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Deep Brain Stimulation for Refractory Focal Epilepsy: Unraveling the Insertional Effect up to Five Months Without Stimulation

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ABSTRACT

Introduction: Following electrode implantation, a subgroup of patients treated with deep brain stimulation (DBS) for focal epilepsy exhibits a reduction of seizure frequency before stimulation is initiated. Microlesioning of the target structure has been postulated to be the cause of this ''insertional'' effect (IE). We examined the occurrence and duration of this IE in a group of patients with focal epilepsy following electrode implantation in the anterior nuclei of the thalamus (ANT) and/or nucleus accumbens (NAC) for DBS treatment.

Materials and Methods: Changes in monthly seizure frequency compared to preoperative baseline were assessed one month (14 patients) and five months (four patients) after electrode implantation. A group analysis between patients with implantation of bilateral ANT-electrodes (four patients), NAC-electrodes (one patient) as well as ANT and NAC-electrodes (nine patients) was performed.

Results: In this cohort, seizure frequency decreased one month after electrode implantation by 57.1 ± 30.1%, $p \leq 0.001$ (compared to baseline). No significant difference within stimulation target subcohorts was found ($p > 0.05$). Out of the four patients without stimulation for five months following electrode insertion, three patients showed seizure frequency reduction lasting two to three months, while blinded to their stimulation status.

Conclusion: An IE might explain seizure frequency reduction in our cohort. This effect seems to be independent of the number of implanted electrodes and of the target itself. The time course of the blinded subgroup of epilepsy patients suggests a peak of the lesional effect at two to three months after electrode insertion.

Keywords: Anterior thalamus, deep brain stimulation, focal epilepsy, lesional effect, microlesional effect, nucleus accumbens

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INTRODUCTION

Neuromodulatory treatments represent a therapeutic option in pharmacoresistant epilepsy when resective surgery is either not indicated or declined by patients. Deep brain stimulation (DBS) of the anterior nuclei of the thalamus (ANT) was approved in the EU in 2011 and in the United States in 2018 after efficacy and safety was shown in a large-scale multicenter randomized controlled trial (1). The insertional effect (IE), defined as ''a reduction in or abolition of symptoms with insertion of DBS electrodes alone'' (2) was first described as ''microthalamatomy'' for electrode insertion in patients with essential tremor. The mechanisms of the IE, also known as ''microlesioning effect,'' remain unclear, though inflammation, oedema, and metabolic or neuromodulatory changes have been suggested (3). In movement disorders, IE has been described for several thalamic and extra-thalamic subcortical structures, leading to significant clinical improvements reaching a magnitude comparable to DBS therapy itself. In these conditions, IE has been observed peri-operatively (4) and up to six months after insertion (5).

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For epilepsy patients, IE was described in detail after ANT electrode insertion by Hodaie et al. (6). The duration of this effect in epilepsy patients varies from several days to months (1,7) but may last up to several years (7,8). In patients with focal epilepsy, DBS is usually initiated one month after electrode insertion (1,6), thus IE can only be distinguished from a possible neuromodulative effect during this period. Placebo effects caused by the patient's or investigator's expectations also have to be considered. The IE has been observed in direct stimulation of the seizure focus in cortical structures, and it has been suggested that it is predictive for responding to DBS (9,10).

We present a cohort of 16 consecutive patients with pharmacoresistant focal epilepsy eligible for DBS, in which the frequency of disabling seizures after electrode implantation prior to the initiation of DBS was compared to baseline. This cohort comprised patients with bilateral ANT- (four patients), NAC- (one patient), and ANT and NAC-electrode implantation (nine patients). A group analysis was performed to investigate whether the IE in patients with epilepsy is confined to the ANT or also applies to the NAC. In four patients with ANT- and NAC-electrode implantation, DBS was initiated five months after implantation, allowing for study of the time course of a putative IE. Despite the small cohort, these data provide valuable further insights into the IE, both for ANT- and NAC-electrode implementation and time course of IE.

MATERIALS AND METHODS

Patient Cohort

This cohort of 16 patients (nine females) comprises previously published (11,12) and unpublished data from patients who were consecutively implanted with intracerebral electrodes between January 2011 and December 2015. Two patients were excluded from analysis due to occurrence of de novo psychogenic non-epileptic seizures, diagnosed during their follow-up period. An overview of the clinical characteristics of the remaining 14 patients is provided in Table 1. These 14 patients were followed up with recording of seizure frequency for one month (25.1 ± 8.8 days), four of them for up to five months (142.0 ± 2.8 days) before DBS was started. Details of patients' electrode placement, status of blinding in respect to DBS and relevant seizure frequency data (disabling seizures) on a month-by-month basis are summarized in Table 2.

Table 1. Clinical Characteristics of Our Cohort.

Patients (no.)	14
Sex (m:f)	6:8
Age at surgery (years)	37.4 ± 10.1
Age at epilepsy onset (years)	19.3 ± 9.7
Etiology (no. of pat.)	
Nonlesional	8
Symptomatic	6
Epilepsy syndrome (no. of pat.)	
Frontal	6
Temporal	7
Parietal	1
Target of electrode placement (no. of pat.)	
ANT	4
NAC	1
ANT and NAC	9
Responder-status during initial three-month DBS (no. of pat.)	
ANT-DBS (ANT group)	2 of 4
NAC-DBS (ANT and NAC group)	4 of 8

Allocation to the Different Groups

Due to technical reasons bilateral implantation of electrodes in both the ANT and the NAC was only possible in the first 11patients. Allocation to the different groups was consecutive and based solely on clinical or ethical grounds: one patient was not eligible for receiving both the ANT and the NAC electrodes because she was a minor (patient #2), two patients of the ''ANT group'' decided against implantation of additional electrodes in the NAC because of its experimental character (patients #3 and #8) and one patient (patient #13) could not be offered additional electrode implantation the NAC because he entered the study after the maximum number of simultaneous ANT and NAC electrode implantations was reached. One patient received only bilateral NAC-electrodes, since his left ANT was not detectable on MRI as a consequence of an extended prenatal left medial cerebral artery infarction (patient #14).

In summary, targets of electrode placement were bilateral ANT (''ANT group''; four patients; patients #2, #3, #8, #13), bilateral NAC (''NAC group''; one patient; patient #14) or bilateral both ANT and NAC (''ANT and NAC group''; nine patients; patients #1, #4-#7, #9-#12).

Surgical procedures were carried out on the four patients in the ANT group according to the EU standard indication of DBS for phamacoresistant focal epilepsies.

Out of the nine patients of the ANT andNAC group, the first consecutive four Due to a stimulus-dependent induction of habitual auras while testing DBS-treatment, one patient in the ANT and NAC group never received DBS (13). The four patients were blinded according to a randomized controlled double-blinded, crossover design. Prior to randomization, all patients consented to this procedure knowing that they might be allocated to the group which would not receive DBS treatment for five months. Allocations to the groups were performed by a person not involved in the research. For three patients, this randomization design arbitrarily resulted in a five-months observation period, before DBS was initiated (Fig. 1).

No changes were made to patients' concomitant antiepileptic drug regimens, to the stimulation parameters or to the stimulated electrode contacts.

Seizure Count

Patients or close caregivers documented seizure frequency using a seizure diary. Only focal seizures with impaired awareness and/or focal to bilateral tonic–clonic seizures were considered, since they represent clinically significant ''disabling seizures.'' Data of seizure frequency were documented each month and analyzed retrospectively. A three-months preoperative timeframe served as referential baseline period. Preoperative seizure frequency varied from 2 to 96 seizures per month, averaging 13. Patients who experienced a reduction of at least 50% of the disabling seizures compared to the baseline period were defined as responders.

Table 2. Single Patients' Electrode Placement, Their Status of Blinding in Respect to Deep Brain Stimulation and the Relevant Seizure Frequency Data (Disabling Seizures).

Patient	Electrode placement	Blinded	Time frame	Monthly seizure frequency	Relative change to baseline
1	ANT and NAC		Baseline	5	
		Unblinded	First month	23.333	−0.5395
2	ANT		Baseline	96	
		Unblinded	First month	67	−0.3021
3	ANT	Unblinded	Baseline	33.333	
			First month	0	−1
4	ANT and NAC		Baseline	73.333	
		Blinded	First month	7	−0.0541
		Blinded	Second month	5	−0.3243
		Blinded	Third month	4	−0.4595
		Blinded	Fourth month	9	0.2162
		Blinded	Fifth month	2	−0.7297
5	ANT&NAC		Baseline	2	
		Unblinded	First month	0	−1
		Unblinded	Second month	5	1.5
		Unblinded	Third month	0	−1
		Unblinded	Fourth month	0	−1
		Unblinded	Fifth month	0	−1
6	ANT and NAC		Baseline	26.667	
		Unblinded	First month	13.659	−0.4878
7	ANT and NAC		Baseline	8	
		Unblinded	First month	31.111	−0.6111
8	ANT		Baseline	11	
		Unblinded	First month	2	−0.8182
9	ANT and NAC		Baseline	43.333	
		Blinded	First month	3	−0.3023
10	ANT and NAC		Baseline	16.667	
		Unblinded	First month	0	−1
11	ANT and NAC		Baseline	20.3333	
		Blinded	First month	9	−0.5574
		Blinded	Second month	11	−0.459
		Blinded	Third month	9	−0.5574
		Blinded	Fourth month	21	0.0328
		Blinded	Fifth month	4	−0.8033
12	ANT and NAC		Baseline	4	
		Blinded	First month	3	−0.25
		Blinded	Second month	2	−0.5
		Blinded	Third month	3	−0.25
		Blinded	Fourth month	6	0.5
		Blinded	Fifth month	4	0
13	ANT		Baseline	33.333	
		Unblinded	First month	2	−0.4
14	NAC		Baseline	66.667	
		Unblinded	First month	22.105	−0.6684

Surgery

Implantation of DBS systems was performed under general anesthesia and by use of a standardized stereotactic technique: two (five patients) or four (11 patients) Medtronic Model 3387 DBS leads (Medtronic, Minneapolis, MN, USA) were implanted bilaterally into the NAC and/or the ANT and subsequently connected to one (15 patients) or two (one patient) impulse generators (IPG; Activa-PC, Medtronic, MA, USA). Details concerning the surgical procedure have been published previously (11,12). The Institutional Review Board of the University of Magdeburg approved the surgical procedure (registration number 03/08). Two patients were operated on following an individual decision by the Institutional Review Board of the University of Magdeburg. All patients or their legal guardian granted written informed consent for implantation of the neurostimulation system.

Electrode Position Relative to ANT and NAC Targets

When critically rating final electrode positions achieved in 26 ANT electrodes, 54% were rated as "clearly inside," 35% as most likely inside accounting for difficulties in clearly defining the myelin sheath by which the nucleus is embedded. This calculation amounts to 89% successful implantations. 11% were rated as "possibly inside" indicating that it was not possible to visualize the mammillothalamic tract nor the bottom myelin sheath of the

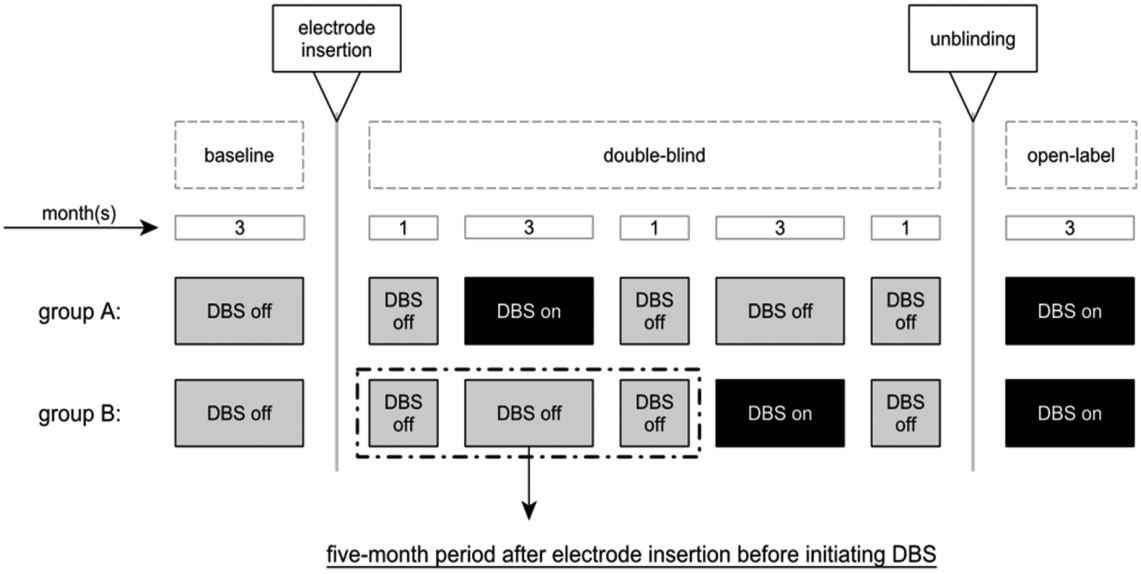

Figure 1. Protocol of a double-blind case series of NAC-DBS adapted and modified from original article (11). The randomized controlled crossover design resulted in a five-months observation period before initiation of DBS in three patients ("group B" – patients).

Table 3. Position of Active Electrode Contacts of the Anterior Nuclei of the Thalamus (ANT) and/or the Nucleus Accumbens (NAC).

A: Mean values for of active contact coordinates in the ANT in relation to the midcommissural point (MC) (negative y-values indicating position anterior to MC).

	x (SD)	y (SD)	z (SD)
Left	−6.0 (1.0)	−2.1 (1.0)	14.1 (2.3)
Right	4.2 (4,0)	2.3 (3.1)	14.2 (2.0)

B: Mean values for active contact coordinates in the NAC in relation to the anterior commissural point (AC) (negative values indicating position anterior to AC)

	x (SD)	y (SD)	z (SD)
Left	−7.3 (1.9)	−4.2 (4.5)	−3.4 (1.5)
Right	5.9 (2.4)	−4.6 (1.9)	7.4 (1.9)

ANT. Therefore targeting relied solely on atlas coordinates. For the nucleus accumbens target, coordinates were 2–2.5 mm anterior 4–6 mm below and 6–8 mm lateral to the anterior commissural point. The final target point was adjusted according to landmarks. Details concerning the active electrode positions of the cohort are summarized in Table 3.

Statistical Methods

SPSS Statistics Version 21.0 (IBM, Armonk, NY, USA) was used for statistical operations and graphical display. Two-sided *t*-tests were used to assess significant differences for each group against their respective baseline and for the blinded vs. nonblinded subcohorts of the ANT and NAC group. Shapiro–Wilk test confirmed a normal distribution within the respective groups. yEd Version 3.19 (yWorks GmbH, Tuebingen, Germany) was used for diagram creation.

RESULTS

Insertional Anti-Seizure Effect After One-Month Period

In the cohort as a whole, the number of disabling seizures significantly decreased one month after electrode implantation compared to the preoperative baseline period (−57.1% ± 30.1%, $p \leq 0.001$, $n = 14$). Likewise, the seizure frequency significantly decreased in the ANT group ($p \leq 0.05$; $n = 4$) and in the ANT and NAC group ($p \leq 0.001$, $n = 9$) compared to baseline. There was no significant difference in reduction of seizure frequency comparing both groups ($p > 0.05$).

Since the ANT and NAC group was partially comprised of blinded patients, a subanalysis was performed concerning the blinded and the nonblinded patients: among the nonblinded patients in the ANT and NAC group, the reduction in seizure frequency was significantly ($p = 0.027$) higher (−72.8% ± 25.2%, $n = 5$) compared to the blinded group (−29.1% ± 20.7%, $n = 4$) in the ANT and NAC group. Compared to baseline, the seizure frequency was only significantly reduced in the nonblinded subcohort of the ANT and NAC group ($p \leq 0.003$, $n = 5$). For an overview of the results after one month (Fig. 2).

Insertional Effect on Responder Status After One Month

Seven out of 14 patients experienced a reduction in seizure frequency of more than 50% (two patients of the ANT group, one patient of the NAC group, and four of the ANT and NAC group).

We also analyzed to what extent a reduction in seizure frequency of at least 50% was predictive for seizure outcome after the initial three months of DBS treatment. The single patient of the ANT and NAC group, who did not receive DBS treatment because he reported stimulus-dependent induction of habitual auras while testing DBS-treatment (13), was excluded for this subanalysis because he did not receive DBS treatment, so no data concerning his responder status was available. In the ANT group, one of two patients was also a responder after three months of ANT-DBS. Patients of the ANT and NAC group were NAC stimulated during the initial three months of DBS treatment. Two of

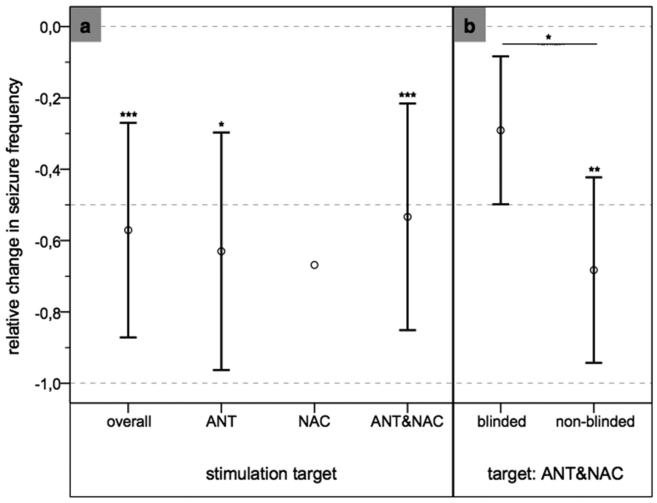

Figure 2. Relative change in frequency of disabling seizures in the first month after electrode insertion compared to three-month presurgical baseline. *$p < 0.05$; **$p < 0.01$, and ***$p < 0.001$ mark significant differences in respective groups to baseline (a) or between groups (b). Error bars represent 1 SD of uncertainty. a. Sorted for all patients (overall) and the stimulation target subcohorts ANT only (four patients), NAC only (one patient) and ANT and NAC (nine patients). The seizure frequencies of all patients, of the ANT group, and the ANT and NAC group were reduced in comparison to their respective baseline. b. Patients with ANT- and NAC-electrodes, distinguished between blinded (four patients) and nonblinded patients (five patients). The seizure frequency of the nonblinded patient group was significantly reduced in comparison to baseline and to the blinded group.

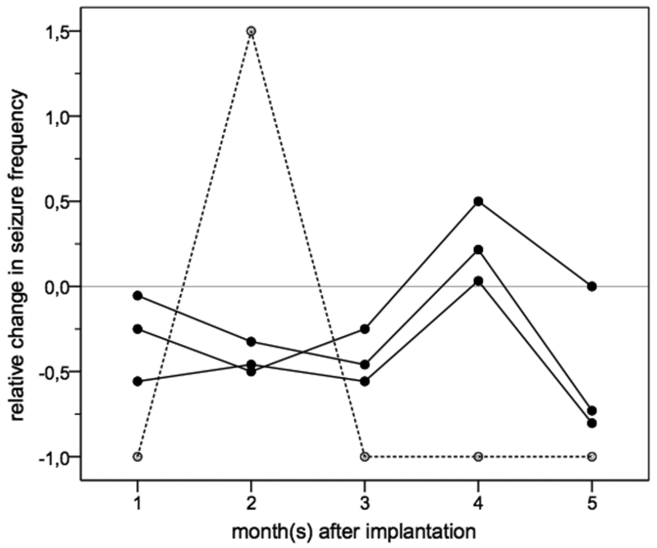

Figure 3. Relative change in frequency of disabling seizures over a period of five months with no stimulation after electrode implantation. Four of 14 patients could be included. Reference to seizure frequency is a three-months preoperative baseline. Dotted lines mark course of the one non-blinded patient, continuous lines that of the three blinded patients treated according to "group B" protocol of the randomized controlled crossover design (Fig. 1). Note both the specific time course of the normalized seizure frequency in the blinded patients group and the similar trend among the individual blinded patients.

these four patients remained responders under NAC-DBS. All in all, the insertion effect of the first month was not predictive of DBS seizure outcome in our cohort.

Insertional Anti-Seizure Effect After Five Months

Four patients of the ANT and NAC group could be followed for five months after insertion of electrodes without initiation of DBS-treatment. Three of these four patients were blinded as part of the above-mentioned case study (11). These three patients showed a strikingly similar trend of seizure frequency over time (Fig. 3; continuous lines). The peak seizure reduction was observed after two to three months, with seizure frequency rising above baseline again after the third month. The remaining nonblinded patient showed seizure freedom except for a single seizure cluster during the second month (Fig. 3; dotted line).

DISCUSSION

Even in our small cohort of DBS-treated epilepsy patients, there was a significant seizure frequency reduction one month after DBS-surgery, suggestive of either a placebo or an insertional effect (IE), or a combination of both. A subcohort showed a reduction in seizure frequency over the first three months during a blinded five-months period, this finding corroborates the initial hypothesis of a true IE in our cohort.

Our data also suggest that:

1. the study design itself might affect the post-surgical seizure frequency outcome. Arguments are provided by the distinct and significant discrepancy in seizure outcome between blinded and nonblinded patients during the first month (Fig. 2b) and the strikingly similar trend of seizure frequency during the five-months observation period among blinded patients (Fig. 3);
2. there is a specific time course of the IE in placebo-controlled patients (Fig. 3); and
3. the IE seems to be independent of the targets selected, the number of targets, and subsequent responder status.

The initial reduction of seizure frequency one month after electrode implantation corroborates earlier findings of an IE (6,10). The reason why the blinded subcohort's seizure frequency reduction is lower compared to the respective non-blinded cohort after one month remains unclear. One possible explanation could be an overt placebo effect. Nonblinded patients' knowledge of DBS treatment initiation could trigger either a reduction in seizure frequency or a diminished seizure perception (14). In phase III antiepileptic drug trials, only between 4 and 19% of patients in the placebo group achieve 50% seizure frequency reduction (15). However, it seems possible that patients undergoing an invasive and new technical approach might be subject to experience a more pronounced placebo effect (16).

Concerning the time course of seizure frequency reduction over five months without stimulation (and therefore putatively an IE effect), our findings are in line with the observations of the SANTE trial (1). Only the three blinded patients recorded a seizure frequency decrease in the three successive months after electrode implantation. Since placebo studies found that a response due to elevated postinterventional expectancy becomes negligible with elapsing time (17), a placebo effect seems not to be the cause for this observation over five months. There have also been single case reports which suggest that IE can develop slowly and last much longer than three months; the possibility of an IE for the duration of years has been discussed both after DBS (8,18) and after responsive neurostimulation surgery (7).

Our cohort is unique since it compromises epilepsy patients with four instead of two DBS-electrodes. An increased number of targets presumably leads to more disturbances of the epileptic network and we consequently expected a more pronounced IE (i.e., seizure frequency reduction) in the ANT and NAC group.

In larger studies on patients with movement disorders, the evidence concerning the relationship between IE and targeted volume is not entirely conclusive. Maltête et al. (19) found that the number of tracts used for microrecording in unilateral subthalamic nucleus (STN) correlates with the clinically observed IE. Mann et al. compared the IE in 47 patients with Parkinson's disease undergoing unilateral DBS either in the STN or the globus pallidum internum. They found a more pronounced clinical effect in the smaller volume target (STN) (5). Also, it seemed unclear whether the IE depends on the volume or the specific function of the target for specific movement disorder (5).

Data concerning the IE in movement disorders is so far limited and conflicting. However, these findings suggest that the IE depends not only on the volume of the targets, a finding which is line with the findings of our cohort.

Whether an IE in patients with epilepsy is itself a marker for subsequent responder status (9,10) remains a matter of debate; our data could not confirm this hypothesis, likely due to the limited number of patients. Other biological surrogate markers for possible responder status, such as the recruitment of frontal EEG-activity (20), an increased number of DBS-induced arousals (21) or the absence of intrathalamic spikes (22), await confirmation in larger, controlled and blinded trials.

The main limitations of this study remain the small number of patients, the varied sizes of the different subcohorts and the fact that only a limited number of the patients (four of 14) was blinded to the initiation of DBS-treatment. Generally, the question of whether the IE is truly microlesional due to electrode-induced processes close to the target (3,23) or whether there is an independent connection to surgery itself (e.g., a placebo effect) is difficult to assess without morphological data. Thus, larger prospective data analysis is needed to further unravel the conundrum of IE in patients with epilepsy and DBS.

CONCLUSION

Our findings suggest that there is a reduction in seizure frequency following DBS surgery but prior to electrical stimulation, which may be due to an insertional effect (IE). This effect seems to last approximately three months. Not surprisingly, our findings also suggest that analysis of IE is hampered by nonblinded patients. In order to define the development of the IE over time, further cumulative long-term data of larger cohorts with stable antiepileptic medication are required. In this regard, study designs that take into account patient expectations prior to the intervention would be helpful in further characterizing the IE and differentiating it from a possible confounding "patient's expectation" effect. Perhaps more importantly, designing future studies with this in mind could also help to understand how patients' expectations influence seizure outcome measurement. The IE itself remains difficult to unravel without an objective seizure outcome measurement, such as long-term intracranial recordings, which would be feasible in large-scale clinical DBS trials.

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Authorship Statements

Dr. Schmitt and Dr. Thuberg designed and conducted the study, including patient recruitment, data collection, and data analysis. Prof. Voges and Dr. Büntjen performed the surgery. Dr. Thuberg, Dr. Büntien and Dr. Schmitt prepared the manuscript draft with important intellectual input from Drs. Kitay, Lee and Prof. Holtkamp. All authors approved the final manuscript. No funding for the study or statistical support in analyzing the data was provided. Drs. Schmitt and Thuberg had complete access to the study data. We would like to thank Prof. Voges and Prof. Heinze for their additional support during preparation of this manuscript.

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REFERENCES

1. Fisher R, Salanova V, Witt T et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;51: 899–908.
2. Tasker RR. Deep brain stimulation is preferable to thalamotomy for tremor suppression. *Surg Neurol* 1988;49:145–153.
3. Casquero-Veiga M, García-García D, Desco M, Soto-Montenegro ML. Understanding deep brain stimulation: in vivo metabolic consequences of the electrode insertional effect. *Biomed Res Int* 2018;2018:8560232.
4. Barnikol UB, Popovych OV, Hauptmann C, Sturm V, Freund HJ, Tass PA. Tremor entrainment by patterned low-frequency stimulation. *Philos Trans A Math Phys Eng Sci* 2008;366:3545–3573.
5. Mann JM, Foote KD, Garvan CW et al. Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry* 2009;80: 794–797.
6. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002;43:603–608.
7. Krishna V, King NK, Sammartino F et al. Anterior nucleus deep brain stimulation for refractory epilepsy: insights into patterns of seizure control and efficacious target. *Neurosurgery* 2016;78:802–811.
8. Thuberg D, Voges J, Holtkamp M, Schmitt FC. Patience can be a virtue with deep brain stimulation of the anterior thalami: another case report. *Epileptic Disord* 2017;19:114–115.
9. Valentín A, Navarrete EG, Chelvarajah R et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. *Epilepsia* 2013;54:1823–1833.
10. Cukiert A, Cukiert CM, Burattini JA, Mariani PP, Bezerra DF. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: a prospective, controlled, randomized, double-blind study. *Epilepsia* 2017;58:1728–1733.
11. Kowski AB, Voges J, Heinze HJ, Oltmanns F, Holtkamp M, Schmitt FC. Nucleus accumbens stimulation in partial epilepsy-a randomized controlled case series. *Epilepsia* 2015;56:e78–e82.
12. Schmitt FC, Voges J, Heinze HJ, Zaehle T, Holtkamp M, Kowski AB. Safety and feasibility of nucleus accumbens stimulation in five patients with epilepsy. *J Neurol* 2014;261:1477–1484.

13. Schmitt FC, Kopitzki K, Holtkamp M et al. Case report: transient proconvulsive effect of acute deep brain stimulation – Relationship to volume of activated tissue. *Z Epileptol* 2012;25:38.
14. Ernst E, Resch KL. Concept of true and perceived placebo effects. *BMJ* 1995;311: 551–553.
15. Goldenholz DM, Goldenholz SR. Response to placebo in clinical epilepsy trials-old ideas and new insights. *Epilepsy Res* 2016;122:15–25.
16. Bystad M, Bystad C, Wynn R. How can placebo effects best be applied in clinical practice? A narrative review. *Psychol Res Behav Manag* 2015;8: 41–45.
17. Hyland ME. Motivation and placebos: do different mechanisms occur in different contexts? *Philos Trans R Soc B Biol Sci* 2011;366:1828–1837.
18. Hartl E, Bötzel K, Mehrkens JH, Noachtar S. Seizure reductions outlast DBS explantation. *Brain Stimul* 2018;11:636–638. https://doi.org/10.1016/j.brs.2018.01.033.
19. Maltête D, Chastan N, Derrey S et al. Microsubthalamotomy effect at day 3: screening for determinants. *Mov Disord* 2009;24:286–289.
20. Zumsteg D, Lozano AM, Wennberg RA. Rhythmic cortical EEG synchronization with low frequency stimulation of the anterior and medial thalamus for epilepsy. *Clin Neurophysiol* 2006;117:2272–2278.
21. Voges BR, Schmitt FC, Hamel W et al. Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. *Epilepsia* 2015;56:e99–e103. https://doi.org/10.1111/epi.13045.
22. Sweeney-Reed CM, Lee H, Rampp S et al. Thalamic interictal epileptiform discharges in deep brain stimulated epilepsy patients. *J Neurol* 2016;263: 2120–2126. https://doi.org/10.1007/s00415-016-8246-5.
23. Jech R, Mueller K, Urgosik D et al. The subthalamic microlesion story in Parkinson's disease: electrode insertion-related motor improvement with relative Cortico-subcortical Hypoactivation in fMRI. *PLoS ONE* 2012;7:e49056.

