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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - MOVEMENT DISORDERS

MRI-guided DBS of STN under general anesthesia for Parkinson's disease: results and microlesion effect analysis

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Abstract

Background The efficacy of the subthalamic nucleus (STN) stimulation for Parkinson's disease has been widely established. The microlesion effect (MLE) due to deep brain stimulation (DBS) electrode implantation has been reputed to be a good predictor for long-term efficacy of the procedure but its analysis in asleep implantation is still unclear. We thus analyzed MLE rate in our strategy of targeting the STN on MRI under general anesthesia and its correlation with our long-term results.

Method We retrospectively analyzed 32 consecutive parkinsonian patients implanted with a DBS targeting the STN bilaterally under general anesthesia between October 2013 and December 2020. Targeting was performed after head frame and localizer placement using a stereotactic peroperative robotic 3D fluoroscopy (Artis Zeego, Siemens) fused with preoperative CT and MRI data. We collected intraoperative data, postoperative occurrence of MLE, modification of Unified Parkinson Disease Rating Scale item III (UPDRS III) postoperatively and at subsequent visit, as well as reduction of medication.

Results The mean operative time was 223 min. No permanent complication occurred. MLE was observed in 90.7%. The mean follow-up time was 17 months. The UPDRS III for the off medication/on stimulation condition improved by 64.8% from baseline. The mean dose reduction of Prolopa after the surgical procedure was 31.3%.

Conclusions Direct targeting of STN under general anesthesia based on preoperative CT and MRI data fused with a preoperative 3D fluoroscopy is safe. It allows for a high rate of postoperative MLE (90.7%) and results in prolonged clinical improvement.

Keywords Deep brain stimulation · STN · General anesthesia · Parkinson's disease · Microlesion effect

Introduction

Stimulation of the subthalamic nucleus (STN) is considered an effective and safe technique in Parkinson's disease (PD) treatment and its interest is beyond debate [7, 18].

Through times, different procedures have been described regarding anesthesia modality, targeting method, use of microelectrode recording (MER), and lead position assessment.

The microlesion effect (MLE) [5] is characterized by a postoperative clinical improvement without stimulation [9] and originates from the microlesion caused by the electrodes on nearby structures. This is thus thought to indirectly assess the adequate placement of the electrode placement within the target [17]. A positive correlation between MLE and symptoms improvement with active stimulation has been reported [1, 9, 17, 24].

In order to assess the accuracy of our implantation protocol using direct MRI targeting of the STN under general anesthesia, we retrospectively analyzed the MLE rate and its correlation to functional outcomes after implantation.

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Method and materials

Patient selection

We retrospectively reviewed all patients suffering from severe PD who underwent bilateral STN-targeted implantation between October 2013 and December 2020. Patients' characteristics are summarized in Table 1. All patients were selected for implantation based on the criteria of our national health organization and after multidisciplinary discussion on the best suited therapeutic strategy (significant dyskinesia or motor fluctuation limiting patient's daily activities despite best medical treatment without major surgical contraindications). We excluded patient with insufficient postoperative data due to lack of follow-up.

Informed consent for participation was obtained from all patients and they were included after clearance of the study protocol by our institutional ethics commitee (Comité d'Ethique Hospitalo-Facultaire de l'Université catholique de Louvain).

Table 1 Demographic characteristics and results in the 32 patients

	N/mean (range)
Age (*y*)	60.8 (36–77)
MLE group	63 (60–67)
No MLE	58 (36–77)
Sex ratio (M/F)	2.2/1
Duration of disease (*y*)	11 (4–28)
MLE group	11
No MLE	9
Preoperative UPDRS III (Mean)	
Med on	13.3
Med off	37.9
MLE group	38
No MLE	36
Postoperative UPDRS III (Mean)	
Med on ($N = 25$)	7.9
Med off ($N = 32$)	11.4
MLE group	10.4
No MLE	21
UPDRS III off med vs. on stim/off med reduction ($N = 32$)	%
Total	− 65
MLE group	− 68
No MLE	− 38
Subjective on med vs. on stim and med improvement	− 64.4
Levodopa daily dose reduction	− 31.3
Operative complications (*N*)	
Infections	2
Confusion/hallucinations	1
Side effects (*N*)	
Dysarthria	6
Dyskinesia	2
Gait disorders	1

The mean Unified Parkinson's Disease Rating Scale part III (UPDRS III) improved by 54% in the on medication/on stimulation condition and by 64.8% in the off med/on stim condition 64.8% from baseline. The mean improvement from baseline in UPDRS III was 68% for the patients who had presented a microlesion effect (MLE) and 38% in the group without MLE. N, number

Implantation and stimulation protocol

The same implantation protocol was applied for every patient (Fig. 1). Preoperative neuroimaging is performed at least 1 week before surgery on a 3 T MR system, under general anesthesia to limit motion-artifact, using a standardized protocol including 3D T2 and contrast-enhanced 3D T1 acquisitions. On the day of surgery, antiparkinsonian drugs are withdrawn. The procedure is carried out under general anesthesia in a similar way as described in a previous study by our group [4]. The STN targeting is based on a preoperative CT for skull identification and peroperative MRI for anatomical identification fused with the preoperative CT ($n = 24$) or robotic 3D fluoroscopy ($n = 8$) (Artis Zeego) performed with the localizer fixed on the patient (fusion and planification: Integra and Stealth S8 Station (Medtronic®, USA)).

The DBS electrodes (Model 3389 Medtronic) are implanted on both sides and lead positioning is then assessed using a new peroperative imaging using a peroperative 3D fluoroscopy, fused with the preoperative MR examination. If the localization is deemed correct, the internal pulse generator (IPG) (Activa/Percept PC, Medtronic) is implanted in the same session.

Postoperatively, anti-parkinsonian drugs are discontinued until the day following stimulation initiation. Stimulation is only started when the MLE, if present, disappears. In case of absence of MLE, patients are stimulated on postoperative day 2. The stimulation contacts yielding the best clinical response without side effects (paresthesia, dizziness, …) are selected, and the stimulation parameters are started with a frequency of 130 Hz and a wave length of 60 µs. The parameters are then progressively increased to the maximal amplitude allowing for the best clinical response without side effects. The anti-parkinsonian drugs are usually reduced based on clinical response.

Data collection

We reviewed the electronic charts of patient to retrieve and derive data.

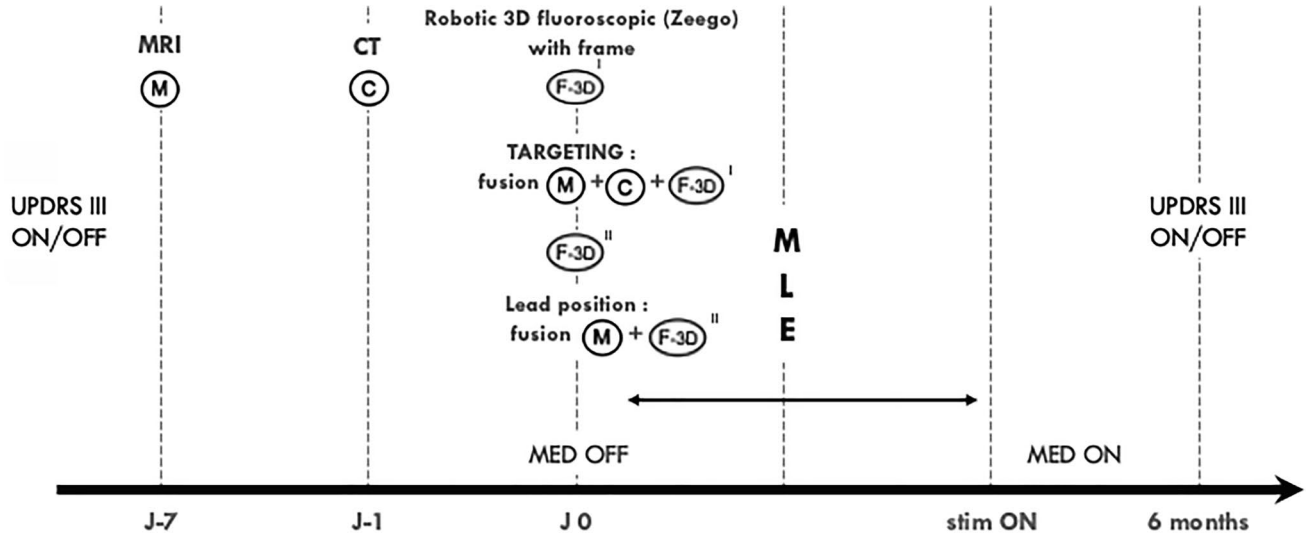

Fig. 1 Current schematic workflow of the implantation process in our institution: a baseline clinical evaluation was performed preoperatively based on the UPDRS III in on/off medication conditions. A 3 T MRI was performed 1 week before surgery and a CT the day before. On the day of surgery, under general anesthesia, a peroperative robotic 3D fluoroscopy (F-3D'; $N=8$) was performed after stereotactic frame placement. The subthalamic nucleus targeting was based on fusion of preoperative CT, MRI, and peroperative fluoroscopy fusion using the anterior and posterior commissures line (AC-PC) and anatomical landmarks. The DBS electrodes were implanted and the lead position was assessed after a new peroperative robotic 3D fluoroscope (F-3D") fused with the preoperative MRI for anatomical analysis. After confirmation of the anatomically correct position, lead extensions and the internal pulse generator were implanted. The microlesion effect (MLE) was assessed by a clinical evaluation postoperatively. After MLE dissipation and reappearance of the symptoms, the stimulation was started. The antiparkinsonian medication was withdrawn the day of the surgery until the MLE dissipation

Baseline clinical status score was evaluated by the preoperative UPDRS-III in on and off medication condition. Intraoperative characteristics (duration of procedure, adverse events) were collected as well as occurrence of postoperative adverse events during follow-up.

Occurrence and duration of MLE were assessed by the neurosurgical team during daily ward evaluation. Quantification of the MLE was not available. MLE was considered significant as long as the postoperative motor evaluation (tremor, akinesia, rigidity, dyskinesia) of the patient without stimulation and medication was better than the preoperative on medication motor evaluation.

The postoperative UPDRS III in an on stimulation/off medication, occurrence of adverse events, and reduction of levodopa were also analyzed based on patient's charts at 6 months postoperatively. If follow-up at 6 months was unavailable, the next available follow-up was used.

Statistical analysis

All statistical analyses were conducted in R v. 3.4.1 and X Quartz v. 2.7.11 (The X Window System). Shapiro–Wilk normality tests were used. Simple linear regressions (one-way ANOVA) were performed to estimate the association between quantitative variables. The quality of the statistical models was evaluated using the R^2 value. A p-value ≤ 0.05 was considered statistically significant.

Results

Forty-eight patients were implanted for bilateral STN DBS during the study period. We excluded 2 patients who died from unrelated cause: one patient presented an acute cardiorespiratory arrest after an alimentary choking 4 months after surgery and one patient suffered from a community acquired pneumonia 5 months after surgery. For the second patient, withdrawal of care was decided between the family, the patient, and caregivers. None of this patient had complication or side effects related to the DBS procedure reported at time of death. We further excluded 14 patients with incomplete data. We thus included 32 patients (22 males and 10 females) with 13 patients evaluated at 6 months postoperatively and 19 patients evaluated later than 6 months. Mean follow-up was 17 months (range: 6–50 months).

The flowchart is shown in Fig. 2.

Postoperatively, a MLE was observed in 90.7% of patients and lasted on average 2.6 days (range 1–8). The baseline

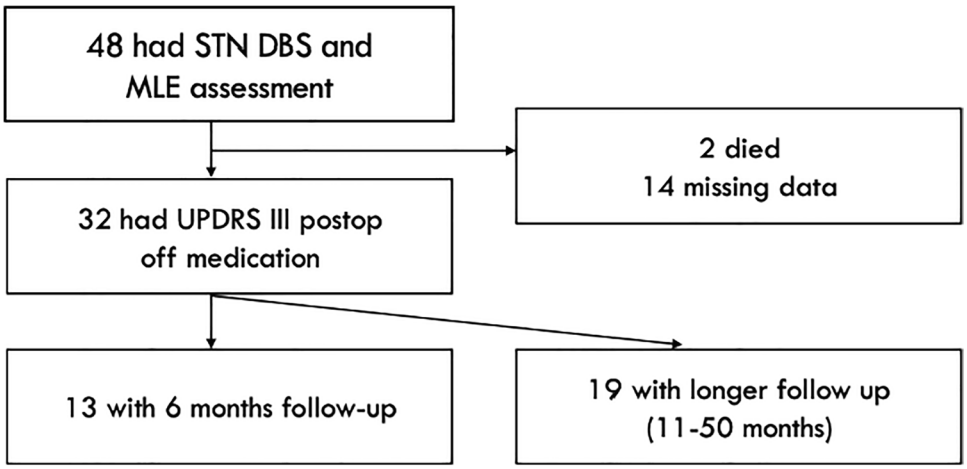

Fig. 2 Study flowchart. STN, subthalamic nucleus; DBS, deep brain stimulation; MLE, microlesion effect; UPDRS III, Unified Parkinson's Disease Rating Scale part III

characteristics between the MLE group and no-MLE group were comparable but statistical comparison between the 2 groups was not possible due to the small sample size ($n=3$ in no-MLE group). The mean age was 63 in the MLE group and 58 in the no-MLE group. The mean preoperative UPDRS III score on medication was 13.7 ± 8.19 and that off medication was 41.1 ± 14.3. The mean preoperative levodopa dose was 956 mg daily (range: 350–2250). The mean duration of disease was 11 in the MLE group and 9 years in the no-MLE group. The demographic data are summarized in Table 1.

The mean operative time was 223 min from frame placement to skin closure after IPG implantation and 151 min starting from frame placement to skin closure after the second 3D fluoroscopy done to analyze leads position before IPG implantation.

Two electrodes (in 2 patients, 1 per patient) had to be repositioned intraoperatively after unsatisfactory lead placement on the fused fluoroscopy check.

No permanent and/or serious complication occurred. One patient presented one episode of confusion. Two patients developed an IPG infection respectively at 2 and 5 years after the DBS procedure. The first patient was treated in another center and we do not have further information. The second patient had a wound dehiscence at 4 months after IPG replacement, the complete DBS was removed, and he received antibiotic treatment. Reimplantation was performed 6 months later.

No complication occurred in the group without MLE. Side effects of the stimulation were reported in 8 patients: dysarthria in 6 patients, dyskinesia deterioration in 1 patient, and gait disorders in 1 patient.

The mean UPDRS III on stimulation and off medication improved by 64.8% (±32.1) from baseline (mean score: 42.2 points preoperatively vs. 11.2 at follow-up). Patients reported subjective improvement in 62% at follow-up (Fig. 3). A mean dose reduction of levodopa of 31.3% was achieved.

The mean UPDRS III on stimulation/on medication was available for only 25 patients and improved by 42.7%.

In the MLE group, the UPDRS III improvement was 68% compared with only 38% improvement in the no-MLE group (Fig. 4). Conversely, there was no significant correlation between MLE duration and the UPDRS III improvement.

Those results are displayed and summarized in Table 1 and Fig. 4.

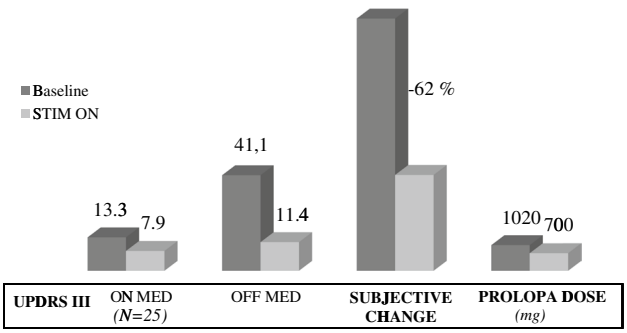

Fig. 3 Mean response to STN DBS for Parkinson's disease. Column graph showing improvement after DBS implantation: the mean UPDRS III in the on medication/on stimulation condition improved by 42.7%. The mean UPDRS III in the off medication/on stimulation condition improved by 64.8%. According to patients, the symptoms were subjectively improved by 62% and the mean reduction of Prolopa doses was 31.3%

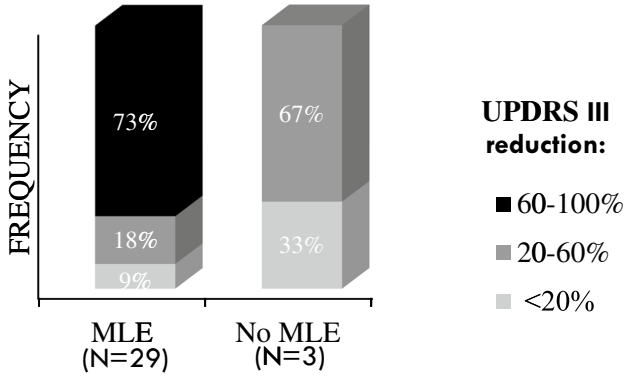

Fig. 4 UPDRS III change from baseline (off medication state) in the MLE vs. no-MLE groups. Comparison of improvement between MLE and no-MLE patients: using the UPDRS III among the patients with MLE: 73% had a reduction of 60–100% of symptoms, 18% had a reduction of 20–60%, and 9% had a reduction of less than 20%. In comparison, patients without MLE had a UPDRS III reduction of 60–100% in only 67% of cases (2 patients) and in 33% of cases (1 patient) a reduction of less than 20%

Discussion

We retrospectively analyzed the MLE in 32 patients implanted under general anesthesia with a STN DBS for PD. Regarding functional outcome, our cohort had a mean improvement in UPDRS-III on stimulation/off medication of 64.8%, which is greater than the usual reported range between 37 and 51% in other studies (Table 2) [9, 18, 19, 21, 25, 26]. When evaluated at 6 months, patients presented with a 68% improvement of UPDRS III. For patient evaluated later than 6 months ($n = 19$, mean evaluation at 24.6 months, range 11–50 months), the mean reduction of UPDRS III was 65% suggesting persisting efficacy. We could suspect that these results are related to a more accurate positioning due to our protocol using direct targeting. This is further supported by the fact that 90.7% of patients presented a MLE.

Indeed, MLE has frequently been linked in the literature with functional outcome [1, 4, 11, 14, 17]. The suspected mechanisms are micro hemorrhages, local edema [1, 11], and leakage of neurotransmitters inactivating neurons surrounding the electrode [2, 13]. The transient damage of STN and vicinity connections obviously contributes to the MLE [24] and explains why its occurrence is usually correlated with an accurate location and subsequently a significant functional outcome. An unresolved question is the relation between MLE, micro-electrodes insertion, and definite electrode insertion. Interestingly, the peroperative MER fails to reveal a correlation with MLE in the literature [17]. Usually, the rate of MLE reaches 21 to 46% using MER [9, 17, 24], in contrast with the 90.7% that we have achieved in our cohort, even though this percentage needs to be tampered by the fact that no quantitative analysis of MLE was available, which can induce an overestimation of MLE percentage. We can thus hypothesize that the insertion of MER does not induce MLE but that the reactions needed to induce an MLE only occur with definite electrodes (when in the accurate location). Unfortunately, our study could not show any correlation between the electrode position at target and MLE due to our small sample of patient without MLE. When looking at individual positioning, no clear difference was visible (Fig. 5), it would be interesting to further evaluate this aspect systematically in another study. Cerosismo et al. [11] further demonstrated that postoperative duration of MLE was associated with better postoperative improvement in the off condition. Our data failed to demonstrate the same correlation.

Even though MLE is usually a good prognosis factor for postoperative reduction of symptoms, some patients show poor response despite MLE. According to literature [3, 23], this can be explained by older age, weak preoperative levodopa responsiveness, and dominance of axial symptoms. In our MLE group, 2 patients had a poor response (UPDRS-III improvement < 20%) but they were young (age 41 and 60) and had no dominance of axial symptoms. One patient had a weak preoperative levodopa responsiveness. This underscores the need of further understanding the link of MLE with stimulation outcome.

The mean reported operative time with MER in reported studies was 279.8 min (without anesthesia and IPG implantation) [8, 15, 20] strongly contrasting with only 151 min in the present study. The reduction in operative time results in a decreased risk of infection [22]. Besides, the use of fewer intraparenchymatous trajectories also decreases infection rate [10] as well as the risks of hemorrhage [6, 12, 16]. All those benefits advocate, in our opinion, for a direct anatomical targeting which can further be done in general anesthesia to increase the patient's as well as the surgeon's comfort.

The main limitation of the study is, as stated earlier, the inherent bias related to the retrospective nature of our study which leads to lack of quantitative scale for MLE assessment, significant variability between patient evaluation, and significant loss of data in 1/3 of patient.

Conclusions

We reviewed 32 PD patients implanted under general anesthesia for a STN DBS and analyzed the association of MLE with clinical outcome based on the UPDRS III. We confirm that the MLE is a good predictor of efficiency with 68% of UPDRS improvement in the MLE group as compared with only 38% of improvement in the group without MLE. Direct targeting of STN under general anesthesia based on the fusion of preoperative CT and MRI with a preoperative CT scan or 3D fluoroscopy is a safe, time-saving, and efficient technique achieving a rate of 90.7% postoperative MLE.

Table 2 UPDRS III change from baseline, adverse events in DBS STN studies

Study	Characteristics	Follow up (months)	N[1]	UPDRS[2] III reduction (%)		Medication decrease (%)	Adverse event (%)					
							Cerebral hematoma	Infection	Psychiatric disorder	Dysarthria	Dyskinesia	Gait disorder
Deuschl et al. 2006 NEJM [5]	Randomized-pair trial Awake surgery	6	156	Off On	41 23	49	4	3	10	10	26	NDA
Williams et al. 2010 The Lancet [26]	Prospective multicenter RCT No data about surg technique	12	366	Off On	22 12	34	2	9	4	NDA	NDA	NDA
Okun et al. 2012 Lancet [18]	Prospective multicenter RCT Awake surgery	3	136	Off On	37 17	34	6	6	18	9	5	6
Schuepbach et al. 2013 NEJM [21]	Prospective multicenter RCT[3] Awake surgery	24	124	Off On	53 26	39	NDA	NDA	39	NDA	15	14
Vitek et al. 2020 [25] Lancet	Prospective multicenter double-blind sham controlled RCT Awake surgery	12	196	Off On	51 24	NDA	NDA	NDA	4	NDA	17	20
Saint-Luc, current data	Bilateral STN DBS; not awake Intraop fluoroscopy	17 ± 13.5	32 25	Off On	65 43	31.3	0	6	0	18.8	6.6	3.1

[1] N numbers of patients; [2]Unified Parkinson's Disease Rating Scale part III; [3]randomized controlled trial; NDA, no data available

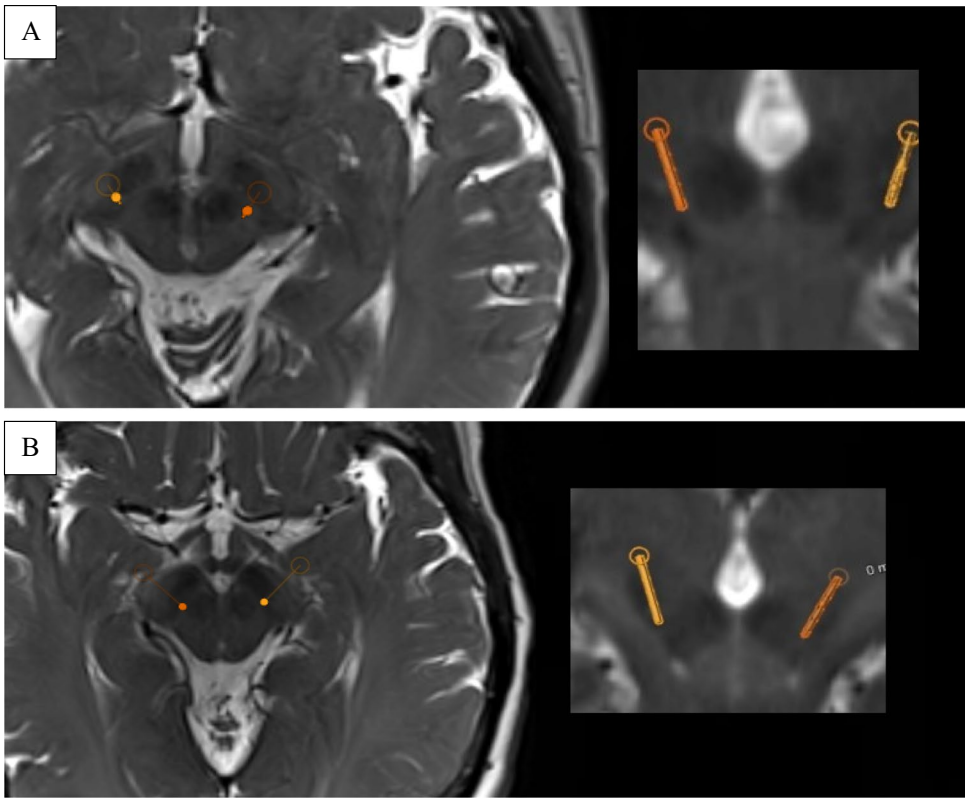

Fig. 5 Electrode location in MLE vs. no-MLE patients. Axial and coronal preoperative MRI-postoperative fluoroscopy fusion at the level of the STN target showing location of a typical electrode in a patient who had MLE (**A**) and one who had not (**B**). We did not find a clear discrepancy

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Local Ethics Committee (Comité d'Ethique Hospitalo-Facultaire de l'Université catholique de Louvain, CE B 403) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all patients included into the study.

Conflict of interest The authors declare no competing interests.

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