Original research article

Intracerebral electroencephalography in targeting anterior thalamic nucleus for deep brain stimulation in refractory epilepsy

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ABSTRACT

Background: Results of DBS of ATN in refractory epilepsy depend on accuracy of the electrode's location. We searched for characteristic intraoperative, intracerebral EEG recording pattern from anterior thalamic nuclei (ATNs) as a biological marker for verifying the electrode's position.

Methods: There were six patients with refractory epilepsy scheduled for deep brain stimulation (DBS) procedure. At surgery, to map the target, we recorded EEG from each lead of DBS electrodes. One patient underwent a 24 hours EEG with continuous recording from both ATNs before internalization of stimulator units.

Results: In all patients we recorded spontaneous bioelectric activity of ATNs. The pattern of the recording from the ATN was similar in all cases. In the one patient where 24-hour recording was done with simultaneous scalp EEG, a complex partial seizure was captured.

Conclusion: This is the first report of using DBS electrode for intraoperative EEG recordings from the ATN in patients with refractory epilepsy. Since we managed to find the characteristic pattern of bioelectric activity of ATN, this technique seems to be a promising method for targeting this structure during the operation.

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1. Introduction

Since its introduction deep brain stimulation (DBS) has been successfully used in movement disorders [1] and in neuropsychiatry [2]. Essentially, DBS inhibits pathologic network activity of a chosen brain region in a reversible way without damaging brain tissue [3]. Thus, although it provides no cure, it lessens the symptoms and improves quality of life. A list of DBS targets in refractory epilepsy includes cerebellum [4–6], subthalamic nucleus [7,8], hippocampus [9,10], basal ganglia and various thalamic nuclei [11,12], however, so far no optimal target suitable for the majority of the patients has been defined. In recent years, a controlled multicentre trial SANTE was published, showing very promising results of the bilateral ATN stimulation [13,14]. The candidates recruit out of those

with refractory partial seizures, including secondarily generalised seizures, in whom the epileptic focus cannot be localised, or it is located in an eloquent brain area, or else if there are multiple epileptic foci. ATN stimulation was also used in patients after failed resective epilepsy surgery. Efficacy of the procedure primarily depends upon the choice of the target and precision of positioning the electrodes. However, all currently employed methods of localising the ATN are subject to bias. The aim of our study was to find the characteristic intraoperative, intracerebral EEG recording pattern from the ATN, which could be used as a biological marker for verifying accuracy of the electrode's position. Understandably, finding of such a marker could improve on precision of the electrode placement and efficacy of the stimulation which would translate into better operative results. Another goal was to assess the influence of the intraoperative high-frequency bipolar ANT stimulation on bioelectric activity of the both ATNs and of the cerebral cortex, the latter visible on the surface EEG recording.

2. Materials and methods

The study plan was approved by the Ethical Committee. All patients have given their informed consent for participation in the research study. There were six patients with refractory epilepsy scheduled for DBS procedure. Before surgery, in attempt to localise the ictal onset zone, we performed an MRI scanning and long-term video-EEG (LTM), which lasted 72 h. Clinical features of the patients are summarised in Table 1. In each patient the DBS electrodes (Medtronic model 3387 or 3389) were implanted streotactically (Stryker–Leibinger stereotactic frame) to both ATNs. The target and trajectory were chosen individually basing on typical MRI landmarks. Surgical plan was performed using Brainlab software. The surgical target was chosen 5–6 mm lateral, 12 mm superior and up to 2 mm anterior to midcomissural point (MCP). The target was verified taking into account individual anatomy of the mamillo-thalamic tract, which was considered as a landmark. The trajectory was planned to avoid major vascular structures seen in contrast enhanced T1-weighted MR images. All

procedures were carried out under general anaesthesia – TIVA (total intravenous anaesthesia: midazolam 0.1–0.4 mg on induction and propofol 6–12 mg per 1 kg per hour along with fentanyl 0.05 mg/10 kg throughout the procedure). In every patient we recorded an intracerebral EEG (Grass Technologies, USA) directly from the DBS electrodes (separately from each lead for at least 30 min on each side) placed in the ATNs and simultaneously we performed a scalp EEG with gold-cup electrodes placed at points Fp1, Fp2, F7, F8, T3, T4, T5, T6, O1, O2 according to the international 10–20 system. The other surface EEG electrodes, which would have to be placed in the operating field, thus incommoding the surgeon, were not used. For the scalp EEG recording the conventional referential montage was used. The location of the leads in the ATN was confirmed by means of single-unit microelectrode recordings (MER) – (LeadPoint, Medtronic). Then, in all the patients we performed high-frequency bipolar stimulation of the ATN with the implanted DBS electrode (two adjacent contacts, 1–5 V, 90 µsek, 145 Hz; the stimulation pattern was: 2 cycles of 3 min on – 2 min off) whilst assessing influence of the stimulation on the recording from the ipsilateral and opposite ATN as well as on the scalp EEG. Moreover, before internalisation of the stimulator units and tunnelling the electrode and extension wires, one patients underwent a 24 h surface EEG monitoring with continuous intracerebral recording from both ATNs (taken from each lead of the implanted DBS electrodes). After surgery, the electrodes position was verified on the postoperative thin slice CT fused with the preoperative MR images [15].

The clinical results were assessed at 3 months intervals on follow-up out-patient clinic. The total follow-up period was from 18 to 24 months. Reduction of 40–50% in the frequency of the seizures was noted in all cases. The detailed dates were given in Table 2. However, side effects were also observed: depression in 3 cases and memory impairment in 5 patients.

3. Results

MER turned out to be useful and confirmed the correct position of the ATN electrodes in every case (Fig. 1). The intracerebral

Table 1 – Clinical data.						
Patient	Sex	Age	Years with epilepsy	Previous epilepsy surgery	MRI	Seizure onset zone
1	F	59	43	Left temporal lobectomy, VNS	Left temporal lobe resected. A small hypointense lesion in the right leticular nucleus.	Multifocal
2	M	43	12	Anterior callosotomy	CVM in the left temporal lobe. Ischaemic changes in the right frontal lobe	Multifocal
3	M	51	45	–	A small hyperintensive lesion in the left hippocampus (a vascular malformation?), DVM in the right occipital lobe.	MTLE R
4	M	34	29	Left temporal lobectomy	Thickening of dura in the region of the operation for cerebral abscess.	Left fronto-temporal
5	F	38	14	–	Right temporal and occipital heterotopia	Multifocal
6	M	39	38	–	Normal	Bi temporal
CVM = cavernous venous malformation, DVM = developmental venous malformation, MTLE R = mesial temporal lobe epilepsy right side, VNS = vagal nerve stimulator.						

Table 2 – Assessment of seizure severity after ATN-DBS surgery in the Engel outcome scale [16].						
Time after ATN-DBS surgery (months)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
3	II B	III A	II B	II A	III A	II A
6	II A	III A	II B	II B	III A	II B
9	II D	III A	III A	II B	III A	III A
12	II D	III A	III A	II D	III A	III A
15	III A	II D	II C	II D	III A	II B
18	III A	II D	II C	II D	III A	II B
21	–	III A	II B	II D	III A	–
24	–	III A	–	II D	–	–
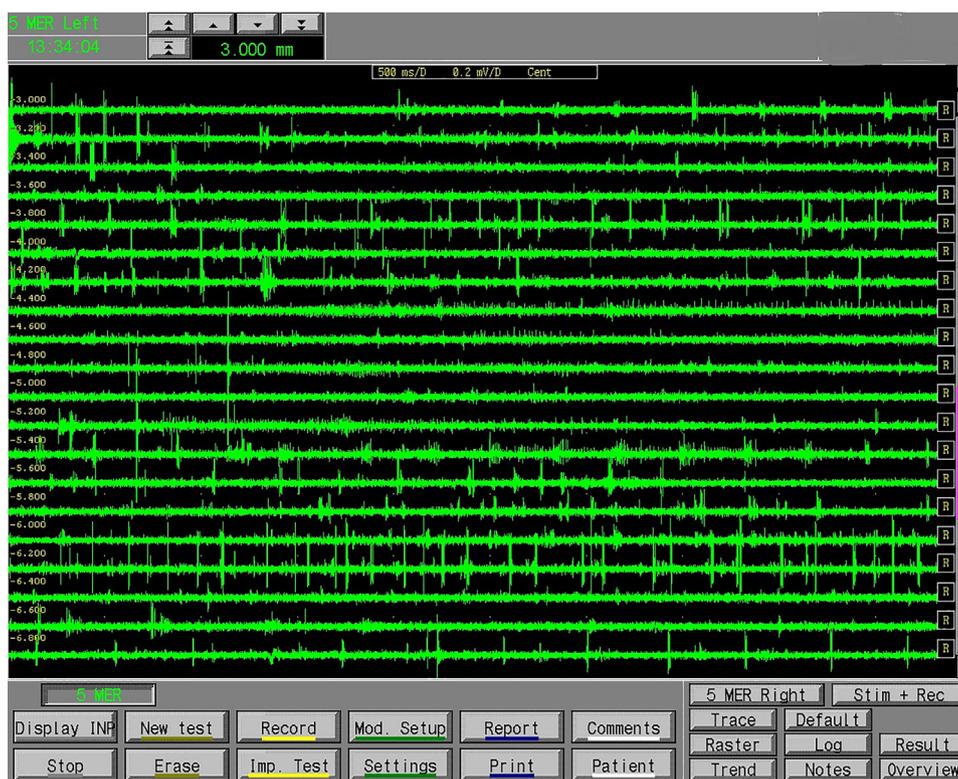
Fig. 1 – Intraoperative MER recordings for the accurate target localisation.

recording from DBS electrodes placed in both ATNs (SEEG with DBS leads) was performed in every patient. In all the cases it showed spontaneous local field discharges. The activity was present in both ATNs in three cases, whilst in the other three patients it was seen on one side only and it was always the side of seizure origin. Interestingly, in two of these patients the epileptiform discharges were simultaneously recorded on the scalp EEG. The pattern of the recording from the ATN was similar in all the patients, i.e. on the background monomorfic activity of 5–7 Hz, there were bursts of rhythmic delta activity lasting 2–3 s, usually followed by repetitive sharp waves at 5 Hz or spike and slow wave complexes (Fig. 2). If this activity was present in both ATNs, the discharges were not synchronous, but in some instances groups of sharp waves and spikes propagated to the surface EEG (Fig. 3). During the operation external high frequency bipolar stimulation with the DBS electrode was performed. Simultaneous recording from the leads which were not currently used for the stimulation showed an oscillatory pattern as the stimulus artefact whilst there were no changes either on the scalp EEG or on the other

deep contacts of the electrode placed at the contralateral ATN (Fig. 4). No adverse effects of the stimulation were observed.

The continuous 24 h video-EEG monitoring with simultaneous recording of intracerebral activity from DBS-ATN leads, carried out in one of our patients before implantation of the stimulator unit, showed repetitive, lasting 2–3 s, bilateral rhythmic sharp and slow waves at the DBS leads with no changes on the surface EEG and with no clinical manifestation. However, we observed one instance when the intracerebral epileptiform activity lasted up 20 s and then appeared also at the surface temporal electrodes on the right side and subsequently also in the left temporal region. At this point of time the patient lost contact with motionless staring and chewing.

4. Discussion

A two to five-year follow-up study of the patients with refractory epilepsy who underwent bilateral DBS procedure
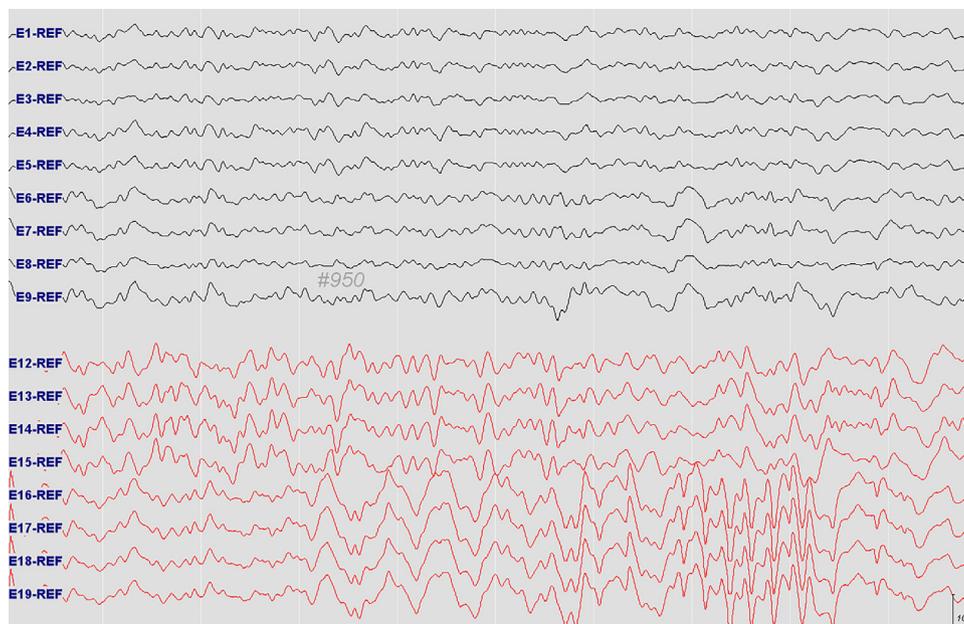
Fig. 2 – Intraoperative bioelectric activity, recorded simultaneously from ATN-DBS leads and scalp EEG; there were burst of rhythmic delta discharges in the right ATN. E1–E9 scalp EEG respectively: F7, T3, T5, Fp1, F3, F8, T4, T6, Fp2 (10–20 system), referential montage; E12–E15 – the left ATN – leads 0–3, respectively; E16–E19 – the right ATN – leads 0–3, respectively; 1 vertical line = 1 s.
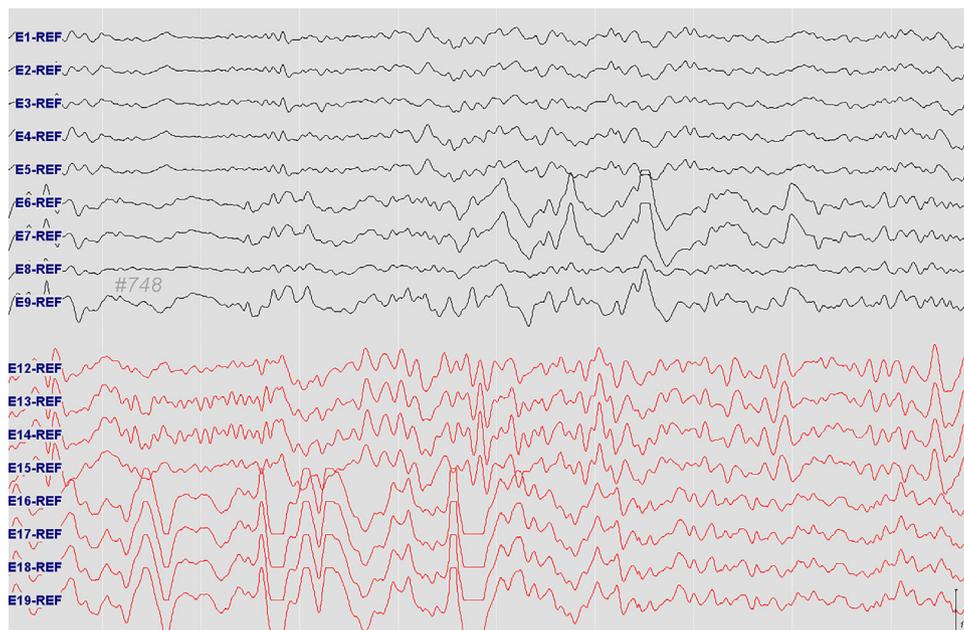

Fig. 3 – Intraoperative bioelectric activity, recorded simultaneously from ATN-DBS leads and scalp EEG; the epileptiform discharges from the right ATN-DBS leads propagated to the scalp EEG (right hemisphere). E1–E9 scalp EEG respectively: F7, T3, T5, Fp1, F3, F8, T4, T6, Fp2 (10–20 system), referential montage; E12–E15 – the left ATN – leads 0–3, respectively; E16–E19 – the right ATN – leads 0–3, respectively; 1 vertical line = 1 s.

showed that stimulation to the ATNs reduces frequency of seizures by 56–69% [14,17,18]. Our results are slightly worse than that which can be explained by the fact that 3 our patients had been already previously operated on as shown in Table 1. ATN seems to be a good target for DBS as it is a part of the Papez circle which is known to take part in generating and propagation of epileptic activity [19,20]. The stimulation to the ATN is thought to influence the superior-mesial frontal cortex and the mesial temporal cortex, both of which are involved in the pathoanatomy of refractory epilepsy [21].
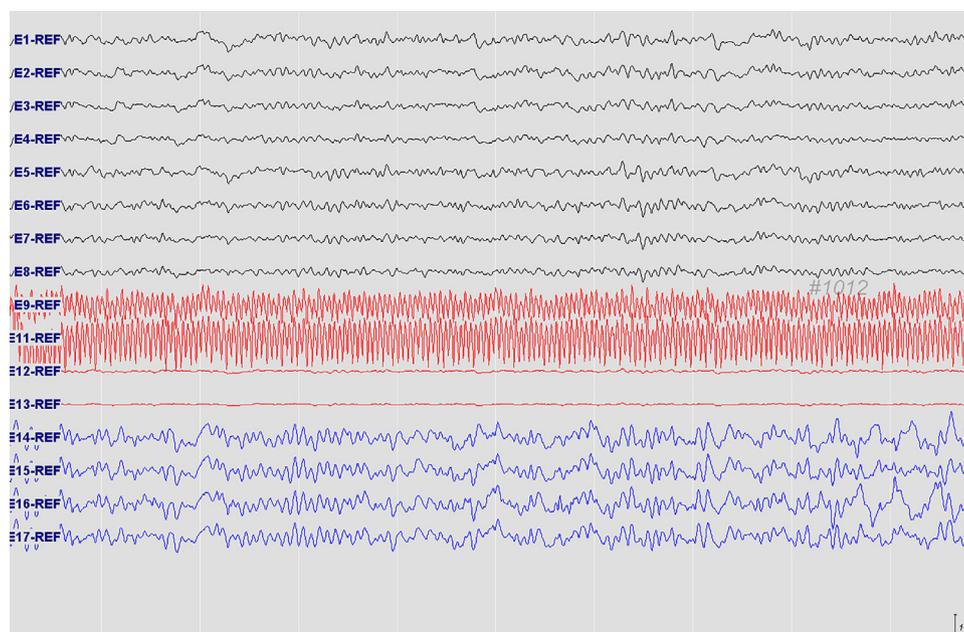
Fig. 4 – Simultaneous recording from ATN-DBS leads and scalp EEG performed during intraoperative bipolar stimulation; the leads which were not currently used for the stimulation showed an oscillatory pattern as the stimulus artefact whilst there were no changes either on the contralateral ATN-DBS leads or on the scalp EEG. External stimulator (5 V, 90usek, 145 Hz), E12 (−), E13 (+); E1–E8 scalp EEG respectively: F7, T3, T5, O1, F8, T4, T6, O2, 10–20 system, referential montage; E9–E13 – the left ATN – leads 0–3, respectively; E14–E17 – the right ATN – leads 0–3, respectively; 1 vertical line = 1 s; the E10 channel was nonfunctional and omitted from the figure.

Although the mechanism of the DBS in epilepsy is poorly understood, it is known that high frequency stimulation blocks epileptic activity in cerebral cortex whereas low frequency DBS synchronises cortical activity [22]. The usual DBS settings used in epilepsy are as follows: 1 min on, 5 min off, frequency 145 Hz, pulse width 90 μs, amplitude 5 V [13]. Understandably, efficacy of the stimulation depends on precision of the implantation of the electrodes. The correct position of the leads is confirmed during the operation by means of MER, particularly if transventricular trajectory was chosen [23] and by low frequency DBS to elicit scalp EEG driving response [24]. However, Byung-chul et al. [25], reported false positive responses with the latter technique. Unfortunately, those methods are not ATN specific, since the responses may originate in other thalamic nuclei, e.g. central medial nucleus of thalamus (CMN) and dorsomedial nucleus of thalamus (DMN). Furthermore, the diameters of the ATN are on average 10 × 5.5 × 4 mm and one observes a high inter- and intra-individual variability of its location (the right ATN is often placed more anteriorly) [26]. This along with a fact that the ATN is surrounded by the third and the lateral ventricles, makes the accurate positioning of the leads quite challenging. In SANTE trial [14], more than 8% of the electrodes were found outside the target. According to some authors, the correct position of the leads should be verified after surgery on 3T MRI scan [26,27], so that if all the leads are shown to be outside the target, the patients could be operated on again. Certain articles, both experimental and clinical, indicated that the optimal target for DBS in epilepsy is only the anterior aspect of the ATN, so that most cranially located leads at the ATN stimulated anteromedial and anterior principal subnuclei [28–31]. In view of this developing an intraoperative technique suitable for confirming the location of the ATN would be of utmost importance. To our best knowledge, this is the first report presenting both intra- and postoperative intracerebral recordings of local field activity from the ATN using the DBS electrode. We managed to show that the DBS electrode after externalisation may be successfully employed for this purpose, providing high quality recording comparable to that obtained from depth and grid electrodes used in invasive LTM performed in patients with refractory epilepsy. Recordings from subcortical structures had been taken many times before, albeit by means of depth electrodes rather than with DBS electrodes [30,32–37]. We are aware of only one paper by Wennberg and Lozano [34] reporting use of DBS electrodes for the ATN recording. This was done simultaneously with scalp EEG, outside operating theatre. We did not find any study on intraoperative DBS-ATN recording. The pattern of the recording from the ATN was similar in all the patients, as characterised in the Results section. If the activity was present in both ATNs, the epileptiform discharges were not synchronous and in some instances propagated to the surface EEG. However, to be sure that the shown activity is specific to the ATN and cannot be observed in the other parts of the thalamus will require to be verify in further studies. In three patients the epileptic discharges were recorded in one ATN only, which obviously raised doubts if the opposite electrode was correctly placed. However, in each case the postoperative CT scan was
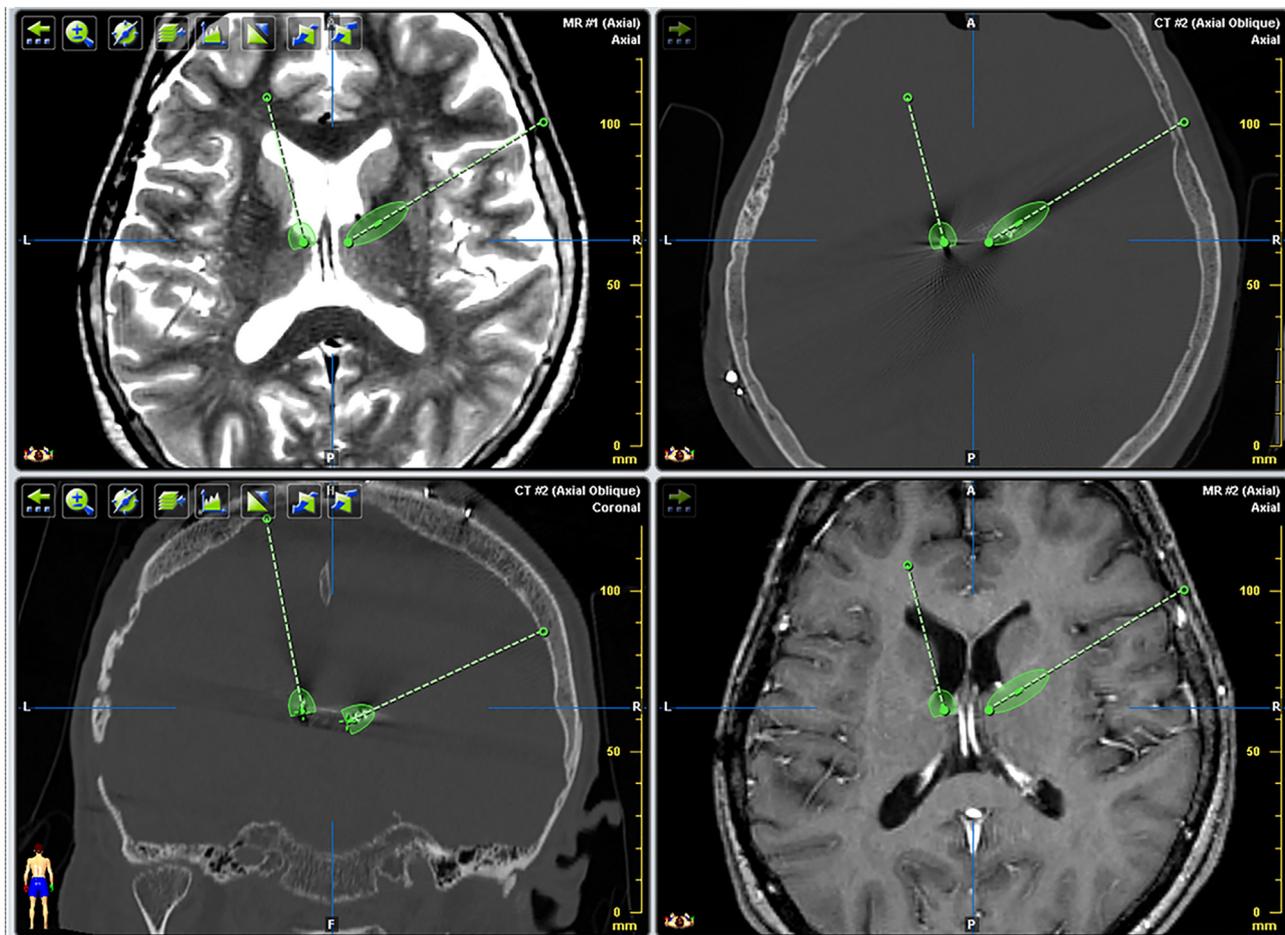
Fig. 5 – The postoperative high definitions CT fused with the preoperative MR images for verifying the correct position of the leads.

done and fused by means of Brainlab software with preoperative MR images used for planning, thus the accurate position of the leads was confirmed in every case (Fig. 5). The patient in whom we recorded an epileptic seizure on the video-EEG, first had synchronous epileptiform discharges in both ATNs, which later spread to the scalp EEG. Probably those discharges spread throughout the ATN from other subcortical structures. To confirm that, one would need a simultaneous recording from various parts of the Papez circuit. Van Gompel et al. [30] recorded evoked potentials from the ATN and the hippocampus but this was not a spontaneous activity and it is actually unclear how the recording was done. In our recordings from ATN-DBS electrodes we found the characteristic EEG pattern which in fact was the same as one shown by Cantero et al. [37] on recordings by depth electrodes from hippocampus during REM sleep. This may suggest that similar bioelectrical activity may be found in different structures of the Papez circuit. We believe that this pattern may be useful for targeting ATN in DBS patients. The presented technique generates no extra costs in terms of material used and the only disadvantage is that it is time consuming and thus it may e.g. increase the costs of anaesthesia.

Obviously enough, our sample is small and heterogeneous, hence the efficacy of the procedure cannot be confirmed and the MR remains as gold standard for the correct lead position.

Our report is rather to inform about our experience with a new technique which needs further investigation.

Conflict of interest

None declared.

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