Anterior thalamic deep brain stimulation in refractory epilepsy: a randomized, double-blinded study.

Helle Herrman^{1,2,3}, Arild Egge⁴, Ane E. Konglund⁴, Jon Ramm-Pettersen⁵, Espen Dietrichs^{1,3}, Erik Taubøll^{1,3}

¹Department of Neurology, Oslo University Hospital – Rikshospitalet, Oslo, Norway

² National Center for Epilepsy, Oslo University Hospital, Oslo, Norway

³Faculty of Medicine, University of Oslo, Norway.

⁴Department of Neurosurgery, Oslo University Hospital – Rikshospitalet, Oslo, Norway

⁵Department of Neurosurgery, Oslo University Hospital – Ullevål, Oslo, Norway

Corresponding author:

Helle Herrman

Department of Neurology

Oslo University Hospital – Rikshospitalet

PO Box 4950 Nydalen

0424 Oslo

Norway

Phone: +47 23073580

Fax: +47 23070490

e-mail: hherrman@ous-hf.no

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Abstract

Objectives

The safety and effect on seizure frequency of anterior thalamic nucleus deep brain stimulation (ANT-DBS) were studied in this prospective, randomized, double-blinded study. Patients were followed for 12 months. The first 6 months were blinded with regard to active stimulation or not. After 6 months, all patients received active stimulation.

Material and methods

Bilateral ANT electrodes were implanted into 18 patients suffering from focal, pharmacoresistant epilepsy. Antiepileptic treatment was kept unchanged from three months prior to operation. The Liverpool seizure severity scale (LSSS) was used to measure the burden of epilepsy.

Results

There was no significant difference between the 2 groups at the end of the blinded period at 6 months. However, when considering all patients and comparing 6 months of stimulation with baseline, there was a significant, 22% reduction in the frequency of all seizures ($p=0.009$). Four patients had $\geq 50\%$ reduction in total seizure frequency and 5 patients $\geq 50\%$ reduction in focal seizures after 6 months of stimulation. No increased effect over time was shown. LSSS at 6 months compared to baseline showed no significant difference between the 2 groups, but a small, significant reduction in LSSS was found when all patients had received stimulation for 6 months.

Conclusions

Our study supports results from earlier studies concerning DBS as a safe treatment option, with effects even in patients with severe, refractory epilepsy. However, our results are not as encouraging as those reported from many other, mainly unblinded, and open studies.

Introduction

Difficult-to-treat epilepsy is a life-disabling condition with a dramatic impact on quality of life. It is tightly linked to severe morbidities, the risk of deterioration of cognitive function, and mortality. In addition, patients often suffer unacceptable adverse effects associated with antiepileptic medication and seizure-related injuries, along with psychiatric comorbidities. Resective surgery is an option for only a minority of patients with refractory epilepsy (1), and therefore novel therapies are in high demand.

Deep brain stimulation (DBS) is one of the most promising neuromodulatory techniques available today and, over recent decades, has been shown to be a safe and effective treatment for many conditions, including refractory epilepsy (2,3). The SANTE study, so far the only randomized, double-blinded DBS trial with bilateral implantation to the anterior thalamic nucleus (ANT), found a 29% greater reduction in seizures compared with the control group after a three-month blinded period (4). After that, the authors followed their patients in an open continuation of the study. They reported that 5 years after implantation, the median seizure frequency was improved by 69% from baseline (5).

The ANT is known to modulate activity from the temporal lobe including hippocampus, areas believed to be important in the maintenance of epileptic activity (6, 7). Disconnecting the circuits between these nuclei, the Papez circuit, may have a favourable effect on seizure frequency. The ANT is an accessible target for DBS, not too close to vascular structures and not situated too deeply in the brain. However, the ANT is not readily visualized on standard MRI, and the nucleus is usually localized indirectly by recognizing nearby structures, such as the mamillothalamic tract.

The aim of our study was to investigate the possible effect of ANT-DBS on seizure frequency, and to evaluate possible adverse effects and peri- and postoperative complications. To obtain this, we chose to use a design very similar to the SANTE study (4), but with a longer blinded period.

2. Patients and Methods

This was a single-centre study with a prospective, randomized, double-blinded design. Eighteen patients (11 women, 7 men) with pharmaco-resistant focal epilepsies were operated with bilateral ANT electrodes. Eight of the 18 patients were randomized to receive active stimulation from the day of operation.

Eligible patients were adults aged between 18 and 70 years, with an IQ of at least 70, suffering from focal epilepsy, with or without secondary generalization. All patients had gone through evaluation for resective epilepsy surgery during the last 2 years without being accepted. Vagal nerve stimulators (VNS) were always removed before ANT-DBS.

Exclusion criteria were psychogenic non-epileptic seizures, generalized epilepsy, pregnancy, other neurological diseases, and serious medical conditions including psychiatric illnesses.

At inclusion, information about the study was given, and informed consent was signed by the patient and the investigator. The study was conducted according to the Declaration of Helsinki, and approved for by the Regional Committee for Medical and Health Research Ethics, REC South East, Norway. An in-hospital ethical board, consisting of a neurosurgeon and a neurologist, both professors in their fields and independent with regards to the study, evaluated safety during the course of the investigation and performed an interim analysis halfway through the study, primarily to evaluate the safety of the procedure.

Patients kept a seizure diary from three months prior to operation, noting frequency, type, and severity of seizures. Focal seizures with intact awareness (FA) were not included in the analyses as these are not necessarily related to limbic or temporal structures supposed to be affected by ANT stimulation. Medication was kept unchanged in the same time span, and preferably also during the study period.

At the hospital, prior to the operation, neurological examination was performed, as well as blood tests, including serum concentrations of antiepileptic medication, EEG, and MRI scans of the brain.

The Liverpool seizure severity scale (LSSS) was completed, both prior to the operation and at every control during the study period.

The study period for each patient lasted 12 months. The first 6 months represented the double-blinded period. As soon as the operation was over, patients were randomized to either “stimulation on” or “stimulation off” while in the operating theatre before awakening, and stimulation started at 5V in the “on” group. The randomization was performed by staff not involved in the study and not taking part in follow-up or evaluation of the patients. After 6 months all patients received stimulation. Stimulation parameters were kept unchanged during the study period, unless unacceptable adverse effects were experienced.

Patients were followed-up at 3, 6, 9, and 12 months, with particular emphasis on collecting data on changes in seizure frequency, changes in types of seizures, and possible adverse effects.

Our study was originally planned to include 40 patients. However, the halfway interim analysis revealed that a number of patients had an increased seizure frequency under active stimulation, and there was no difference between patients with and without stimulation after the blinded period (see Results). Thus, although unacceptable adverse events were not seen, we chose to stop inclusion to this invasive-treatment study because of the lack of significant improvement effects, and with possible worsening in some patients.

A flow chart of the investigative set up is provided in Figure 1.

3. Surgical procedure

The operation was performed under general anaesthesia. Prior to operation, a stereotactic frame was fixed to the skull and CT scan performed according to stereotactic principles. We used Iplan Stereotactic planning software, Brainlab AG, for target planning, based on a pre-operatively acquired cerebral MRI and the stereotactic CT. The ANT target identification was performed the same way as in the previous SANTE study (4), using the anterior commissure and posterior commissure line (AC-PC line) and the following coordinates; 1 mm behind the mid-commissure point, 4 mm lateral to the AC-PC line, and 9 mm cranial to the commissure plane. Small adjustments to these pre-set coordinates were allowed to compensate for anatomical variations like brain asymmetry and unusual ventricle size. The entry point was placed at or anterior to the coronal suture. The electrode trajectories were placed lateral to the ventricles to minimize the possibility of complications, especially the risk of haemorrhage. During the operation, the head frame was fixed to the upper end of the operation table. Incisions and drill holes were made bifrontally and electrodes inserted into the ANT. A Stim Lock skullcap was used to fix the electrodes in place. The final position of the electrodes was controlled with intraoperative stereotactic fluoroscopy. The stimulator was placed on the chest, below the left clavicle, and connected to the electrodes using extension cables. All incisions were closed with sutures. Prophylactic antibiotics were given according to standard guidelines. The sutures were removed day 10 postoperatively.

The equipment used was Medtronic DBS Lead Model 3389. The length of the cable was 40 cm, the diameter 1.27 mm. The distance between each stimulation site was 0.5 mm and the length of the stimulating site 1.5 mm.

Stimulation was given in a cyclic manner, one minute on and five minutes off, with 5 Volt amplitude, 90-microsecond duration of each stimulus, and 150 Hertz frequency. The lowest contacts were chosen; number (-1) in the left electrode and (-9) in the right electrode, with the electrode negative (cathode) to the stimulator box (anode).

A postoperative CT scan was performed one day after the operation to check for post-operative sequelae, especially haematoma.

4. Statistics

Statistical analyses were performed in IBM SPSS version 23. Seizure frequency was our primary effect variable, with LSSS and adverse effects as secondary variables. When comparing a variable at 2 different time points, a paired t-test was used. When comparing a variable in 2 separate groups, an independent samples t-test was used.

5. Results

5.1 Patient characteristics

Eleven women and 7 men were operated on from April 2010 to March 2015. Ages ranged from 18 to 52 years (table 1).

The patients represent an epilepsy cohort with the most severe epilepsies. The mean duration of epilepsy was 24 years. Six patients had gone through resective surgery, 6 had tried VNS, and one had tried a ketogenic diet. The mean number of antiepileptic drugs (AEDs) tried was 13 (ranging from 5 to 15). Mean seizure frequency was 53.1/month.

At the time of inclusion, 10 patients were treated with three different AEDs, the other eight patients used 2.

Of the 18 patients, 16 had finished high school, 2 had a university degree, either Bachelor or Master. Two patients were working full time, 6 had facilitated employment services, and 10 drew a disability pension. Ten patients lived in stable relationships, while 8 lived alone. Ten patients have children of their own.

5.2 Seizure frequency

After 6 months, at the end of the blinded period, there was a significant reduction in total seizure frequency to 77% of baseline in the “on” group ($p=0.048$), but no reduction in the “off” group (table 2). There was, however, no significant difference between the “on” and “off” groups after 6 months.

When looking at focal seizures with impaired awareness (FIA) separately, a significant reduction in the “on” group to 79% from baseline was seen at 6 months ($p=0.038$), but there was no significant change in the “off” group and no difference between the 2 groups. Comparing only focal to bilateral tonic-clonic seizures (FBTC) in the 2 groups was not considered to provide meaningful results, given the very small number of FBTC seizures in the “on” group.

Comparing seizure frequency after 6 months of stimulation with baseline in all patients (“on” group after 6 months, “off” group after 12 months), there was a significant reduction in FIA to 80% ($p=0.009$). Patient 13 was not included in the analyses after 12 months, as her stimulator was turned off after 9 months.

After 6 months of stimulation, 4 of 18 patients had $\geq 50\%$ reduction in the total number of seizures and 5 of 18 had $\geq 50\%$ reduction in FIA seizures. Twelve months after implantation, none of the 18 patients were seizure free. Two patients had a more than 20% increase in total seizure frequency, and 1 had $>20\%$ increase in FIA seizures. Among the 11 patients with GTC seizures, 3 had $>20\%$ increase in seizure frequency and only 1 had $>50\%$ seizure reduction.

Compared with baseline, the seizure frequency for all seizures in the “on” group was 77% after 6 months and 83% after 12 months, indicating no trend towards any improved effect with time. Corresponding figures in the “off” group was 111% at 6 months and 78% at 12 months.

5.3 Change in seizure severity scale (LSSS)

The difference in mean LSSS between the 2 randomized groups preoperatively was not significant, with a p-value of 0.058. The “on” group had a LSSS score of 29, the “off” group of 46 (table 3).

Comparing LSSS scores between the “on” and “off” groups after the 6-month blinded period, no significant difference could be found ($p=0.56$). Furthermore, there was no difference in the change in LSSS between the 2 groups at 6 months. A small, but significant, reduction from 38 to 33 points in LSSS was observed when all 18 patients had tried stimulation for 6 months ($p=0.044$).

There was no significant change in LSSS over time in any of the treatment groups. One patient (no. 13, in the “off” group) experienced a relapse of GTC after DBS was turned on at 6 months, and the active stimulation was therefore stopped after nine months. This affected her LSSS score both at nine months (55 points, not shown in the table) and again at 12 months (only 5 points). She reported an overall reduction in LSSS by 43 points from baseline at the end of the study period. This may reflect that she experienced fewer FBTC seizures for the final three months, when the DBS had been turned off. Results from this patient have been omitted from all calculations regarding LSSS scores.

5.4 Complications and adverse effects

Per – and postoperative complications

There were no peroperative complications, but a few complications occurred postoperatively (table 4). One patient (no. 2) had their left electrode explanted and reinserted since the internal capsule was affected (the patient experienced twitches in the right side of his face and neck every time the stimulation cycle started). Another patient (no. 9) developed dysarthria and left central facial nerve palsy three days after the implantation. Cerebral CT showed an area with low attenuation, and perfusion CT showed reduced cerebral blood flow and cerebral blood volume, located cranially to the electrode on the right side, changes usually seen in infarction. She experienced a total remission in the following week. Later CT scans and MRI of the brain were normal, and her clinical status has been normal.

Adverse events of the stimulation

One patient (no. 13) had a recurrence of GTC seizures after her DBS was turned on at 6 months, and another patient (no. 2) reported an increase in both FIA and FBTC seizures. A third patient (no. 12) reported, postoperatively, a good effect improving over time until the DBS was turned on at 6 months. The reported effect was reduced with active stimulation, but still notable.

One patient (no.18) experienced a cerebral stroke 4 months after implantation. This was considered to be unrelated to the operation, but due to his condition of general health.

Other symptoms reported in individual patients during the study period included: headache, dizziness, vertigo, memory deficit, transient depression, “strange thoughts”, changed perception of reality, problems finding words, and altered circadian seizure pattern (table 4). Some patients reported more energy, better sleep, shorter and less intense seizures, shorter postictal phase, less frequent seizures with corresponding falls and traumas, and better cognitive functioning.

6. Discussion

Our study is the second published randomized, double-blinded trial examining ANT-DBS in epilepsy. The main finding was that there was no significant difference in seizure frequency after the blinded period between patients with or without stimulation. This includes both FIA and FBTC seizures. Our study was designed in a similar way to the SANTE study (4), but inclusion to our study was halted after the halfway interim analysis because of a lack of beneficial effect, and with possible worsening in some patients. The difference between our results and those of the SANTE study may have several explanations. Compared to those in the SANTE study, our patients probably have more serious and severe epilepsies. The SANTE investigators reported a monthly median seizure frequency of 19.5. In our study, the mean seizure frequency was 43.5 per month for FIA seizures (783/18) and 9.6 per month for FBTC seizures (173/18). Of our patients, 30% had been through resective surgery, 30% had tried VNS, and the mean number of AEDs tried was 13. In contrast to the SANTE study, which collected patients from 19 different centres where the patients were evaluated and examined by several different specialists, our patients came from a single epilepsy centre, the National Centre for Epilepsy in Norway. It seems likely that the heterogeneities in patients and types of epilepsies are larger in the SANTE study, and that our cohort represents a group with more refractory epilepsies (4).

However, when looking at both total seizure frequency and frequency of FIA after 6 months of stimulation for all patients, we found a significant 20% reduction compared with baseline. This is not very different from the SANTE study, which reported an overall 29% reduction after their three-month blinded period (4).

Our study did not show a progressively increasing effect with time. This is somewhat in contrast to other studies (5, 8), but may relate to the short observation time of our study and the low number of patients.

In addition to seizure frequency, seizure severity as measured by LSSS scores is an important outcome in the evaluation of clinical studies (17,18). In our study, there was a small, but significant, reduction in mean LSSS score from 38 to 33 points after DBS for all patients after 6 months of stimulation. A change in LSSS score of 5 points has probably limited clinical implications. There were, however, large inter-individual differences. For example, two patients had a reduction in LSSS score of more than 20 points, which is thought to be of clinical relevance. A reduction in seizure severity is consistent with other studies; stimulation is effective against the most serious seizures, with a concomitant reduction in injuries. (2,4,8,21,22,23,24,25,26,27,28,29).

We did not experience any serious adverse events, except for one patient (patient no. 9) who had a central paresis of the left facial nerve the day after the implantation. The paresis resolved in a few days and left no clinical or radiological trace. In particular, there were no infections, haemorrhages, status epilepticus, or SUDEP during the study period. Therefore, the safety of DBS performed according to the procedure used here appears to be good.

Limitations

A possible micro-lesion effect was seen in a total of 12 of our 18 patients. This is a well-known confounder to the actual effect of stimulation (4, 9,10,12,13,14,15,16). This is also why we chose a 6-month blinded phase in our study, because the effect of the lesion can last for several weeks. In the “off” group, 7 of 10 patients reported less frequent seizures, a shorter duration of seizures, and not as debilitating seizures in the first four weeks postoperatively. In one patient, seizure frequency after 6 months without stimulation was 30% compared with baseline. When we turned the stimulator on, seizure frequency increased to 70%. Active stimulation was stopped again 12 months after the operation, and the seizure frequency was again reduced to 30% of baseline. This observation is not easily explained, but could possibly be related to a lasting micro-lesion effect; sustained effects from micro-lesions are well known and have also been reported in other studies (4, 9, 13,16). The reason for this is unclear, and the micro-lesion effect was not sustained in other patients in our study. In the “on” group, 5 of 8 patients reported fewer and shorter seizures in the first four weeks postoperatively.

In general, most patients are unaware of whether the stimulator is active or not (4). In our study, double blinding was continued for the whole 6-month period for all patients. However, three of the patients stated that they knew that the system was active postoperatively during the blinded period. They were all correct, and their assumptions were based on different experiences: a tingling sensation at the site of the electrode (one patient), a sense of joy and happiness every 6th minute (one patient), and twitches in the face spreading to the neck and the rest of the body on one side every 6th minute (one patient). The other patients were not able to determine whether the stimulator was on or not during the blinded period.

The role of DBS in treatment of epilepsy

Several studies on the effect of DBS in epilepsy have been performed over the last decades. Most of these are small, uncontrolled trials with different designs and a wide diversity in results (3). Different neuroanatomic structures were targeted, such as the centromedian nuclei of the thalamus (CMT), the subthalamic nuclei (STN), hippocampus, cerebellum, and the ANT. The mean reduction in seizure frequency reported for the other targets was 80.6% for CMT, 70% for hippocampus, and 29% for STN. Looking particularly at the trials targeting the ANT, most studies have been open with only small numbers of patients included. The reported effect of stimulation in the different studies has varied greatly, from 0 to 100 %. The average effect reported for ANT stimulation has been approximately 60% (3).

In a Cochrane review, Sprenger et al. (16) concluded that there is evidence for a moderate reduction in seizure frequency (15-30%) after short-term (one to three months) stimulation of the ANT when treating patients with multifocal epilepsies and that the evidence on ANT stimulation is of moderate to high quality. However, several authors claim that certain targets are better suited than others in the treatment of the different epilepsies (8-10, 11,17,24,25,27-31). If so, the selection of patients may also be important when evaluating different implantation sites for DBS in epilepsy.

The role of DBS treatment in refractory epilepsy still remains to be clarified. We need better understanding of how electrical stimulation affects the brain, and on how to optimize the selection of patients, targets, and stimulation protocols (30,32,33). Larger, well-designed trials are needed to determine the efficacy and safety of these treatment options and to compare them to other available treatments.

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Conflict of interests

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Table 1 Patient characteristics

No	Gender	Duration	Aetiology	Co-morbidity	Seizure semiology	Current medication	No. of AEDs tried	EEG	MR cerebrum	Prior surgery
1	F	37	Idiopathic	No	FA, FIA, FBTC, ATYPICAL FIA and FBTC	VPA, LTG, CZP	>15	Epileptic activity in several foci, multifocal	Venous angioma, right temporo-parietal	Callosotomy, VNS
2	M	35	Idiopathic	Asthma	FA, FIA, FBTC	LAC, LEV, CLB	>15	Theta, right temporal	Postoperative changes	Temporal resection right
3	F	20	Idiopathic	No	FA, FIA, FBTC	CBZ, CLB	>15	Low amplitude theta	negative	NO
4	F	26	Meningitis, head trauma	No	FIA	LTG, OXC, CLB	>15	Rhythmic theta in central sagittal region, left hemisphere	negative	NO
5	F	15	Cortical dysplasia close to the Sylvian fissure, left	No	FA, FIA, FBTC	PB, PHT, CLB	>15	Focal dysrhythmia left temporal	Cortical dysplasia in relation to the Sylvian fissure, left	NO
6	F	18	Idiopathic	Encephalopathy	FA, FIA, FBTC	LAC, PB, OXC	>15	Epileptic activity from both hemispheres, general dysrhythmia	Negative	Temporal resection right, VNS
7	M	22	Post-traumatic?	No	FA, FIA	LTG, PHT	10	Possible epileptic activity left temporal	Negative	NO
8	M	6	Idiopathic	Diabetes mellitus, encephalopathy	FA, FIA, FBTC	VPA, LTG	5	Suspect epileptic activity in both temporal regions	Negative	NO
9	F	14	Idiopathic	No	FA, FIA, FBTC	VPA, LTG	10	Left temporal activity, possible ictal start in both temporal lobes	Bilateral hippocampal sclerosis	Left temporal resection
10	F	19	Posttraumatic/ idiopathic	Encephalopathy	FA, FIA, FBTC	VPA, LTG, TPM	10	Possible ictal start in the left hemisphere, temporolateral	Negative	NO
11	M	23	Idiopathic	Hyperlipidemia hypertension	FIA	VPA, LTG	10	Epileptic activity in both temporal region	Negative	NO
12	M	35	Idiopathic	No	FA, FIA, FBTC	CBZ, VPA, LTG	>15	Theta- and epileptic activity in multiple foci	Negative	VNS
13	F	23	Remaining resection cavity after previously operated oligodendroglioma frontally right side.	No	FA, FIA, FBTC	OXC, CZP, TPM	>15	Epileptic activity frontocentrally right	Oligodendroglioma frontally right, gliosis	Resection in 2003 and 2009
14	F	8	Idiopathic	No	FA, FIA, FBTC	TPM, LTG	10	Theta on both sides parietooccipally	Negative	NO
15	F	30	Cerebral paresis, multiple	Hypertension, cerebral palsy	FIA	OXC, VPA, CLB	>15	Epileptic activity in motor cortex left side	Infarcts, left side behind	Subpial transections

			infarctions						the central region	centrally left hemisphere
16	F	37	Idiopathic, born 10 weeks premature	Thyroiditis	FA, FIA, FBTC	OXC, CZP, TPM	>15	Theta left side, incl epileptic activity on both sides temporally	Negative	VNS
17	M	16	Idiopathic	No	FA, FIA, FBTC, atypical FBTC with tonic seizures	FBM, OXC	>15	Seizure start in both temporal regions	Negative	VNS
18	M	42	Idiopathic, encephalopathy	Hypertension	FA, FIA, FBTC, atypical FBTC with tonic seizures	VPA, OXC	>15	Interictal epileptic activity temp right, no focus	Encephalo-malasia/gliosis	VNS

F: female. M: male. CBZ: Carbamazepine. CLB: Clobazam. CZP: Clonazepam. FBM: Felbamate. LAC: Lacosamide. LEV: Levetiracetam. LTG: Lamotrigine. OXC: Oxcarbazepine. PB: Phenobarbital. PHT: Phenytoin. TPM: Topiramate. VPA: Valproate. VNS = vagal nerve stimulation. FA: Focal aware seizures. FIA: Focal seizures with impaired awareness. FBTC: Focal to bilateral tonic-clonic seizures.

Table 2. Seizure frequency during the study period compared with baseline

<u>DBS,</u> initial stimulation		Mean seizure frequency_per month, during last 3 months before inclusion = baseline period	Seizure frequency – all seizures (FBTC+FAI) Baseline=100%		Frequency of FBTC seizures Baseline =100%		Frequency of FIA seizures Baseline =100%		Comparing 6 months of stimulation, all patients (ON group after 6 months, OFF group after 12 months) with baseline. Baseline=100%		
	ON/OFF		6 months	12 months	6 months	12 months	6 months	12 months	FBTC + FIA	FBTC	FIA
1	On	200 FIA, 4 FBTC	101	99	150	75	100	100	101	150	100
5	On	7 FIA, 2 FBTC	100	81	-	-	100	81	100	-	100
6	On	42 FIA, 4 FBTC	71	65	100	100	68	61	71	100	68
7	On	150 FIA	87	88	-	-	87	88	87	-	87
10	On	25 FIA	33	100	17	22	50	100	33	17	50
11	On	19 FIA, 2 FBTC	40	10	-	-	40	10	40	-	40
15	On	34 FIA	94	129	-	-	94	129	94	-	94
16	On	8 FIA	92	96	-	-	92	96	92	-	92
2	Off	3 FIA, 1 FBTC	470	102	255	59	520	137	102	59	137
3	Off	2 FIA, 2 FBTC	75	127	150	217	67	119	127	217	119
4	Off	120 FIA	55	44	-	-	55	44	44	-	44
8	Off	120 FBTC	58	50	-	-	58	50	50	-	50
9	Off	13 FIA	91	100	67	100	100	100	100	100	100
12	Off	8 FIA, 1 FBTC	30	70	30	70	-	-	70	70	-
13	Off	16 FIA	100	123#	-	600#	100	108#	123#	600#	108#
14	Off	122 FIA	48	52	33	67	50	50	52	67	50
17	Off	2 FIA, 31 FBTC	91	100	81	106	300	77	100	106	77
18	Off	12 FIA, 6 FBTC	91	61	91	61	91	61	61	61	61
ON Group, Mean (SD)			77* (27)	83 (35)	89 (67)	66 (40)	79** (23)	83 (35)			
Range			33-101	10-129	17-150	22-100	40-100	10-129			
OFF Group Mean (SD)			111 (128)	78 (29)	98 (79)	97 (56)	91 (159)	80 (35)			
Range			30-470	44-127	30-255	59-217	50-520	44-137			
All patients, after 6 months of stimulation		Mean (SD)							78*** (27)	95 (56)	79*** (29)
		Range							33-127	17-217	10-137

*: There is a significant reduction in seizure frequency to 77% of baseline when we compare all seizures at baseline to 6 months postoperatively for the “on” group, $p=0.048$, but not for the “off” group, $p=0.85$. Comparing the 2 groups with each other at 6 months did not give a significant difference between the 2 groups, $p=0.5$

**: Comparing 6 months of stimulation for FIA seizures in the 2 groups to baseline gave a significant reduction to 79% of baseline in the “on” group, $p=0.038$, not so in the “off” group, $p=0.85$.

***: Seizure frequency for all seizures (FIA + FBTC) was significantly reduced to 78% of baseline after 6 months of stimulation for all patients; $p=0.009$.

#: Calculations of mean, standard deviation (SD) and range after stimulation have been done without including patient 13 who did not have stimulator on at the end of the study.

FIA: Focal seizures with impaired awareness. FBTC: Focal to bilateral tonic-clonic seizures.

Table 3. The Liverpool seizure severity scale preoperatively, and at 6 and 12 months postoperatively

Patient number	DBS	Liverpool seizure-severity scale			
	ON/OFF	Preoperatively	6 months	12 months	6 months of stimulation, all patients
1	On	28	28	33	28
5	On	38	38	33	38
6	On	50	33	28	33
7	On	15	15	10	15
10	On	38	48	53	48
11	On	18	15	15	15
15	On	23	15	10	15
16	On	20	33	25	33
2	Off	88	88	83	83
3	Off	68	60	65	65
4	Off	10	13	10	10
8	Off	25	30	3	3
9	Off	40	38	30	30
12	Off	35	28	23	23
13	Off	48	28	5#	5#
14	Off	60	50	53	53
17	Off	53	48	55	55
18	off	32	55	35	35
Mean (SD) – “On” group		29 (12)	28 (12)	26 (15)	28 (12)
Range		15-50	15-48	10-53	15-48
Mean (SD) – “Off” group		46 (23)	44 (21)	36 (26)	36 (26)
Range		10-88	13-88	3-83	3-83
Mean (SD) all patients		38 (20)	37 (19)	32 (22)	33* (21)
Range		10-88	13-83	10-83	3-83

There was no significant difference in LSSS score between the “on” and “off” groups after 6 months, the end of the blinded period. Furthermore, no difference in the change in LSSS between the 2 groups from baseline to 6 months could be detected.

*: Significantly reduced compared to baseline when all patients had experienced stimulation for 6 months (“on” group after 6 months, “off” group after 12 months), $p=0.004$.

#: Calculations of mean, standard deviation (SD) and range after stimulation have been done without including patient 13 who did not have stimulator on at the end of the study.

Table 4. Adverse effects

Nr	On/off 6 months	Adverse effects at 3 months	Adverse effects at 6 months	Adverse effects at 9 months	Adverse effects at 12 months	Change in AED	Other medication	Change in stimulation during study period
1	On	No	No	No	No	Yes, after > 6 months	No	Yes, after 6 months
5	On	No	No	No	No.	No	No	No
6	On	No	No	No	No	No	No	No
7	On	No	Slept better, less tired, more energy	Slept better, more energy	Slept better, more energy, less tired	No	No	No
10	On	No	Memory deficit	Memory deficit	Memory deficit	No	No	No
11	On	Sense of joy every 6 min followed by depression lasting five min	Same sensation, but less intense	Same sensation, less intense	Same sensation, less intense	No	No	No
15	On	No	No	No	No	No	No	No
16	On	No	Increasing seizure frequency	Increasing seizures	Increasing seizure frequency	No	No	
2*	Off	Short depressive episodes lasting few hours. Known depression, but different after DBS, twitches in the face and neck on the right side	Rapid depression, suicidal thoughts	Diplopia, vertigo, headache Stimulation induced twitches on the right side of head, neck and extremities	Decreased sensibility right side of the face Lower voltage due to adverse effects described at 9 months	Yes, clobazam added after 2 months	No	Yes, after 1 month
3	Off	No	No	Vertigo, depressed, “strange thoughts”, changed perception of reality, problem finding words, memory deficit	Memory deficit, but not as much as before	No	No	Yes, at 6, 9 and 12 months
4	Off	No	No	No	No	No	No	No
8	Off	No	No	No	No	No	Fontex	No
9**	Off	No	No	No seizures for five weeks after DBS was turned on, then back to baseline	No	No	No	No
12	Off	Slept better, more energy, and better appetite	Slept better, more energy and better appetite	Tired, less energy, vertigo, dizziness, less appetite after DBS was turned on	Tired, less energy, vertigo, dizziness, less appetite.	No	No	No
13 ***	Off	No	No	Increased seizure frequency, intensity, strength, return of FBTC	Increased seizure frequency (FBTC)	No	Fluoxetine, started 02/13	Yes, turned on after 7 months, off after 9 months and has been off since
14	Off	No	No	No	No	No	Hormone IUD	

17	Off	No	No	Awake, more energy, quick in response to others, participating in activities	Many FBTC, tired, slow, no energy.	No	No	No
18	Off	No	Headache, memory deficit	Same situation, not back to work	No	No	No	No

*Patient no. 2 had to have his left cord removed and a new one implanted immediately after the study period due to the cord being placed too close to the internal capsule therefore result in twitches every 6th minute when the DBS was turned on.

** Patient no. 9 had a left central facial paresis, remission during the first week.

*** Patient no. 13 experienced a recurrence of FBTC seizures that she had not had in many years when the DBS was turned on at 6 months.

Flowchart of experimental plan