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Original Investigation

Learning Curve in Anatomo-Electrophysiological Correlations in Subthalamic Nucleus Stimulation

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ABSTRACT

AIM: Advances in neuroradiological planning techniques in deep brain stimulation have put the need for intraoperative electrophysiological monitoring into doubt. Moreover intraoperative monitoring prolongs surgical time and there is potential association between the use of microelectrodes and increased incidence of hemorrhagic complications. The aim of this study was to analyze the correlation between the anatomically planned trajectory and the final subthalamic electrode placement after electrophysiological monitoring in patients with Parkinson's disease and its change with the increasing experience of the surgical team.

MATERIAL and METHODS: The trajectories of right (first implanted) and left electrodes were compared in the first 50 patients operated on (Group 1) and the next 50 patients (Group 2).

RESULTS: In Group 1, 52% of central trajectories were on the right and 38% on the left; in Group 2, the percentage of central trajectories was 76% on the right and 78% on the left; the difference was statistically significant (p=0.021 and 0.001). The difference in the percentage of posterior trajectories reflecting brain shift between the right and left sides was statistically insignificant in Groups 1 (26% and 28%, p=0.999) and 2 (18% and 12%, p=0.549). The percentage of bilateral central electrodes was 14% and 62% in Groups 1 and 2, respectively.

CONCLUSION: The correlation between anatomically planned trajectory and final electrode placement markedly improves with the number of patients. However the significant percentage of patients with final electrode trajectory differing from anatomically planned target supports the use of intraoperative monitoring.

KEYWORDS: Deep brain stimulation, Parkinson's disease, Subthalamic nucleus, Frame-based stereotaxy, Intraoperative monitoring

ABBREVIATIONS: DBS: Deep brain stimulation, **STN:** Subthalamic nucleus, **MRI:** Magnetic resonance imaging, **CT:** Computer tomography, **AC-PC:** Anterior commissure – posterior commissure, **FAT SAT:** Fat saturation, **GE MPR:** Gradient echo multiplanar reformatting

INTRODUCTION

Deep brain stimulation (DBS) by means of stereotactically implanted intracerebral electrodes is an established treatment method for motor problems in patients with Parkinson's disease and other movement disorders, but not limited to them (4,13). The anatomical target definition based on neuroradiological investigation can be supported by intraoperative microrecording using simultaneously or sequentially implanted intracerebral microelectrodes and intraoperative

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stimulation (6,31). However, intraoperative monitoring prolongs surgical time and there are reports suggesting an association between the use of microelectrodes and increased incidence of hemorrhagic complications (24,32). Moreover, according to some data, advances in neuroradiological techniques that precisely delineate the most commonly targeted structure in patients with Parkinson's disease, the subthalamic nucleus (STN), have put the need for electrophysiological monitoring into question (12,33).

Studies advocating intraoperative electrophysiological monitoring have indicated the difference between the electrode implantation target based on presurgical neuroradiological planning and the final target after electrophysiological monitoring (5,10). Numerous factors have been deemed responsible for the discrepancy. Brain shift, possibly occurring during DBS surgery, may change the position of intracerebral structures (19). Other potential causes of the anatomo-electrophysiological difference must also be considered, including the difference between target locations using different targeting techniques, spatial distortion of magnetic resonance imaging (MRI), variability of the target structures, interpretations of radiological and electrophysiological data, and possible technical inaccuracies during surgery (3,8,15). All these factors can be influenced to some degree by the experience of the surgical team. Therefore, the learning curve must be considered not only in terms of surgical complications and adverse events (28).

The aim of this study was to analyze the difference between the anatomical electrode implantation target based on neuroradiological planning and the final target refined after intraoperative electrophysiology in patients with late motor complications of Parkinson's disease who underwent frame-based bilateral implantation of STN electrodes with intraoperative micromonitoring and stimulation. The studied group of 100 patients was divided into two subgroups: Group 1 (patients 1 to 50) and Group 2 (patients 51 to 100). The hypothesis was that as the number of patients operated on increased, the correlation between anatomical and electrophysiological targets would improve. The system for intraoperative monitoring and final electrode implantation uses a set of monitoring electrodes implanted in parallel at defined distances from the central anatomical trajectory. The hypothesis can be re-defined: The percentage of final electrodes implanted along the anatomically planned trajectory will increase.

The second aim of this study was to analyze the causes of the difference between the anatomically planned trajectory for the implanted electrodes and the final position by comparing the percentages of electrodes implanted in the different trajectories on the right side (first implanted) and left side in each group.

■ MATERIAL and METHODS

Our group consisted of 100 consecutive patients with bilateral STN electrodes implanted between 2003 and 2014 using a frame-based technique (Zamorano-Dujovny stereotactic system Inomed Germany, ceramic MRI-compatible frame Leibinger, Freiburg, Germany and the MicroDrive system Medtronic) with intraoperative microrecording and stimulation. All the surgeries were performed by the same surgeon (JC) with one of two specialists performing the intraoperative monitoring (MBa or MBo).

The imaging protocol for STN electrode implantation included T2W Fat Saturation (FAT SAT) in the axial and coronal planes, and MRI angiography and T1W Gradient Echo Multiplanar Reformatting (3D GE MPR) after contrast administration. The image sets were merged in a computer planning workstation using Praezis Plus stereotactic planning software (Tatramed, Slovakia). The initial coordinates for the dorsolateral STN were determined in reference to the intercommissural line or anterior commissure – posterior commissure – (AC-PC) line using an indirect targeting technique, initially 11 mm lateral, 3 mm posterior, and 5 mm ventral to the center of the AC-PC line. The final target coordinates were modified according to the individual patient's anatomy (direct STN identification on T2 W FAT SAT and the relationship of the target structure to the red nucleus anterior margin at the level of the largest red nucleus cross-sectional area).

The principle of MicroDrive system used for microelectrode monitoring is the simultaneous implantation of up to five parallel microelectrodes with one central anatomical trajectory. The remaining four ports are marked as anterior (2.5 mm anterior to the central trajectory), lateral (2.5 mm laterally), medial (2.5 mm medially), and posterior (2.5 mm posteriorly). In Group 1, microelectrodes were implanted through all five ports. However, the use of the medial port was then abandoned in order to facilitate the process of microrecording by having only four traces simultaneously visible on the monitor screen, to reduce the number of brain penetrations, and to eliminate the pass of the medial electrode in the vicinity of the ventricular wall, because of the fear of ventricular wall violation including the subependymal veins and possible postoperative mental status alterations (9). Therefore, the combination of central, anterior, lateral, and posterior electrodes was used in Group 2. In all patients, microrecording was started 10 mm above the anatomical target and microelectrodes were advanced in 1 mm steps until 5 mm above the anatomical target, and then in 0.5 mm steps.

The motor part of the STN was identified by its typical electrophysiological features: a bursting pattern characterized by asymmetrical spikes at high frequency with a proprioceptive response to passive and active manipulation of the contralateral limbs. After the completion of the microelectrode monitoring, intraoperative stimulation by the electrodes with the best recording was performed: the effect of stimulation on rigidity, tremor, and bradykinesia was monitored and possible adverse events were identified. After the monitoring was completed, the trajectory for the final electrode implantation was selected. The final electrode implantation was controlled using intraoperative fluoroscopy and the final electrode position was checked using computed tomography (CT). In all patients, right and left electrodes were implanted during a single surgical session with the right electrode implanted first.

In both Group 1 (the first 50 patients, patients 1 to 50) and Group 2 (the second 50 patients, patients 51 to 100), the following parameters were studied: age, Parkinson's disease and late motor complication duration, and the percentage of the electrode position as defined by the MicroDrive ports (central - anatomical, posterior, lateral, anterior, and medial) on both right and left sides.

For descriptive statistics, continuous variables were represented by median, minimum, and maximum values; categorical variables were represented by percentages. For comparative statistics, the parameters were tested using the Mann-Whitney U test in continuous variables and Fisher's exact test in categorical variables. The comparative study of the left side and right side was done using McNemar's test.

■ RESULTS

The basic characteristics of both groups are summarized in Table I. There was no statistically significant difference in age or in duration of late motor complications between Groups 1 and 2. The duration of Parkinson's disease before surgery was significantly shorter in Group 2.

Bilateral STN electrode implantation was successfully completed in all patients. There were no cases of intracerebral bleeding requiring surgical evacuation and no patient had to be re-operated for electrode malposition.

Table II summarizes the number and percentage of final electrodes implanted through the individual MicroDrive ports. In Group 1, the central electrode was the most frequently implanted electrode on both sides. On the left side, the percentage of central electrodes was lower (38%), but the difference did not reach the level of statistical significance. Posterior electrodes were the second most frequently implanted, without a statistically significant right–left difference.

In Group 2, the central electrode was the most frequently implanted on both sides, but the percentage of central electrodes was higher than in Group 1 and almost equal on both sides (76% right, 78% left). The posterior electrode was the second most frequently implanted, without a statistically significant right–left difference.

Table III compares the percentage of electrodes implanted through the individual ports between Groups 1 and 2. The percentage of central electrodes was significantly higher in Group 2 on both sides. The percentage of posterior electrodes on both sides was lower in Group 2 than in Group 1, but the difference does not reach the level of statistical significance. The higher percentage of anterior electrodes on the left side in Group 1 compared with Group 2 is statistically significant.

In Group 1, the position of the final electrodes (related to MicroDrive ports) was symmetrical in only 13 patients (26%) and both electrodes were implanted along central – anatomical

Table I: Patients with Parkinson's Disease – Group Description

Characteristics	Group of patients		p
	Group 1 (n = 50)	**Group 2 (n = 50)**	
Age (Years)	62.5 (49.0–69.0)	62.0 (45.6–69.0)	0.569
Parkinson's disease duration (Years)	11.0 (5.0–22.9)	9.5 (6.0–15.5)	**0.026**
Duration of late motor complications (Years)	4.0 (1.0–11.5)	4.0 (2.0–8.9)	0.837

Table II: Comparison of Right-Side and Left-Side Electrodes in Groups 1 and 2

Characteristics	Right-side electrodes	Left-side electrodes	p
Group 1			
Central port	26 (52.0%)	19 (38.0%)	0.265
Anterior port	9 (18.0%)	10 (20.0%)	0.999
Posterior port	13 (26.0%)	14 (28.0%)	0.999
Lateral port	0 (0.0%)	5 (10.0%)	–
Medial port	2 (4.0%)	2 (4.0%)	0.999
Group 2			
Central port	38 (76.0%)	39 (78.0%)	0.999
Anterior port	2 (4.0%)	2 (4.0%)	0.999
Posterior port	9 (18.0%)	6 (12.0%)	0.549
Lateral port	1 (2.0%)	3 (6.0%)	0.500

Table III: Comparison of the Frequency of Individual Trajectories Between Groups 1 and 2

	Group of patients		p^2
	Group 1 (n = 50)	Group 2 (n= 50)	
Right-side electrodes			
Central port	26 (52.0%)	38 (76.0%)	**0.021**
Anterior port	9 (18.0%)	2 (4.0%)	0.051
Posterior port	13 (26.0%)	9 (18.0%)	0.470
Lateral port	0 (0.0%)	1 (2.0%)	0.999
Medial port	2 (4.0%)	–	–
Left-side electrodes			
Central port	19 (38.0%)	39 (78.0%)	**< 0.001**
Anterior port	10 (20.0%)	2 (4.0%)	**0.028**
Posterior port	14 (28.0%)	6 (12.0%)	0.078
Lateral port	5 (10.0%)	3 (6.0%)	0.715
Medial port	2 (4.0%)	–	–

trajectories in 7 patients (14%). In Group 2, the final electrodes were implanted in symmetrical positions in 35 patients (70%), and bilateral central trajectories prevailed (31 patients, 62%).

■ DISCUSSION

The difference between the anatomically defined target for DBS electrode implantation and the position of the final electrode after electrophysiological monitoring is an important issue in stereotactic neurosurgery with many potential responsible factors. Brain shift, imaging technique limitations, MRI image distortion, individual experience in target planning, anatomical anomalies of the target structure, interpretation of microrecording results, and technical aspects of stereotactic surgery, including surgical errors and mechanical inaccuracies of the operating system, are the most frequently mentioned (1,6,22,30).

The potential mechanism of brain shift affecting the final electrode position is complex. According to Miyagi et al., intracranial air entry after dural opening for the implantation of the first electrode results in contralateral and dorsal (posterior) brain shift. After a durotomy for the implantation of the second electrode, the equilibrium is established in a mediolateral direction because of air entry from the second side. However, together with this mediolateral equilibration, a significant dorsal (posterior) brain shift occurs (14). According to this mechanism, the effect of brain shift, particularly in a posterior direction, should be more prominent on the second side implanted. Assuming that brain shift is the main cause of anatomo-electrophysiological discrepancy, the percentage of anatomical trajectories should be higher on the side implanted first. This was only partially confirmed by Bour et al., who described a non-significant trend towards a less frequent choice for the central electrode on the second side implanted (5). Sadeghi et al. found the necessity to adjust electrode positions in only 26.7% of electrodes on the first side implanted and in 50% of electrodes on the second side (23). In a paper published by Amirnovin et al., the frequencies of central- anatomical electrode trajectories were 39% on the first side implanted (left) and 42% on the second side implanted (right)(2). Although our results confirmed a higher percentage of central electrodes on the first side implanted (right) in Group 1 (right 52%, left 38%), the difference is not statistically significant. In Group 2, the percentages of central electrodes on the right (76%) and left sides (78%) were almost equal.

Another result raising doubts about the dominant role of brain shift is the percentage of posterior electrodes. Taking into consideration the brain movements caused by intracranial air entry during bilateral implantation of DBS electrodes, more frequent posterior electrode trajectories resulting from posterior brain shift could be expected on the second side operated on. However, according to Sadeghi et al., there was a tendency for the second implanted electrode to be more anterior and lateral on the mediolateral and anteroposterior axis than the anatomical target (23). Our study did not confirm a higher percentage of posterior electrodes on the second side operated on in either Group 1 or 2. Taken together, the results do not confirm a dominant role of brain shift as a decisive factor responsible for the anatomo-electrophysiological difference.

The higher percentage of anterior electrodes on the left side in Group 1 compared with Group 2 should be noted. If the technique of intracranial air entry avoidance during electrode implantation improves with experience, it is logical to anticipate more prominent brain shifts in the early cases, resulting in a lower percentage of anterior trajectories. This is contrary to the actual results achieved. Therefore, factors other than brain shift should be sought that are responsible for the anatomo-electrophysiological difference.

The role of improving anatomical planning, potentially resulting in the better definition of anatomical targets, is illustrated in papers by Temel et al. (29) and Kocabicak and Temel (11). In the first paper, the STN targeting technique was based on the atlas coordinates and the predefined target was refined by intraoperative monitoring. The central-anatomical trajectory was used for the final electrode implantation in only about one third of the patients (29). When the coordinates were individually refined after T2-weighted MRI, the final electrode was implanted along the central trajectory in two thirds of the patients (11). Although in our study, the improvement in the percentage of central trajectories between Groups 1 and 2 (52% to 76% on the right side and 38% to 78% on the left side) as well as in the percentage of electrodes implanted symmetrically in central trajectories (Group 1 at 14% and Group 2 at 62%) is significant, it is important to emphasize that neuroradiological planning did not change substantially during the study period. The combination of direct STN visualization on T2W FAT SAT MRI in the axial and coronal planes and indirect targeting (relationship of STN to AC-PC line and stereotactic atlases) in cooperation with experienced neuroradiologists was used in both groups. The increasing experience with target planning (learning curve) was undoubtedly influenced by feedback from the microrecordings and the correlation of this feedback with anatomical targeting.

Another problem is the anatomical variability of STN size and orientation confirmed on high resolution MRI resulting in significant differences between left and right sided x and y coordinates (18). Although it can be argued that abnormal STN location should be recognizable during presurgical planning, the variability in STN signal intensity caused by the inhomogeneous distribution of iron responsible for STN hypointensity on T2-weighted and T1-weighted Inversion Recovery MRI and also associated with age make the delineation of the target area more difficult. Moreover, the boundary of the hypointense substantia nigra located caudally to the STN may not be easily detectable (25). The exceptional occurrence of some important variations of the STN (anteromedially displaced STN with a 1% incidence) combined with unfamiliarity with them also weakens the proposition about the unequivocal recognition of the STN during planning (21).

The average age and duration of late motor complications were comparable in Groups 1 and 2, but the history of Parkinson's disease was longer in Group 1. However, according to a study published by our group, the percentage of anatomical electrodes is not influenced by age, Parkinson's disease or late motor complication duration (7). The shortening of the duration of Parkinson's disease before surgery may reflect the ongoing development of the candidate selection process, leading to a decrease in disease duration at the time of the operation, as reflected by EARLYSTIM study results (27).

Another important point is the relationship between the STN borders defined by anatomical and microelectrode recordings. A paper published by Schlaier et al. showed that microrecordings-defined STN borders exceeded the STN signal area on MRI (26).

When comparing the correlation between anatomical and final targets between the first and second side operated on, the correlation was better on the first operated side in Group 1 according to the percentage of anatomical electrodes. The role of increased brain shift for this worsening discrepancy was not confirmed by our results, but a paper by Sadeghi et al. indicated a decreasing quality of intraoperative monitoring on the second side operated on caused by fading cooperation with the patient during lengthy surgery as a potentially responsible factor causing anatomo-clinical differences (23). However, decreasing percentage of anatomical trajectories on the second side operated on was not confirmed in our Group 2. Therefore, the experience gained in surgical technique as well as in intraoperative monitoring performance and interpretation should be considered responsible for the improving anatomo-electrophysiological correlation. Despite this learning curve, even in Group 2, 38% of the patients had at least one electrode implanted somewhere other than the central trajectory, supporting the need for intraoperative electrophysiology.

The impact of the use of intraoperative electrophysiology on the post-DBS clinical outcome is less clear, because the treatment outcome does not depend only on the precise implantation of the stimulating electrode into a well-defined target structure, but also on other factors unrelated to the surgery, including the selection of the patients. Some studies present better clinical outcomes in patients with microelectrode recordings (6,20), but others do not (16,17).

The abandonment of the medial microelectrode in Group 2 may be considered a drawback of our study, but this fact was considered during the statistical analysis of the results. Although the study may appear to be retrospective, it analyzes prospectively collected data. Despite the long study period, all the surgeries were performed in a standardized fashion by the same surgeon and the intraoperative microrecordings and stimulation were performed by one of two movement disorder experts.

■ CONCLUSION

The correlation between the anatomically planned trajectory and final trajectory after intraoperative electrophysiology significantly improves with the number of patients operated on. The analysis of the right–left differences did not confirm a dominant role of brain shift in this anatomo-electrophysiological discrepancy. The results support the importance of the learning curve for bilateral implantation of subthalamic electrodes; however, despite this improving correlation, the need for intraoperative electrophysiological monitoring is supported by the significant percentage of patients with differing anatomical planning and intraoperative electrophysiological monitoring results.

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