Original Article

Application of Diffusion Tensor Imaging (DTI) Tractography as a Targeting Modality for Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN)

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Introduction: We carried out diffusion tensor imaging (DTI) to detect the corticospinal tract (CST) during deep brain stimulation (DBS) of the subthalamic nucleus (STN), and we examined whether CST-based targeting could provide reliable internal fiducial markers for STN-DBS.

Materials and Methods: Twenty-eight patients underwent bilateral simultaneous implantation of DBS electrodes for STN-DBS. We calculated the absolute values of the differences in the coordinates between the implanted DBS electrodes and the CST demonstrated by tractography in each patient at the level 3 mm inferior to the superior border of the red nucleus (RN). We also compared the distance between the implanted DBS electrodes and the estimated target points planned by RN-based and CST-based targeting.

Results: The average distance from the center of the CST to the center of the implanted DBS electrode was 7.0 ± 2.3 mm in the *x*-direction, 2.1 ± 1.3 mm in the *y*-direction, and -4.3 ± 1.4 mm from the level of the AC-PC line as the *z*-coordinate. The average distance between the DBS electrode and planned targets estimated by RN-based targeting was 2.5 ± 1.1 mm, and that estimated by CST-based targeting was 3.9 ± 1.6 mm. The variances of these planned targets were not significantly different ($p = 0.06$, Mann-Whitney U-test).

Conclusions: The stereotactic coordinates between the target points of STN and CST were confirmed by CST-based targeting in this study. The results were not significantly different between RN-based targeting and DTI-based targeting for STN-DBS. The DTI-based targeting method using an internal fiducial marker has a possibility to become a powerful tool in stereotactic surgery.

Key words: subthalamic nucleus, diffusion tensor imaging, deep brain stimulation, Parkinson disease

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Introduction

Chronic electrical deep brain stimulation (DBS) of the thalamic ventralis intermedius (Vim) nucleus^{1,2)}, the subthalamic region^{3,4)}, the globus pallidus interna (GPi)^{5,6)}, and the subthalamic nucleus (STN)^{7,8)} has become a promising technique for the treatment of various types of involuntary movement disorders. Chronic DBS of the STN is rapidly gaining acceptance for the treatment of symptoms in patients with Parkinson's disease (PD)^{9,10)}. The success of STN-DBS therapy for the treatment of PD depends on the accuracy of the target determination, since the STN is a relatively small structure estimated at $9 \times 7 \times 5$ mm¹¹⁾.

For the target determination of the STN, the line between the anterior commissure and the posterior commissure (the AC-PC line) has been the most commonly used internal reference, and the distance

of the desired target point was calculated from the midpoint of the AC-PC line. Refined magnetic resonance (MR) sequences have offered high-contrast differentiation between gray and white matter, and have made it possible to directly visualize the STN. However, it is usually difficult to determine the exact border of the STN by MRI alone^{12,13)}. The border of the red nucleus (RN) may be identified more easily and accurately by MR imaging^{14,15)}, and it has been reported that MRI-based targeting of the STN using the RN as an internal fiducial marker is superior to the methods of direct STN targeting and indirect targeting using the coordinates of the AC and PC¹⁶⁾.

The technique of diffusion tensor imaging (DTI) using MRI is a recent development allowing the *in vivo* visualization of white matter tracts formed from the axonal projections of cortical and subcortical neurons^{17,18)}. In the present study, we used DTI to detect the corticospinal descending motor tract during

STN-DBS for the treatment of advanced PD. We decided on the final location of the DBS electrodes by using multi-track microelectrode recording (MER)¹⁹⁾. We calculated the stereotactic coordinates for the STN-DBS estimated by corticospinal tract (CST)-based targeting, and we also compared the accuracy between RN-based targeting and CST-based targeting for STN-DBS.

The aim of this study was to determine whether tractography is useful for the targeting of STN-DBS.

Clinical Materials and Methods

Patients Population and Surgical Procedure

Twenty-eight patients (10 men and 18 women; average age, 64.6 ± 8.8 yrs; range 36–77 yrs) with advanced PD were included in this study. All these patients had undergone the bilateral simultaneous implantation of DBS electrodes for STN-DBS. After the patients received a local anesthetic agent, a Leksell Series G head frame (Elekta Instruments, Stockholm, Sweden) was affixed to the skull. The MR imaging was performed at a 1 mm slice thickness.

The obtained MR imaging data sets were then transferred into a Stealth-Station TREON plus navigation system (Medtronic, Minne, MN, USA) with installed stereotactic planning software (Frame LinkTM, Medtronic). The obtained MR imaging data were adjusted to the plane of the AC-PC line. We identified the AC-PC line, RN, and STN, and used a hybrid of these direct and indirect targets to decide the tentative target for STN-DBS. The RN-based target was defined with the *x*-coordinate 3 mm lateral to the most lateral border of the RN and the *y*-coordinate the same as that of the anterior border of the RN in the axial plane, using a T₂-weighted fast spin echo sequence. We established the *z*-coordinate 3 mm inferior to the superior border of the RN in the coronal plane.

For the final placement of the DBS electrodes, we used intra-operative multi-track MER. To perform MER in STN-DBS, we used small (10- μ m width) polyamide-coated tungsten microelectrodes (Medtronic; microTargetingTM Electrode 291A) mounted on a sliding cannula, and three MER/macrostimulation needles were placed in an array with the central, lateral, and posterior positions placed 2 mm apart to choose the final target for permanent DBS electrode implantation. Signals were recorded with the amplifiers of the Leadpoint system (Medtronic).

Diffusion Tensor Imaging and Tractography

With the MAGNETOM SymphonyTM MRI system (Siemens, Erlangen, Germany), the diffusion weighted Imaging (DWI) was captured before the operation without fixing the stereotactic head-frame. The DWI

Fig. 1 The region of interest (ROI) was put on the precentral knob of precentral gyrus (A), the posterior limb of internal capsule (B), and the cerebral peduncle (C).

conditions were as follows: TR = 11400 msec; TE = 141 msec; matrix size, 256×256 pixels (0.9 mm/pixel); 3.0 mm/slice; MPG, 12 axes; *b* = 1,000 s/mm² three-times averaging; non-sloping gantry. Based on the captured DWI, tractography was made preoperatively using Stealth DTITM (Medtronic). Tractography was performed on the basis of fiber assignment by continuous tracking. The fiber propagation was stopped at a fractional anisotropy (FA) threshold of < 0.2.

The region of interest (ROI) was placed on the precentral knob of the precentral gyrus, the posterior limb of the internal capsule, and the cerebral peduncle, and we depicted the regional CST of the upper limb (Fig. 1). This depicted tractography was synthesized in the T₁-weighted image and the T₂-weighted image which was captured preoperatively and transferred to the Frame Link. Finally, the postoperative T₁-weighted image was also transferred to the Frame Link, and we synthesized these three images using image synthesis software (Stealth MergeTM, Medtronic) (Fig. 2).

Fig. 2 The depicted tractography was synthesized in the T_1 -weighted image (*Upper Lt.*) and the T_2 -weighted image (*Upper Rt.*) which was captured preoperatively. The post-operative T_1 -weighted image indicates the location of DBS electrode (*Lower Lt.*). These 3 images were synthesized (*Lower Rt.*).

Application of Tractography for the Targeting of the STN

For the CST-based targeting of the STN, we used the same z -axis as the RN-based targeting, which is 3 mm inferior to the superior border of the RN in the coronal plane. We calculated the absolute values of the differences in the coordinate between the center of the implanted DBS electrode and the center of the CST demonstrated by the tractography in the direction of the x -axis and y -axis in each case, and the average distance of the coordinates between the DBS electrode and the CST was calculated. The optimal target of the STN-DBS could then be predicted from the coordinates of the CST using these average values in each case.

We also compared the distance between the implanted DBS electrode and the estimated target points planned by the RN-based and CST-based targeting in each case. All of the patients and the patients' families provided their written informed consent for this procedure. This study was approved by the Committee for Clinical Trials and Research on Humans of our university and conformed to the principles outlined in the Declaration of Helsinki.

Statistics and a Significant Digit

All values shown are means $\pm$ standard deviations.

Fig. 3 The distance between the center of implanted DBS electrode and the center of CST demonstrated by the tractography was calculated and averaged.

Averaged locations of implanted DBS electrode (*Upper Lt.*), RN-based targeting of the STN (*Upper Rt.*), and Tractography-based targeting of STN (*Lower Lt.*) were indicated. These 3 points were plotted on the same plane (*Lower Rt.*).

Fig. 4 Between CST- and RN-based targeting of the STN, the difference in distances between planned targets and implanted DBS electrodes was statistically non-significant ($p = 0.06$, Mann-Whitney U test).

Averaged locations of implanted DBS electrode (blue), RN-based targeting of the STN (red), and Tractography-based targeting of STN (green).

Spearman's rank correlation coefficient was used to find significant differences using Student's t-test. For comparisons between the two groups of RN-based and CST-based targeting, the Mann-Whitney U-test was used. P-values <0.05 were accepted as significant. We used Ekuseru-Toukei 2008 (Social Survey Research Information Co., Tokyo) for the statistical analyses.

Results

The absolute value of the difference between the implanted DBS electrode and the CST demonstrated by the tractography was calculated in 28 cases (56 sides). The average distance of the coordinates from the center of CST to the center of the implanted DBS electrode was 7.0 ± 2.3 mm (x -coordinate) and 2.1 ± 1.3 mm (y -coordinate). For the z -coordinate, we established the axis 3 mm inferior to the superior border of the RN in the coronal plane, which was -4.3 ± 1.4 mm from the level of the AC-PC line (Fig. 3).

In all 28 cases (56 sides), the RN was visualized clearly by the T_2 -weighted MR image. The average distance between the target point planned by the RN-based targeting and the DBS electrode was 2.5 ± 1.1 mm, and the average distance between the target point planned by the CST-based targeting and the DBS electrode was 3.9 ± 1.6 mm (Fig. 4). Between the CST- and RN-based targeting, the difference in distances between the planned targets and the implanted DBS electrodes was non-significant ($p = 0.06$, Mann-Whitney U-test).

Discussion

In stereotactic operations, we can use indirect targeting, which includes techniques using the positions of the AC-PC line and using the RN as an internal fiducial marker, as well as direct targeting of the STN with some modification. We usually perform a hybrid of indirect and direct targeting. For targeting of the STN, Andrade-Souza et al.¹⁶⁾ examined the accuracy of the target point planned by modified direct targeting, AC-PC line-based targeting, and RN-based targeting compared with the location of the implanted DBS electrode, which was finally implanted with MER monitoring. They reported that the mean distance between the optimal contact position of the DBS electrode and the planned target was 3.19 ± 1.19 mm using the RN-based method, 3.42 ± 1.34 mm using the AC-PC line-based targeting, and 4.66 ± 1.33 mm using the modified direct targeting. Although the modified direct targeting depends on the method of each modification, they concluded that the targeting of the STN based on the position of the RN could replace methods based on the positions of the AC and PC.

In the present study, we used the same method for RN-based targeting as the method reported by Andrade-Souza et al.¹⁶⁾ Here, the average distance between the optimal target point decided by MER and the planned target point was 2.5 ± 1.1 mm using the RN-based method and 3.9 ± 1.6 mm using the CST-based method. The results were not significantly different. It might be better to use RN-based targeting, which is the most commonly used technique. However, the use of CST as an internal fiducial marker seems to be less precise than the RN-based targeting for STN-DBS. The lack of precision may be caused by the distance between the DBS electrode; in addition, the location of the RN is shorter than the location of CST. We also speculate that the target of thalamic stimulation for tremor control may be the best candidate for CST-based targeting. With thalamic stimulation, the distance from the internal capsule and the distance from the thalamic nucleus ventrocaudalis (Vc) are very important for the location of the DBS electrode²⁾. It is important that the locations with a good control of tremor are the outside of the Vc and the inner side of the CST. In addition, we can prevent injuries of the CST by checking the distance from the CST as demonstrated by tractography.

MER seems to be necessary to select the best target of STN, since we can not prevent the occurrence of brain shift during STN-DBS^{20,21)}. In our experience, brain shift occurred mainly to the posterior direction and slightly in the lateral directions²⁰⁾. We used intra-operative multi-track MER at the central, lateral, and posterior positions placed 2 mm apart, and we

could identify the dorsal and ventral border of STN completely in all cases in this study.

We used commercially available software (Stealth DTI) in conjunction with Frame Link for the tractography analysis, and this software was useful in measuring the coordinates in the stereotactic operation. We report here the coordinates of the STN from the center of the CST demonstrated by the tractography, which were 7.0 ± 2.3 mm (x -coordinate) by 2.1 ± 1.3 mm (y -coordinate). For the z -coordinate, we selected a point 3 mm inferior to the superior border of the RN, which was -4.3 ± 1.4 mm from the level of the AC-PC line.

We have used tractography to locate internal fiducial markers for the targeting of the STN. Tractography is also clinically applied for the direct targeting of DBS and to confirm the location of the DBS electrode²²⁾. Coenen et al.²²⁾ visualized the dentate-rubro-thalamic tracts by preoperative DTI and tractography, and directly targeted them stereotactically with the DBS electrode. They used direct visualization of the fiber tract for direct targeting for the treatment of head tremors, and they reported that the control of the head tremors was excellent (>90%). Hunsche et al.²³⁾ also applied DTI-based tractography for the spinothalamocortical tract, and direct stereotactic targeting with DBS electrodes. They reported that electrode stimulation was possible over a length of more than 20 mm with a tractography-based trajectory along the posterior limb of the internal capsule. Lambert et al.²⁴⁾ used DWI and demonstrated that three distinct clusters exist within the human STN, based on brain connectivity profiles. They reported that the STN was successfully sub-parcellated into these regions. As in these reports in which DTI-based targeting was used for the direct targeting of DBS and for the confirmation of the location of the DBS electrode, we speculate that the DTI-based targeting with an internal fiducial marker has a possibility to become a powerful tool in stereotactic surgery.

Conclusion

Diffusion tensor imaging tractography is a clinically useful tool for stereotactic operations. The distance of the STN from the center of the CST was 7.0 ± 2.3 mm (x -coordinate) by 2.1 ± 1.3 mm (y -coordinate), with the z -coordinate being -4.3 ± 1.4 mm from the level of the AC-PC line. Although the accuracy was not significantly different between the RN-based targeting and DTI-based targeting for the STN-DBS, the DTI-based targeting method with an internal fiducial marker has a possibility to become a powerful tool in stereotactic surgery.

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