical landmarks (e.g. anterior commissure, posterior commissure, mid-plane, and red nucleus), surgeon selection of optimal target and entry points; and confirmation of design for a customized miniature stereotactic frame called the mT platform (FHC, Inc.; Bowdoin, ME) to be used in surgery. Details on the platform including a study of its accuracy demonstrating it to be at least as accurate as standard frames have been previously published<sup>50-52</sup>.

During surgery, targeting was modified through the use of micro-electrode recording and stimulation response observations recorded in 3-4 tracks parallel to the planned trajectory using a Ben gun approach. The optimal location for DBS lead implantation was determined by the multidisciplinary surgical team (neurosurgeon, neurologist and neurophysiologist) and defined as the location of the centerpoint of the 4-contact 3389 lead. Post-operatively the locations of the leads and the individual contacts were extracted from the delayed post-op CT. The individual contacts were projected onto the patient pre-op MRIs using rigid registration as shown in figure 2. These were then projected onto the CranialVault atlas using fully automatic non-rigid registration between the patient pre-op MRIs and the atlas MRI. Using a leave-one-out approach, the centroid of the atlas cluster was projected onto each patient's preop MRI using non-rigid registration and subsequently projected onto the delayed post-op CTs using rigid registration between the delayed post-op CT and the pre-op MRI of the patient. This point is referred to as the atlas-based target prediction and the process is illustrated in figure 3. Briefly, the non-rigid registration algorithm we use computes a deformation field that is modeled as a linear combination of radial basis functions with finite support. This results in a transformation with several thousands of degrees of freedom. Two

transformations (one from the atlas to the subject and the other from the subject to the atlas) that are constrained to be inverses of each other are computed simultaneously. Details on this procedure and the algorithms that have been used can be found in several previous publications<sup>53,34</sup>. Our registration algorithms are based on mutual information between the two images as the similarity metric<sup>54, 55</sup> and its accuracy was validated in a population of patients at known anatomical landmarks by Pallavaram et al.<sup>56</sup>. Two variations of the non-rigid registration based target predictions were produced; one used data from both surgeons to make predictions while the other was 'surgeon-specific' where predictions for a particular surgeon's patient were based on that particular surgeon's average selection in a population.

The manual approaches used in this study are commonly used approaches; namely indirect targeting using stereotactic coordinates based on localizing the anterior commissure (AC) and posterior commissure (PC) referred here as ACPC-based targeting, direct targeting based on high resolution MRI T1 and T2 weighted images, and indirect targeting based on standard coordinates defined with respect to the red nucleus referred here as RN-based targeting (11 mm Lateral, -2.3 Anterior, -2.6 Superior), that require the expertise of an experienced functional neurosurgeon. Indirect targeting based on the stereotactic coordinates (12 mm Lateral, -3 mm Anterior, and -4 mm Superior) with respect to the mid-commissural point used to target the center of the motor territory of the STN<sup>3, 9, 21, 31, 57, 58</sup>, (11.8 mm Lateral, -2.4 mm Anterior, and -3.9 mm Superior) which represent the centroid of active contacts from a widely cited study<sup>57</sup>, as well as the centroid of active contacts from our dataset (11.0 mm Lateral, -2.0 mm Anterior, and -2.4 mm Superior) which represent the optimized stereotactic coordinates for this dataset were included. The coordinates for RN-based targeting were 3 mm lateral to the lateral edge, -2 mm superior to the superior edge, and the anterior edge of the RN. For direct targeting, the surgeon selected the center of the STN as visualized on T2 axial images (TR: 3000 mS, TW: 80 ms, imaging frequency: 128 Hz, magnetic field strength: 3T, in-plane resolution: 0.47 mm X 0.47 mm, slice thickness: 2 mm).

The manual selections used in the study to be tested against the CranialVault atlas prediction were performed retrospectively by a single neurosurgeon (S2). To avoid bias in planning, the patients were anonymized and randomized in the order in which they were shown to the surgeon. Furthermore, the surgeon was provided only pre-op imaging for the retrospective target selections and was also blinded to the location of the implantation making the process identical to pre-op planning. Predictions based on the CranialVault atlas and the various manual target selections were validated against the final location of the active contact in the patient achieved through iterative testing and programming and evaluated by each patient's treating neurologist to be the location for optimal therapeutic benefit in that patient.

## Results

Figure 4 shows a bar chart of the accuracy of different targeting methods compared in this study with respect to the final active contacts in 71 STN-DBS cases. On average, targeting using standard stereotactic coordinates corresponding to the center of the motor territory of the STN (12 mm Lateral, -3 mm Anterior, and -4 mm Superior) had the largest error (mean 3.69 mm, standard deviation 1.78 mm). Literature coordinates of the centroid of active

contacts (11.8 mm Lateral, -2.4 mm Anterior, and -3.9 mm Superior) had better accuracy (mean 3.49 mm, standard deviation 1.70 mm). Direct targeting performed comparably to these standard stereotactic coordinates (mean 3.44 mm, standard deviation 1.49 mm). However, average stereotactic coordinates of the active contacts from the 71 cases in this study (11 mm Lateral, -2 mm Anterior, and -2.4 mm Superior) performed substantially better (mean 3.02 mm, standard deviation 1.48 mm). Red nucleus based targeting and the fully automatic CranialVault atlas method of targeting using non-rigid registration performed substantially better than all other methods and were comparable to each other on mean accuracy. Red nucleus based targeting had mean accuracy of 2.75 mm and a standard deviation of 1.49 mm, fully automatic CranialVault atlas based predictions using both surgeons had a mean accuracy of 2.75 mm (same as red nucleus) and a standard deviation of 1.40 mm while the accuracy of the CranialVault atlas improved marginally when using surgeon-specific data for predictions to a mean of 2.70 mm and a standard deviation of 1.17 mm. To be even more comprehensive on the wide range of stereotactic coordinates used across practices, we tested a number of other popular AC-PC based coordinates. For (12 mm Lateral, -2 mm Anterior, -4 mm Superior), the mean accuracy was 3.57 mm (standard deviation 1.65 mm), for (12 mm Lateral, -2 mm Anterior, -3 mm Superior), the mean accuracy was 3.22 mm (standard deviation 1.54 mm), and for (12 mm Lateral, -3 mm Anterior, -5 mm Superior), the mean accuracy was 4.22 mm (standard deviation 1.91 mm).

Of all the tested methods, the non-rigid registration based CranialVault atlas predictions using surgeon-specific data had the highest accuracy and the smallest standard deviation. Performing t-test at 5% level of significance showed that there was a statistically significant difference in accuracy between CranialVault atlas based targeting using non-rigid registration and three manual approaches; standard stereotactic coordinates targeting the center of the motor territory of the STN, standard stereotactic coordinates from literature targeting the centroid of active contacts, as well as Direct targeting of the STN using MRI imaging. There was no statistically significant difference between red nucleus based targeting and the CranialVault atlas targeting using non-rigid registration although the latter had marginally higher accuracy and substantially smaller standard deviation. Performing a two-sample F-test at 5% level of significance revealed a statistically significant difference between the standard deviations of red nucleus based targeting and our atlas-based targeting. This suggests that automated atlas based targeting is no less accurate than traditional methods including red nucleus based targeting, but is also more precise than all manual methods evaluated in this study. Figure 5 shows the location of the atlas centroid overlaid on the 3D renderings of the segmentations of STN and SNr.

## Discussion

Our results show that among the manual methods evaluated in this study, targeting using standard stereotactic coordinates in the literature corresponding to the center of the motor territory of the STN has the largest error while that using standard coordinates relative to the red nucleus has the smallest error. Targeting based on the centroid of surgeon-specific active contacts from the CranialVault atlas projected using fully automatic non-rigid image registration had the smallest error of all methods, was statistically better than standard stereotactic coordinates from literature and direct targeting, and was more precise than any

of the manual methods. The use of surgeon-specific data for predictions seems to marginally improve targeting accuracy. Andrade-Souza et al.<sup>11</sup> had compared modified direct targeting, indirect targeting using standard stereotactic coordinates, and red nucleus based targeting in 28 STN implants against the active contacts. They reported that red nucleus targeting was the best among the manual methods while direct targeting and indirect targeting using standard stereotactic coordinates had substantially inferior accuracy. These are consistent with our results. Our study can be considered an extension over their work using not only a substantially larger dataset but also additionally evaluating a fully automatic method of atlas based targeting using non-rigid registration.

We also examined the difference in the AC-PC or stereotactic space for the different methods as shown in Table 1. We found that the CranialVault atlas-based target predictions seem to differ substantially from standard stereotactic coordinates in literature along all three directions with most standard AC-PC coordinates being more lateral, posterior and inferior to atlas-based predictions. With respect to direct targeting the predominant difference is in the superior-inferior direction with direct targeting being substantially inferior to atlas predictions. Targeting based on red nucleus and centroid of stereotactic coordinates of the active contacts from the study have negligible difference in the lateral component and posterior components, but noticeable difference in the superior-inferior component. Such direct comparison of the ultimate location, however, belies the real power of the CranialVault process, which is its ability to account for anatomical variation. This is best demonstrated in the decreased variance that it exhibits versus all other techniques, suggesting a greater precision in the face of anatomical variation. We presume that of the manual techniques red nucleus based targeting performed best because its proximity to the STN makes its ultimate relationship to the later structure more constant despite variations that may exist in anatomy (in effect the red nucleus moves with the STN in most cases). Although, using this same logic, one might expect direct targeting to outperform other techniques it ultimately was inferior to red nucleus and CranialVault atlas-based targeting. This is perhaps due to inconsistencies in the appearance of the STN even on our high resolution images.

One potential confound to these findings is the extent to which the dominance of one method in our original surgical targeting between the two surgeons might favor the performance of one technique over another when evaluated retrospectively. Our surgeons used a combined approach when choosing their initial target, combining red nucleus based, standard stereotactic coordinates based, and direct targeting methods. The actual weighting of these methods used for targeting the STN was variable between the two surgeons performing these cases. One of the two surgeons, in addition to these manual approaches, had access to the atlas predictions of the middle of the leads but not active contacts and could have been influenced by it in his targeting. Both surgeons however used intra-operative MER and stimulation response (efficacy and side effects) to arrive at their final target for implantation moving from their original target (center track on the BenGun) in greater than 50% of implanted leads. To test if the locations of implantations for the surgeons were impacted differently by their planning approaches we compared the accuracy of the atlas prediction of active contacts between the two surgeons. There was no statistically

significant difference between these two subgroups at 5% level of significance using a two-sample t-test.

## Conclusions

Predictions based on non-rigid image registration using the surgeon-specific CranialVault atlas had the highest accuracy among all the validated methods and the difference was statistically significant when compared to a variety of standard stereotactic coordinates cited in the literature and used in practice as well as with respect to direct targeting. The accuracy of red nucleus based targeting was the best among the manual methods and not statistically different from the CranialVault atlas based predictions. However, predictions based on the CranialVault atlas had the smallest variance of all tested methods and the difference was statistically significant.

Therefore, fully automatic targeting based on non-rigid image registration using the CranialVault atlas is as accurate and more precise than popular manual methods for STN-DBS. A fully automatic targeting method that performs as good as the manual selections by experienced neurosurgeons is not only useful to them but could provide significant assistance to surgeons less experienced in DBS and help make the surgery accessible to more patients. With the increasing accessibility of sophisticated non-rigid image registration packages within and outside of clinical software we believe that fully automatic targeting can become part of routine clinical practice.

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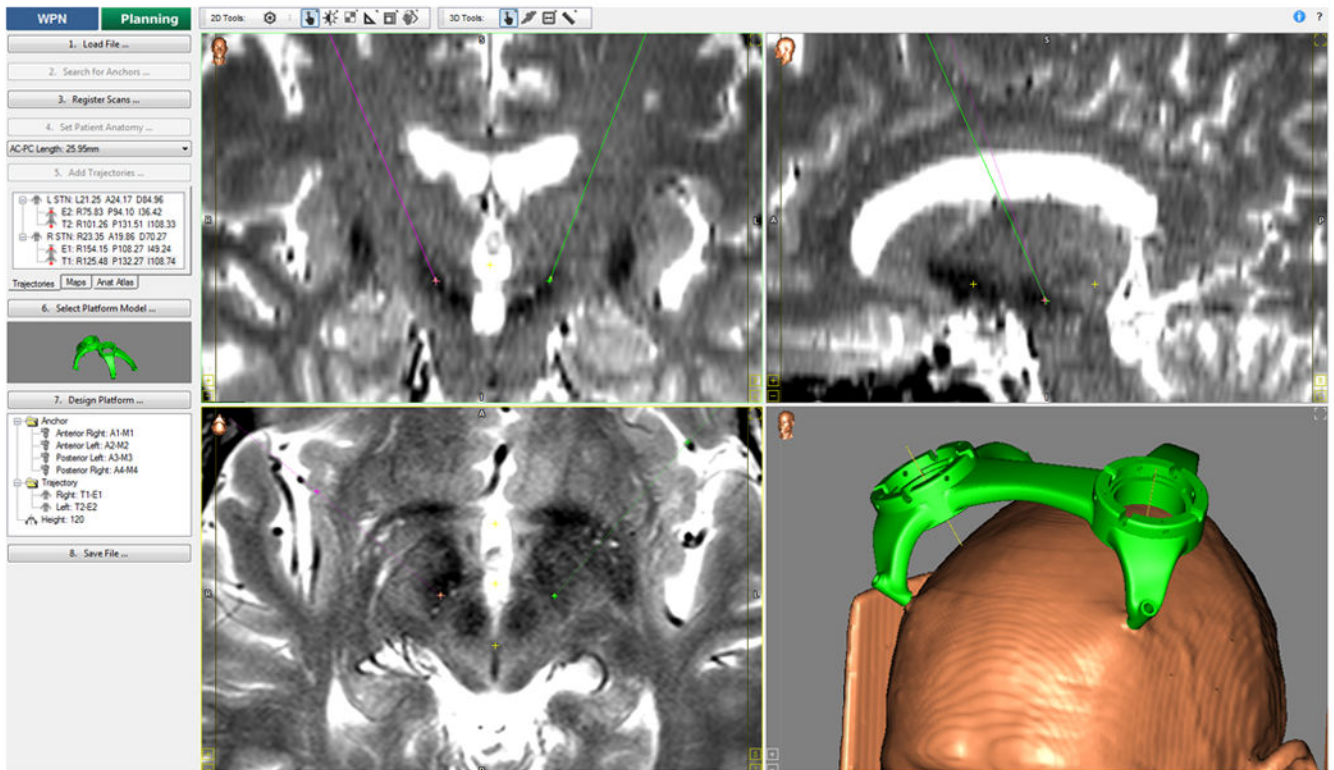
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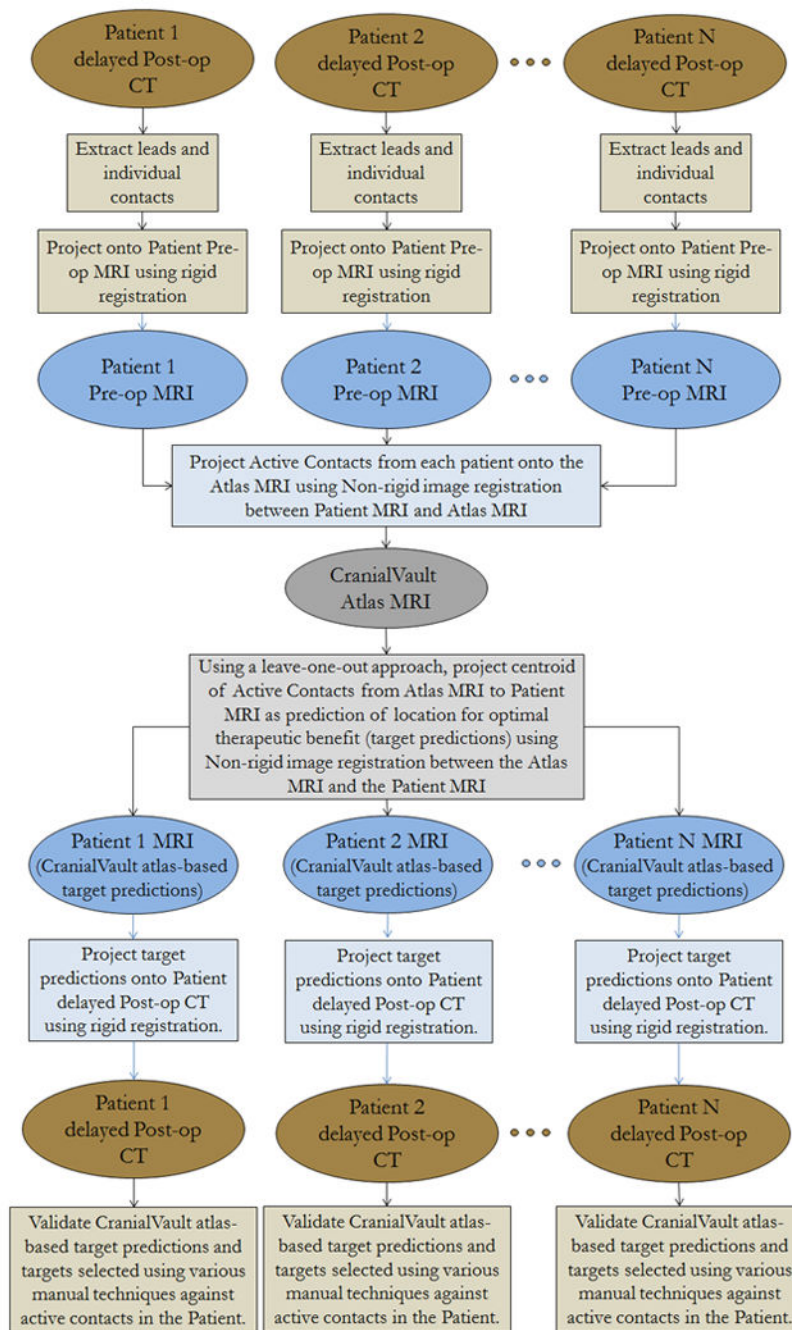
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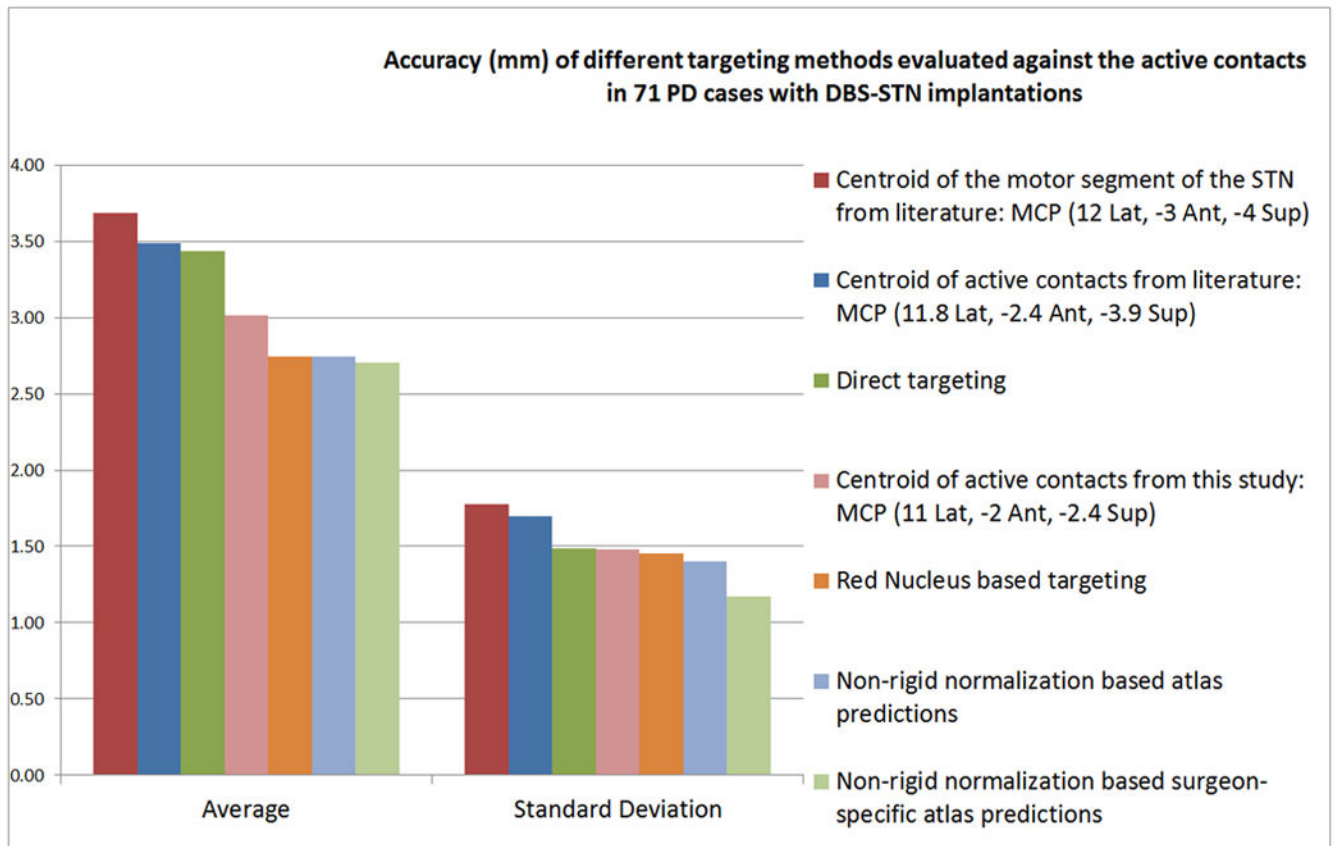
**Figure 1.** WayPoint Navigator software made available to the surgeons for clinical planning as well as for manual target selections in this study. A 3D rendering of the platform and the patient's head based on the CT is also shown along with a sample trajectory for an STN-DBS patient.



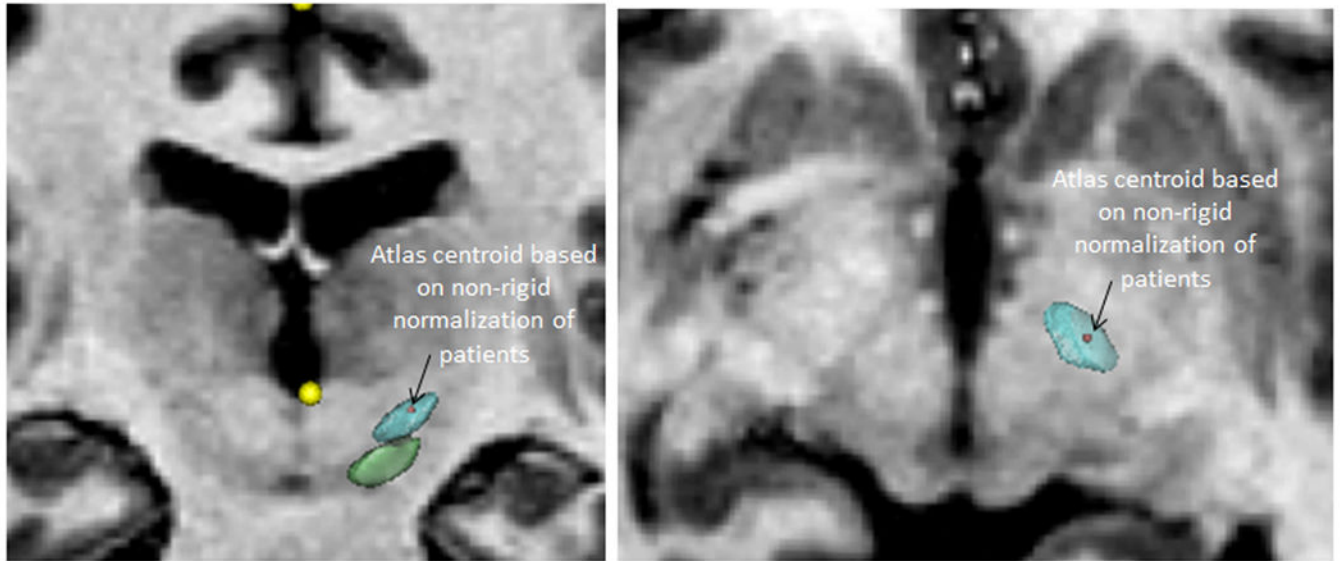
**Figure 2.**  
Individual contacts in a 3389 lead extracted from the delayed post-op CT and overlaid on the pre-op MRI using rigid registration.



**Figure 3.** Flowchart showing how target predictions based on non-rigid image registration are made using the CranialVault atlas by projecting contacts positions from a population of patients onto a new patient.



**Figure 4.** Bar chart showing the average and standard deviation of the Euclidean distances for different targeting methods from active contacts in 71 STN-DBS implants.



**Figure 5.** Coronal and axial views showing the location of the atlas centroid overlaid on the 3D renderings of the segmentations of STN and SNr.

**Table 1**

Components of stereotactic coordinates for different targeting methods.

Mean Stereotactic coordinates of various targeting methods	Lateral	Anterior	Superior
Direct Targeting	11.19	-1.59	-4.31
RN-based Targeting	11.05	-2.26	-2.62
Non-Rigid Registration based targeting using CranialVault Atlas	11.01	-2.01	-2.02
Active contacts from literature	11.80	-2.40	-3.90
Motor segment of the STN from literature	12.00	-3.00	-4.00
Active contacts from the study	11.09	-2.00	-2.40

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