Received: 10 August 2023 | Revised: 24 April 2024 | Accepted: 25 April 2024

DOI: 10.1111/epi.18003

Epilepsia®

RESEARCH ARTICLE

Long-term evaluation of anterior thalamic deep brain stimulation for epilepsy in the European MORE registry

Elisabeth Kaufmann[1] | **Jukka Peltola**[2] | **Albert J. Colon**[3] | **Kai Lehtimäki**[4] | **Milan Majtanik**[5,6] | **Jürgen K. Mai**[5,7] | **Beata Bóné**[8] | **Carla Bentes**[9,10] | **Volker Coenen**[11] | **Antonio Gil-Nagel**[12] | **Antonio J. Goncalves-Ferreira**[13] | **Philippe Ryvlin**[14] | **Rod Taylor**[15,16] | **Thomas C. Brionne**[17] | **Frans Gielen**[18] | **Shannon Song**[19] | **Paul Boon**[20] | **on behalf of the MORE study group**[†]

Correspondence
Elisabeth Kaufmann, Department of Neurology, Epilepsy Center, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany.
Email: elisabeth.kaufmann@med.lmu.de

Funding information
Medtronic

Abstract

Objective: Short-term outcomes of deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) were reported for people with drug-resistant focal epilepsy (PwE). Because long-term data are still scarce, the Medtronic Registry for Epilepsy (MORE) evaluated clinical routine application of ANT-DBS.

Methods: In this multicenter registry, PwE with ANT-DBS were followed up for safety, efficacy, and battery longevity. Follow-up ended after 5 years or upon study closure. Clinical characteristics and stimulation settings were compared between PwE with no benefit, improvers, and responders, that is, PwE with average monthly seizure frequency reduction rates of ≥50%.

Results: Of 170 eligible PwE, 104, 62, and 49 completed the 3-, 4-, and 5-year follow-up, respectively. Most discontinuations (68%) were due to planned study closure as follow-up beyond 2 years was optional. The 5-year follow-up cohort had a median seizure frequency reduction from 16 per month at baseline to 7.9 per month at 5-year follow-up ($p < .001$), with most-pronounced effects on focal-to-bilateral tonic–clonic seizures ($n = 15$, 77% reduction, $p = .008$). At last follow-up (median 3.5 years), 41% (69/170) of PwE were responders. Unifocal epilepsy ($p = .035$) and a negative history of epilepsy surgery ($p = .002$) were associated with larger average monthly seizure frequency reductions. Stimulation settings did not differ between response groups. In 179 implanted PwE, DBS-related adverse events (AEs, $n = 225$) and serious AEs ($n = 75$) included deterioration in epilepsy or seizure frequency/severity/type (33; 14 serious), memory/cognitive

[†]The collaborators of the MORE study group are listed in Appendix.

Trial Registration Information: The trial was registered on clinicaltrials.gov on January 31, 2012 (NCT01521754, https://clinicaltrials.gov/ct2/show/NCT01521754?term=NCT01521754&draw=2&rank=1). The first subject was enrolled on February 21, 2012, and follow-up was complete on June 19, 2019.

For affiliations refer to page 2452.

impairment (29; 3 serious), and depression (13; 4 serious). Five deaths occurred (none were ANT-DBS related). Most AEs (76.3%) manifested within the first 2 years after implantation. Activa PC depletion ($n = 37$) occurred on average after 45 months.

Significance: MORE provides further evidence for the long-term application of ANT-DBS in clinical routine practice. Although clinical benefits increased over time, side effects occurred mainly during the first 2 years. Identified outcome modifiers can help inform PwE selection and management.

KEYWORDS

ANT-DBS, drug-resistant epilepsy, neuromodulation, neurostimulation, predictor of outcome, SANTE

1 | INTRODUCTION

Neuromodulation techniques in epilepsy—including vagus nerve stimulation (VNS), responsive neurostimulation (RNS), external trigeminal nerve stimulation (eTNS), focal cortex stimulation (FCS), and deep brain stimulation (DBS)—are used as an add-on therapy option for adults with drug-resistant focal epilepsy. VNS and eTNS have an additional antidepressant effect,[1,2] RNS can be tailored to the patient's seizure-onset zones and is based on a closed-loop-stimulation mechanism.[3–5] However, RNS requires a localizable seizure focus and is not available in Europe.

A recent technique, DBS of the anterior nucleus of the thalamus (ANT), received the Conformit__ Europ__enne (CE mark) in 2010, and U.S. Food and Drug Administration (FDA) approval in 2018, after its safe and effective use was confirmed by the Stimulation of the ANT for Epilepsy (SANTE) randomized controlled trial[6,7] as well as multiple single-center reports (for review see, e.g., Refs [[8,9]]). Solid knowledge exists on safety aspects, potential ANT-DBS therapy–related adverse events (AEs), as well as on *short-term* clinical effects. Median monthly seizure frequency reduction rates of 41% and 69% were observed after 1 and 5 years, respectively, in the SANTE trial,[6,7] whereas in the observational Medtronic Registry for Epilepsy (MORE) the median monthly seizure frequency decreased by 25.3% at 1 year and 33.1% at 2 years ($p < .001$), with a responder rate of 32.3%.[10] Implantation site pain, infections, discomfort, paresthesia, dizziness, and leads outside the target have been reported among the most frequent AEs.[6,7,10] Only few and mainly small-scaled ANT-DBS reports include *long-term* data exceeding 2 years of follow,-up.[7,11–15]

The most recent long-term follow-up data of the SANTE trial reported a median seizure frequency reduction rate of 75% at 7 years.[11] The limited number of long-term evaluations is surprising considering that the mechanism of ANT-DBS in epilepsy is mainly based on neuromodulation, that is, long-term effects, which become increasingly evident over time.[8] Long-term multicenter observations of the clinical routine use of ANT-DBS are needed to evaluate safety, to confirm clinical trends that are observed during short-term follow-up, and to compare the effectiveness of different patient management approaches. So far it remains largely unclear how patient and stimulation-related parameters impact the clinical response. Furthermore, the SANTE cohort was implanted mainly with earlier generation implantable neurostimulators (INSs) (e.g., Kinetra),[11] and large-scale longevity evaluations in more current generations of INSs in epilepsy (e.g. Activa PC) have not been reported.

The long-term evaluation of the multicenter observational MORE study seeks to evaluate the long-term (1)

Key points

- The efficacy of deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) increased over time, achieving a median seizure frequency reduction of 56% ($n = 46$) at 5 years and a responder rate of 41% ($n = 170$) at last follow-up.
- Seizure-frequency reduction was associated with unifocal epilepsy ($p = .035$) and negative history of resective surgery ($p = .002$).
- Adverse events were typically moderate and reversible and manifested primarily during the first 2 years after implantation.
- Activa PC depletion ($n = 37$) occurred on average after 45 months.
- The incidence rate for sudden unexpected death in eilepsy (SUDEP) was 1.62 events for 1000 person-years.

clinical effects and (2) safety of ANT-DBS therapy upon its clinical routine application, including Activa PC INS longevity, as well as (3) its impact on quality of life and mood. Furthermore, a comparative evaluation of different patient management approaches was performed in order (4) to identify outcome-modifying parameters.

2 | METHODS

2.1 | Study design, approval, and registration

MORE is an open-label, observational, international multicenter phase IV study (NCT01521754; 25 sites in 13 countries including 11 European countries, Canada, and Russia). The study started in March 2012 and allowed for prospective and retrospective enrollment. The primary evaluation ended after 2 years of FU and is described in detail elsewhere.[10]

The protocol was updated to allow optional extension of follow-up up to 5 years in 2016 (CIP vs 4 17Feb2016). The last subject completed 2 years of FU on June 19, 2019, and the study was closed. Thus the majority of patients were discontinued without having had the possibility to continue the observation phase until the 5-year follow-up visit.

The study protocol is in accordance with the ethical standards laid down in the Declaration of Helsinki and was approved by each center's local or central ethics committee. The study was administered and sponsored by Medtronic.

2.2 | Study cohort and patient management

For a detailed description of the study cohort and patient management, we refer to Peltola et al.[10] In short, DBS implantation was performed in adult (≥18 years of age) people with epilepsy (PwE) after completion of at least two full consecutive months of baseline seizure frequency documentation according to the treating centers' standard clinical practice. Although an on-label use of ANT-DBS therapy (Medtronic DBS lead model 3387, dual channel Activa PC neurostimulator) was foreseen in the study protocol, the off-label (according to CE mark) use of Medtronic DBS lead model 3389 or the Activa RC INS was not explicitly excluded. The individual intrathalamic lead positions were evaluated by independent specialists based on the preoperative magnetic resonance imaging (MRI) and the postoperative computed tomography (CT) or MRI data and reported to the treating physicians. Using computational methods, atlas of Mai[16] was non-rigidly co-registered to individual patient's thalamus using MrxBrain software, and location of lead contacts was evaluated by an experienced neurosurgeon (K.L.). The following criterion was defined as a successful bilateral implant: at least one contact in ANT or its border area including the mamillothalamic tract bilaterally.

2.3 | Data acquisition and outcome classification

The follow-up visits were conducted according to clinical practice and, for data analysis, were grouped into intervals of 12 months. During the follow-up visits, the subsequent parameters were assessed: monthly frequency of individual seizure types (reclassified according to the current International League Against Epilepsy (ILAE) classification of seizure semiology from 2017[17]), concomitant medication, neurostimulator programming, study deviations, and health-related quality of life (HRQOL) as assessed by the Quality of Life in Epilepsy Inventory-31 (QOLIE-31)[18] and the Short Form 36 Health Survey (SF-36).[19] The completion of the HRQOL questionnaires and the Beck Depression Inventory II (BDI-II) was optional. AEs including device events were reported per the Clinical investigation of medical devices for human subjects—Good clinical practice (ISO 14155:2011) and classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. All AEs were reviewed by an external adjudication committee for potential relation to DBS therapy, system, or procedures.

Subjects were considered as "responders" if they had a reduction of at least 50% of their average monthly seizure frequency compared to baseline. PwE with worsening or no improvement were classified as "no benefit." PwE with <50% seizure frequency reduction were classified as "improvers."

2.4 | Statistical analysis

Descriptive statistics were used to summarize demographics, clinical cohort characteristics, stimulation settings, and safety aspects. Numerical data are presented as median with interquartile range (IQR) or mean with respective standard deviation (SD). Group comparisons were performed using paired *t* tests, Kruskal–Wallis test, or analysis of variance (ANOVA), as appropriate for continuous variables, or Fisher's exact test for categorical variables. A multivariate analysis was added to identify predictors of seizure frequency reduction, using unifocal epilepsy, history of VNS, history of resection,

gender, age, and cognitive impairment as dependent variables. The Kaplan–Meier method was implemented to estimate INS longevity. The change in average monthly seizure frequency from baseline to last completed follow-up, as well as the change in the QOLIE-31, SF-36, and BDI-II scores were assessed using Wilcoxon signed rank tests. A *p*-value of .05 or less was considered statistically significant.

The safety and INS longevity analyses were performed on all enrolled and implanted subjects (all patients set, *APS*). Cohort characteristics and stimulation parameters are reported for all implanted PwE who met the eligibility criteria (full analysis set, *FAS*). The analyses of the long-term effectiveness and patient-reported outcomes were performed on the available patient set, that is, all PwE who completed the respective study visit. In addition, some analyses focused on patients who had both baseline and follow-up seizure diary data at every relevant visit (constant cohort, *CC*). Patients had to have had the specified visit in order to be included in the relevant analysis.

3 | RESULTS

The participant timeline is summarized in Figure 1, including the reasons for discontinuation. The *FAS* encompassed 170 PwE and a total of 104, 62, and 49 PwE completed the 3-year (mean 37.1 months), 4-year (mean 47.5 months), and 5-year follow-up (55.9 months), respectively. Most discontinuations (68%; 82/121) were due to completion of the primary objective phase of the study at 2-year follow-up to closure of the study observation phase for patients who decided to extend follow-up beyond 2 years. Five PwE left due to a lack of benefit. A comparison of demographic and clinical characteristics of PwE who completed the 5-year follow-up visit and those who did not is given in Table S1: significant group differences were revealed only for the number of anti-seizure medications (ASMs) taken at the time of DBS implantation (5-year completers: 2.7 ± 1.0 vs non-completers: 3.1 ± 1.2; $p = .017$), as well as the prevalence of VNS therapies and epilepsy surgeries performed prior to ANT-DBS (5-year completers vs non-completers: only VNS 40.8% vs 32.2%, VNS and resective surgery 0% vs11.6%; $p = .049$). The cohort characteristics at the time of the annual visits are summarized in Table S2. The mean length of exposure to DBS therapy of all implanted PwE (*APS*, $n = 179$) was 3.4 ± 1.3 years. Subjects were followed for a cumulative total of 617.0 years. A total of 73 *FAS* patients (42.9%) had prior VNS therapy, of which 28 were explanted and 21 turned off upon DBS implantation. In 24 PwE, VNS was continued in parallel with ANT-DBS therapy.

3.1 | Long-term effect on seizure frequency

The median percent change in monthly seizure frequency from baseline at 1- to 5-year follow-up is visualized in Figure 2A. For the *CC* ($n = 46$), a median seizure frequency reduction of −28.3% was observed at 1 year ($p < .001$), which progressively improved up to a −56.1% reduction at 5 years ($p < .001$). Similar reduction rates were calculated for the *FAS* ($n = 170$). Most pronounced effects

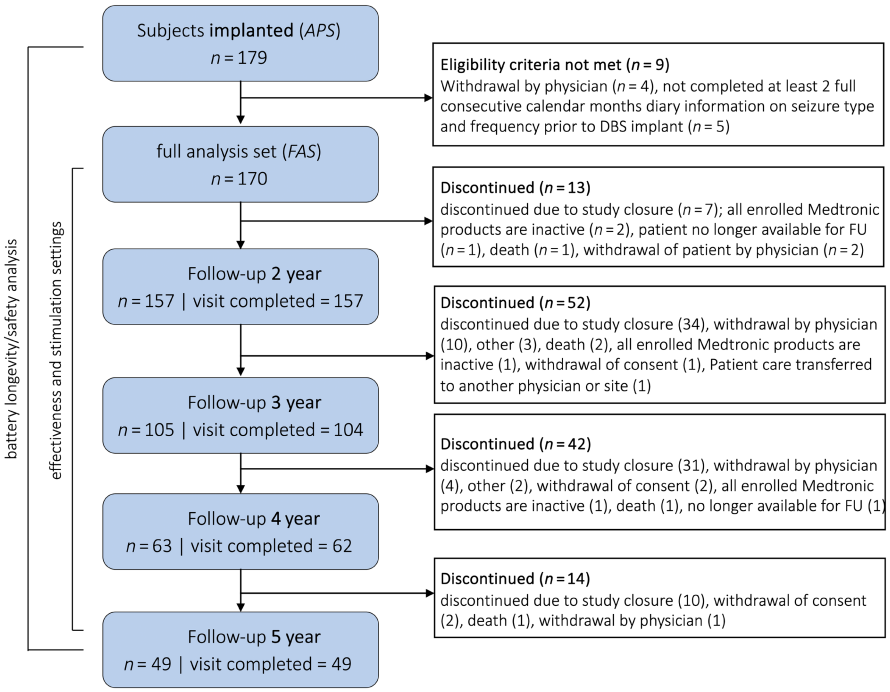
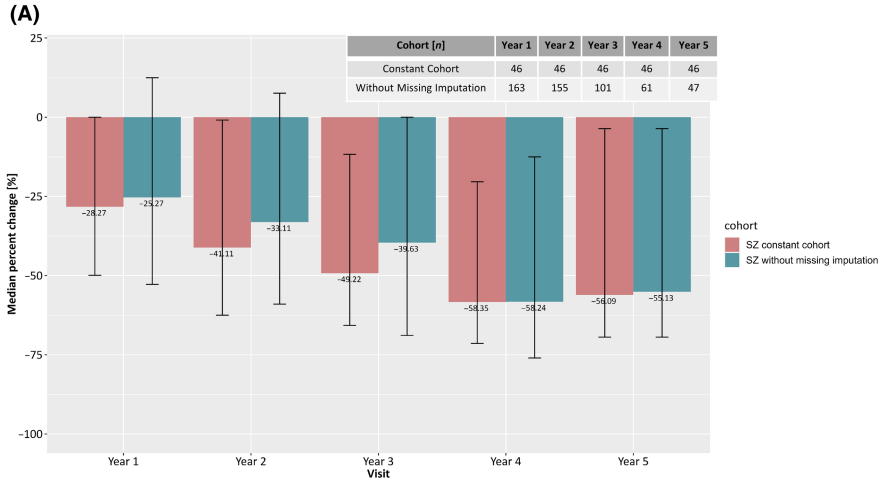


FIGURE 1 Participant timeline. The flow-chart summarizes the number of people with epilepsy (PwE) who completed the annual follow-up clinical visits or discontinued between phases. Most PwE (82/121; 68%) discontinued as planned, as follow-up beyond 2 years was optional. The 3-year follow-up visit took place after a mean observation time of 37.1 months post implantation, the 4-year visit after 47.5 months, and the 5-year visit after 55.9 months post implantation. APS, all patients set; DBS, deep brain stimulation; FAS, full analysis set; FU, follow-up.



	1 Year Median (IQR) [n]	2 Years Median (IQR) [n]	3 Years Median (IQR) [n]	4 Years Median (IQR) [n]	5 Years Median (IQR) [n]
FAS	−9.98 (−45.7 to 50.0) [49]	−30.93 (−70.2 to 7.1) [42]	−40.0 (−67.3 to −6.7) [29]	−45.66 (−81.0 to 32.3) [18]	−55.03 (−68.0 to 5.2) [13]
FIAS	−27.58 (−51.7 to 5.2) [128]	−28.33 (−59.0 to 9.1) [117]	−33.77 (−70.3 to 8.0) [80]	−56.21 (−80.9 to −4.4) [48]	−48.35 (−74.1 to 5.7) [37]
FBTCS	−14.06 (−56.5 to 20.0) [55]	−29.08 (−60.0 to 42.4) [51]	−20.43 (−58.7 to 45.8) [32]	−51.05 (−84.0 to 33.3) [17]	−77.41 (−87.7 to −49.4) [15]

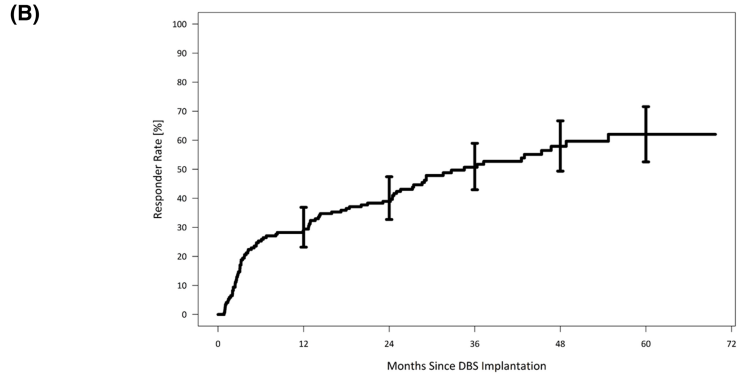


FIGURE 2 Median total monthly seizure frequency percent change from baseline. (A) The median percent change in monthly seizure frequency from baseline at 1 to 5 years post implantation is visualized with reddish bars for the constant cohort ($n = 46$) and with turquoise bars for the calculated outcome for the full analysis set without missing imputation (both cohorts comprised subjects with available seizure diary data). The analyzed number of patients is summarized in the table at the upper-right corner. The median seizure frequency reduction rates regarding seizure semiology are summarized in the lower table. FAS, focal aware seizure; FBTCS, focal to bilateral tonic–clonic seizure; FIAS, focal impaired awareness seizure; IQR, interquartile range; sz, seizure. Error bars represent IQR. (B) Time to first response. Error bars represent 95% confidence intervals.

were observed for focal to bilateral tonic–clonic seizures (FBTCS; $n = 15$; −77.4% at 5 years; $p = .008$), but significant seizure frequency reductions were also achieved for focal impaired awareness seizure (FIAS; $n = 37$; −48.4% at 5 years; $p = .015$) and, by trend, for focal aware seizures (FAS; $n = 13$; −55.0% at 5 years; $p = .191$). At last follow-up (median 3.5 years), most PwE (126/170; 74.1%) showed clinical improvement under ANT-DBS therapy, including 69 responders (40.6%) (Figure S1). Half of these became responders within 13.5 months and 75% within 24 months (Figure 2B). One fourth (44/170; 25.9%), however, did not improve or clinically worsened at last follow-up compared to baseline.

At last follow-up, seven PwE (4%) were seizure-free for a mean duration of 15.3 ± 10.4 months. These PwE had a mean disease duration of 28.9 ± 16.7 years, tried on average 7.0 ± 2.3 ASMs until implantation, with 2.0 ± 1.0 ongoing ASMs at time of implantation. Five of them had a temporal and two had a frontal seizure onset. A summary of the demographics and clinical characteristics by response group is given in Table 1.

3.2 | Patient and site-related seizure outcome modifiers

The comparison of demographics and clinical characteristics of the different response groups, that is, no benefit, improvers, and responders, did not reveal any statistically significant differences except for gender (Table 1, $p = .016$). In the long run, patients with temporal lobe epilepsy (TLE) achieved a slightly stronger reduction in their median monthly seizure frequency than patients with frontal or parieto-occipital lobe epilepsy. Patients with multifocal epilepsy had less favorable outcomes (Table S3).

The multivariate analysis based on mixed models revealed significant effects on seizure frequency reduction rates for negative history of epilepsy surgery ($p = .002$) and for unifocal epilepsy ($p = .035$). No association was found for prior VNS ($p = .678$), age ($p = .835$), gender ($p = .936$), or cognitive impairment ($p = .524$), although univariate models showed by trend better outcomes in PwE without cognitive impairment (last follow-up: −40.0% ($n = 106$) vs −27.9% ($n = 64$); $p = .519$) or who have been implanted at

TABLE 1 Demographic characteristics by response profile at last follow-up.

Variable	No benefit ($n=44$)	Improver ($n=57$)	Responder ($n=69$)	Seizure-free ($n=7$)
Age at baseline, years				
Mean ± SD	34.3 ± 9.5	35.2 ± 9.9	36.9 ± 12.0	38.9 ± 13.2
Gender, *n* (%)				
Female	18 (40.9%)	17 (29.8%)	38 (55.1%)	4 (57.1%)
Site level of implant, *n* (%)				
Number of implants ≤10	26 (59.1%)	34 (59.6%)	28 (40.6%)	3 (42.9%)
Number of implants >10	18 (40.9%)	23 (40.4%)	41 (59.4%)	4 (57.1%)
Disease duration, years				
Mean ± SD	22.2 ± 13.0	22.6 ± 10.0	24.2 ± 13.2	28.9 ± 16.7
Baseline monthly seizure frequency				
Minimum–maximum	0–610	1–392	0–415	0–12
Median	13.2	11.5	18.7	3.3
Psycho-social history, *n* (%)				
Cognitive impairment	23 (52.3%)	19 (33.3%)	22 (31.9%)	2 (28.6%)
Mood disorders	9 (20.5%)	12 (21.1%)	15 (21.7%)	2 (28.6%)
Number of total (prior and current) ASMs taken at baseline				
Mean ± SD (median)	9.0 ± 3.1 (9.0)	8.6 ± 3.4 (9.0)	8.7 ± 3.3 (8.0)	7.0 ± 2.3 (6.0)
Number of ASMs taken at time of implantation				
Mean ± SD (median)	3.1 ± 1.4 (3.0)	2.9 ± 1.0 (3.0)	2.9 ± 1.1 (3.0)	2.0 ± 1.0 (2.0)
Prior surgical procedure for epilepsy, *n* (%)				
VNS implant	23 (52.3%)	26 (45.6%)	24 (34.8%)	1 (14.3%)
Prior resective brain surgery for epilepsy	10 (22.7%)	12 (21.1%)	12 (17.4%)	3 (42.9%)
Surgical categories, *n* (%)				
Neither a VNS nor a prior resective brain surgery for epilepsy	17 (38.6%)	25 (43.9%)	35 (50.7%)	3 (42.9%)
Presence of VNS implant only	17 (38.6%)	20 (35.1%)	22 (31.9%)	1 (14.3%)
Prior resective brain surgery for epilepsy	4 (9.1%)	6 (10.5%)	10 (14.5%)	3 (42.9%)
Both a VNS and prior resective brain surgery for epilepsy	6 (13.6%)	6 (10.5%)	2 (2.9%)	0 (0%)
Seizure type (ILAE, 2017), *n* (%)				
Focal impaired awareness seizures	38 (86.4%)	50 (87.7%)	58 (84.1%)	5 (71.4%)
Focal to bilateral tonic–clonic seizures	31 (70.5%)	37 (64.9%)	41 (59.4%)	3 (42.9%)
Focal aware seizures	16 (36.4%)	18 (31.6%)	33 (47.8%)	2 (28.6%)
Other	1 (2.3%)	1 (1.8%)	3 (4.3%)	0 (0%)
Region of the brain does the seizure most likely originate, *n* (%)				
Unifocal				
Temporal	13 (29.5%)	24 (42.1%)	29 (42.0%)	5 (71.4%)
Frontal	7 (15.9%)	11 (19.3%)	12 (17.4%)	2 (28.6%)
Parieto-occipital	3 (6.8%)	4 (7.0%)	9 (13.0%)	0 (0%)
Other	1 (2.3%)	1 (1.8%)	0 (0%)	0 (0%)
Multifocal				
Diffuse or multifocal	16 (36.4%)	14 (24.6%)	11 (15.9%)	0 (0%)
Other	4 (9.1%)	3 (5.3%)	8 (11.6%)	0 (0%)
Imaging result				
Normal/non-lesional	16 (36.4%)	26 (45.6%)	22 (31.9%)	2 (28.6%)
Abnormal/lesional	28 (63.6%)	31 (54.4%)	47 (68.1%)	5 (71.4%)

TABLE 1 (Continued)

Variable	No benefit ($n=44$)	Improver ($n=57$)	Responder ($n=69$)	Seizure-free ($n=7$)
Temporal: mesial	13 (46.4%)	31 (54.4%)	47 (68.1%)	5 (100.0%)
Sclerosis	4 (50.0%)	7 (58.3%)	3 (25.0%)	2 (40.0%)
Cortical dysplasia	1 (12.5%)	2 (16.7%)	0 (0%)	0 (0%)
Dysembryoplastic neuroepithelial tumor (DNET)—Ganglioglioma	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)
Other	3 (37.5%)	2 (16.7%)	0 (0%)	0 (0%)
Temporal: lateral	3 (23.1%)	5 (25.0%)	12 (42.9%)	2 (40.0%)
Sclerosis	0 (0%)	0 (0%)	1 (8.3%)	1 (50.0%)
Cortical dysplasia	0 (0%)	4 (80.0%)	5 (41.7%)	1 (50.0%)
Inflammatory	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)
Other	3 (100%)	1 (20.2%)	5 (41.7%)	0 (0%)
Temporal: mesial and lateral	2 (15.4%)	2 (10%)	5 (17.9%)	1 (20.0%)
Cortical dysplasia	1 (50.0%)	0 (0%)	1 (20.0%)	0 (0%)
DNET—Ganglioglioma	0 (0%)	0 (0%)	1 (20.0%)	0 (0%)
Other	1 (50.0%)	2 (100%)	3 (60.0%)	1 (100.0%)
Frontal	5 (17.9%)	7 (22.6%)	14 (29.8%)	0 (0%)
Parietal	8 (28.6%)	5 (16.1%)	10 (21.3%)	0 (0%)
Occipital	8 (28.6%)	8 (25.8%)	5 (10.6%)	0 (0%)
All 4 lobes	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: ASM, anti-seizure medication; VNS, vagus nerve stimulation.

experienced centers, that is, centers with more than 10 implantations (last follow-up: −50.6% ($n=82$) vs −27.9% ($n=88$); $p=.202$; Figure S2). The number of ASMs did not change relevantly over time and was comparable between response groups (Table 1).

3.3 | System- and procedure-related seizure outcome modifiers

At 2 and 5 years, 77.6% and 76.7% of implants, respectively, had at least one contact in each ANT or its border area including the mamillo-thalamic tract. However, the surgical success rates were not associated with the clinical response rates at 5-year follow-up (successful implantations: non-responders 85.7%, improvers 66.7%, responders 87.5%).

PwE with transventricularly implanted electrodes achieved by trend better outcomes than PwE with extraventricularly implanted electrodes, but no significant group difference was revealed based on the small subgroups (Table S4). Seizure frequency reduction rates appeared independent of the lead model used (3387: $n=39$ vs 3389: $n=129$ vs mixed: $n=1$).

Throughout the annual visits, the three response groups were stimulated with parameters similar to the ones used in the SANTE trial, that is, cyclic mode (1 min ON, 5 min OFF time), amplitude of 5 V, high frequency stimulation (145 Hz), and a pulse width of 90 μs. Furthermore, no increase in bipolar stimulation occurred (1 year: 15.2%, 3 year: 17.3%, 5 year: 16.3%). Although no clear trend was observed in the stimulation setting over time, the responder group stayed closest to the SANTE parameters, whereas PwE without or only intermittent response revealed a greater variability in their stimulation settings over the course of the study (Table 2; Table S5).

3.4 | HRQOL and depression symptom severity

Figure 3 summarizes the mean changes in HRQOL measures and BDI scores over time. About one third of PwE had an improvement in QOL after DBS implant, with a ≥5-point increase in QOLIE-31, which has been reported to be indicative of a clinically meaningful change in DRE[20]:1 year: 36% (30/84), 3 year: 37% (17/46), 5 year: 41% (7/17). Overall, no significant change from baseline was observed for the mean SF-36 Physical and Mental Component Summary at the annual visits. The depression severity as measured by the BDI-II improved progressively from baseline to 4-year follow-up (9.0 ± 8.1 vs 7.0 ± 5.4)

TABLE 2 Stimulation settings and number of anti-seizure medications at 3- to —5-year follow-up.

	Time point of follow up visit and response groups (number of available data sets)								
	3 year			4 year			5 year		
Programming settings	No-benefit ($n=26$)	Improver ($n=33$)	Responder ($n=42$)	No-benefit ($n=15$)	Improver ($n=14$)	Responder ($n=32$)	No-benefit ($n=9$)	Improver ($n=13$)	Responder ($n=25$)
Cycling									
Measure available, *N* (%)	25 (96.2%)	30 (90.9%)	37 (88.1%)	15 (100%)	14 (100%)	29 (90.6%)	9 (100%)	13 (100%)	22 (88.0%)
On	24 (96.0%)	30 (100%)	37 (100%)	14 (93.3%)	14 (100%)	29 (100%)	9 (100%)	13 (100%)	22 (100%)
ON time [min] mean ± SD	1.0 ± .0	2.0 ± 5.3	1.8 ± 4.8	1.0 ± .0	.9 ± .3	1.0 ± .2	1.0 ± .0	1.0 ± .0	1.0 ± .0
ON time [min–max]	[1]	[1–30]	[1–30]	[1]	[0–1]	[1, 2]	[1]	[1]	[1]
OFF time [min] mean ± SD	4.6 ± .9	4.7 ± .8	4.9 ± .6	4.6 ± .9	4.3 ± 1.4	4.9 ± .7	4.6 ± 1.0	4.6 ± .8	4.8 ± .9
OFF time [min–max]	[2–5]	[2–5]	[2–5]	[2–5]	[0–5]	[1–5]	[2–5]	[3–5]	[1–5]
Off (i.e., continuous stimulation)	1 (4.0%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Amplitude [Volt]									
Left lead									
Measure available, *N* (%)	25 (96.2%)	30 (90.9%)	39 (92.9%)	15 (100%)	14 (100%)	30 (93.8%)	9 (100%)	13 (100%)	23 (92.0%)
Mean ± SD [min–max]	5.0 ± 1.6 [0–9]	5.3 ± 1.3 [2–8]	5.2 ± 1.0 [2–8]	5.4 ± 1.3 [4–9]	5.4 ± 1.8 [0–8]	5.3 ± 1.2 [2–7]	5.7 ± 1.3 [4–8]	5.3 ± 1.1 [4–8]	5.6 ± .8 [4–7]
Right lead									
Measure available, *N* (%)	25 (96.2%)	30 (90.9%)	37 (88.1%)	15 (100%)	14 (100%)	29 (90.6%)	9 (100%)	13 (100%)	22 (88.0%)
Mean ± SD [min–max]	5.0 ± 1.6 [0–9]	5.4 ± 1.2 [2–8]	5.2 ± 1.1 [2–8]	5.4 ± 1.2 [4–9]	5.4 ± 1.9 [0–8]	5.3 ± 1.1 [2–7]	5.7 ± 1.3 [4–8]	5.0 ± 1.8 [0–8]	5.4 ± 1.0 [4–7]
Impedance [Ohms]									
, Left lead									
Measure available, *N* (%)	10 (38.5%)	19 (57.6%)	18 (42.9%)	6 (40.0%)	9 (64.3%)	11 (34.4%)	4 (44.4%)	9 (69.2%)	8 (32.0%)
Mean ± SD [min–max]	913.6 ± 290.5 [506–1634]	962.3 ± 255.5 [263–1548]	914.8 ± 157.7 [617–1202]	990.3 ± 542.2 [402–1839]	939.6 ± 135.4 [709–1202]	735.6 ± 269.7 [284–1093]	954.0 ± 168.3 [840–1202]	729.9 ± 257.8 [283–979]	781.0 ± 209.7 [467–1057]
Right lead									
Measure available, *N* (%)	10 (38.5%)	19 (57.6%)	18 (42.9%)	6 (40.0%)	9 (64.3%)	11 (34.4%)	4 (44.4%)	9 (69.2%)	8 (32.0%)
Mean ± SD [min–max]	878.0 ± 125.4 [727–1067]	921.1 ± 213.3 [295–1408]	1012.4 ± 250.5 [524–1656]	820.0 ± 303.5 [385–1331]	1119.7 ± 425.2 [825–2192]	795.4 ± 139.6 [522–943]	1278.8 ± 622.2 [829–2192]	826.3 ± 195.6 [385–1018]	895.0 ± 224.9 [667–1275]

(Continues)

TABLE 2 (Continued)

Programming settings	Time point of follow up visit and response groups (number of available data sets)								
	3 year			4 year			5 year		
	No-benefit ($n=26$)	Improver ($n=33$)	Responder ($n=42$)	No-benefit ($n=15$)	Improver ($n=14$)	Responder ($n=32$)	No-benefit ($n=9$)	Improver ($n=13$)	Responder ($n=25$)
Pulse width, μs									
Left lead									
Measure available, *N* (%)	25 (96.2%)	30 (90.9%)	39 (92.9%)	15 (100%)	14 (100%)	30 (93.8%)	9 (100%)	13 (100%)	23 (92.0%)
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
60	1 (4.0%)	0 (0%)	4 (10.3%)	1 (6.7%)	1 (7.1%)	2 (6.7%)	1 (11.1%)	2 (15.4%)	2 (8.7%)
90	23 (92.0%)	28 (93.3%)	29 (74.4%)	14 (93.3%)	11 (78.6%)	21 (70.0%)	7 (77.8%)	10 (76.9%)	18 (78.3%)
120–210	1 (4.0%)	2 (6.7%)	6 (15.4%)	0 (0%)	1 (7.1%)	7 (23.3%)	1 (11.1%)	1 (7.7%)	3 (13.0%)
Mean ± SD [min–max]	93.6 ± 25.0 [60–210]	94.0 ± 15.2 [90–150]	93.6 ± 20.2 [60–150]	88.0 ± 7.7 [60–90]	83.6 ± 26.8 [0–120]	99.7 ± 28.2 [60–210]	90.0 ± 15.0 [60–120]	92.3 ± 28.6 [60–180]	91.3 ± 14.2 [60–120]
Right lead									
Measure available, *N* (%)	25 (96.2%)	30 (90.9%)	37 (88.1%)	15 (100%)	14 (100%)	29 (90.6%)	9 (100%)	13 (100%)	22 (88.0%)
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
60	1 (4.0%)	0 (0%)	2 (5.4%)	1 (6.7%)	1 (7.1%)	1 (3.4%)	1 (11.1%)	2 (15.4%)	1 (4.5%)
90	23 (92.0%)	28 (93.3%)	29 (78.4%)	14 (93.3%)	11 (78.6%)	21 (72.4%)	7 (77.8%)	10 (76.9%)	18 (81.8%)
120–210	1 (4.0%)	2 (6.7%)	6 (16.2%)	0 (0%)	1 (7.1%)	7 (24.1%)	1 (11.1%)	1 (7.7%)	3 (13.6%)
Mean ± SD [min–max]	93.6 ± 25.0 [60–210]	94.0 ± 15.2 [90–150]	95.4 ± 19.1 [60–150]	88.0 ± 7.7 [60–90]	83.6 ± 26.8 [0–120]	101.0 ± 27.7 [60–210]	90.0 ± 15.0 [60–120]	92.3 ± 28.6 [60–180]	92.7 ± 12.8 [60–120]
Frequency, Hz									
Measure available, *N* (%)	25 (96.2%)	30 (90.9%)	39 (92.9%)	15 (100%)	14 (100%)	30 (93.8%)	9 (100%)	13 (100%)	23 (92.0%)
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
40	1 (4.0%)	1 (3.3%)	2 (5.1%)	0 (0%)	3 (21.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
60–120	0 (0%)	2 (6.7%)	2 (5.1%)	0 (0%)	0 (0%)	2 (6.7%)	1 (11.1%)	0 (0%)	1 (4.3%)
130–150	23 (92.0%)	25 (83.3%)	30 (76.9%)	14 (93.3%)	10 (71.4%)	26 (86.7%)	7 (77.8%)	10 (76.9%)	21 (91.3%)
160–180	1 (4.0%)	2 (6.7%)	5 (12.8%)	1 (6.7%)	0 (0%)	2 (6.7%)	1 (11.1%)	3 (23.1%)	1 (4.3%)
Mean ± SD [min–max]	139.6 ± 21.2 [40–160]	139.2 ± 20.3 [40–160]	136.2 ± 27.2 [40–180]	144.3 ± 5.0 [140–160]	110.7 ± 53.9 [0–145]	140.0 ± 16.0 [90–180]	137.2 ± 22.4 [80–160]	148.5 ± 11.6 [140–180]	139.8 ± 14.2 [80–160]
Bipolar stimulation									
Bipolar rate	9 (34.6%)	6 (18.2%)	4 (9.5%)	7 (46.7%)	2 (14.3%)	3 (9.4%)	3 (33.3%)	2 (15.4%)	3 (12.0%)

TABLE 2 (Continued)

Programming settings	Time point of follow up visit and response groups (number of available data sets)								
	3 year			4 year			5 year		
	No-benefit ($n=26$)	Improver ($n=33$)	Responder ($n=42$)	No-benefit ($n=15$)	Improver ($n=14$)	Responder ($n=32$)	No-benefit ($n=9$)	Improver ($n=13$)	Responder ($n=25$)
Lead model									
Measure available, *N* (%)	26 (100.0%)	32 (97.0%)	42 (100.0%)	15 (100.0%)	14 (100.0%)	32 (100.0%)	9 (100.0%)	13 (100.0%)	25 (100.0%)
3387	6 (23.1%)	5 (15.6%)	13 (31.0%)	4 (26.7%)	0 (.0%)	10 (31.3%)	1 (11.1%)	4 (30.8%)	8 (32.0%)
3389	20 (76.9%)	27 (84.4%)	28 (66.7%)	11 (73.3%)	13 (92.9%)	22 (68.8%)	8 (88.9%)	9 (69.2%)	16 (64.0%)
Mixed	0 (.0%)	0 (.0%)	1 (2.4%)	0 (.0%)	1 (7.1%)	0 (.0%)	0 (.0%)	0 (.0%)	1 (4.0%)
Implantation approach									
Measure available, *N* (%)	26 (100.0%)	33 (100.0%)	42 (100.0%)	15 (100.0%)	14 (100.0%)	32 (100.0%)	9 (100.0%)	13 (100.0%)	25 (100.0%)
Transventricular	14 (53.8%)	14 (42.4%)	25 (59.5%)	10 (66.7%)	3 (21.4%)	22 (68.8%)	4 (44.4%)	7 (53.8%)	17 (68.0%)
Extraventricular	10 (38.5%)	17 (51.5%)	14 (33.3%)	4 (26.7%)	8 (57.1%)	8 (25.0%)	4 (44.4%)	5 (38.5%)	6 (24.0%)
Mixed	2 (7.7%)	2 (6.1%)	3 (7.1%)	1 (6.7%)	3 (21.4%)	2 (6.3%)	1 (11.1%)	1 (7.7%)	2 (8.0%)
Anti-seizure medication									
Measure available, *N* (%)	26 (100%)	33 (100%)	42 (100%)	15 (100%)	14 (100%)	32 (100%)	9 (100%)	13 (100%)	25 (100%)
Mean ± SD [min–max]	3.58 ± 1.21 [1–6]	3.39 ± 1.09 [1–6]	3.33 ± 1.12 [1–7]	3.53 ± 1.30 [2–6]	3.34 ± .85 [2–5]	3.06 ± 1.01 [1–6]	3.11 ± .60 [2–4]	3.23 ± .93 [2–4]	3.04 ± .89 [1–5]

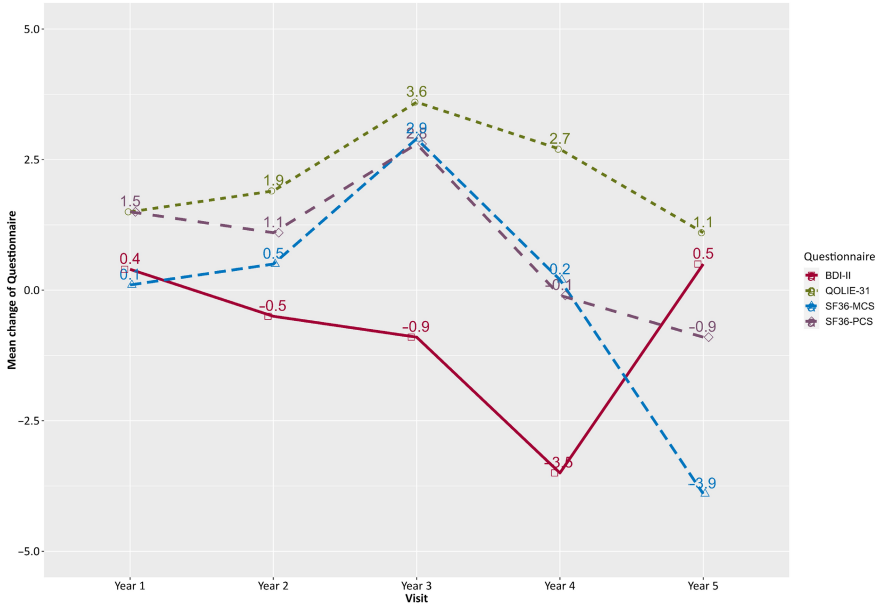


FIGURE 3 Mean change in measures of quality of life and depression from baseline to 5-year follow-up. Mean changes in quality of life at annual visits compared to baseline were measured via standardized questionnaires (QOLIE-31 and SF-36), whereby an increase in the total score reflects an improvement in life quality. The depression severity was assessed via the BDI, whereby a decrease in the total score represents an improvement in depression severity. BDI-II, Beck Depression Inventory; MCS, Mental Component Summary; PCS, Physical Component Score; QOLIE, Quality of Life in Epilepsy; SF-36, Short Form 36.

	1 Year Mean ± SD [*n*]	2 Years Mean ± SD [*n*]	3 Years Mean ± SD [*n*]	4 Years Mean ± SD [*n*]	5 Years Mean ± SD [*n*]
BDI-II	0.4 ± 8.6 [84]	−0.5 ± 8.3 [76]	−0.9 ± 10.3 [46]	−3.5 ± 9.1 [25]	0.5 ± 9.5 [16]
QOLIE-31	1.5 ± 8.9 [84]	1.9 ± 8.0 [78]	3.6 ± 9.4 [46]	2.7 ± 11.0 [24]	1.1 ± 9.8 [17]
SF36 MCS	0.1 ± 12.3 [77]	0.5 ± 11.9 [71]	2.9 ± 12.5 [43]	0.2 ± 11.1 [24]	−3.9 ± 10.8 [16]
SF36 PCS	1.5 ± 7.7 [77]	1.1 ± 8.4 [71]	2.8 ± 9.8 [43]	−0.1 ± 8.4 [24]	−0.9 ± 9.9 [16]

but did not reach significance. No association was found between the HRQOL or BDI and the individual change in seizure frequency (data not shown). Subgroup analyses by response groups were not meaningful, most likely due to the small number of available data sets at the 3- to 5-year follow-up. PwE with discontinued VNS therapy ($n = 49$), which is known to have an antidepressant effect, did not experience a deterioration in depression severity.

3.5 | Adverse events

During the 5-year follow-up, 655 AEs were reported in 156 of 179 (87.2%) implanted subjects, of which 225 of 655 AEs (34.4%) were classified as DBS-related (Table 3). The incidence rate was 1061.5 events for 1000 person-years, and most AEs (76.3%) occurred during the first 2 years after DBS implantation. AEs occurring in at least 5% subjects are reported in Table S6. In addition, a total of 222 severe adverse events (SAEs) occurred in 102 of 179 subjects (57.0%), of which 75 of 222 SAEs (33.8%) were rated as DBS related. The most frequently (≥2%) reported DBS-related AEs/SAEs by Preferred Term (PT) were seizure/epilepsy related events (33/655, 5.0%) and memory/cognitive impairment (29/655, 4.4%) (Table 3). Thereby, seizure AEs referred to an increased seizure frequency or severity or to the occurrence of a new seizure type.

Most of the (DBS-related and unrelated) *seizure* AEs/SAEs (38/53 events; 71.7%) occurred during the first 2 years after implantation. Except for four PwE, the seizure AEs were resolved in all PwE at last follow-up. Furthermore, three status epilepticus AEs including one potentially DBS-related status epilepticus were reported in three PwE from implantation to 5-year follow-up.

Memory impairment was reported in 28 of 179 (15.6%) PwE, 9 of which had prior history of memory impairment. Most (19/29, 65.5%) memory AEs were categorized as moderate, 9 of 29 (31.0%) as mild, and 1 (3.4%) as severe. About three fourths ($n = 21$, 72.4%) were rated as DBS related and only one (3.4%) of these AEs was not resolved at last follow-up.

A total of 33 *depression* (includes depression and depressed mood) AEs (14 DBS-related) was reported in 28 of 179 (15.6%) PwE and rated as mild in 7, moderate in 22, and severe in 4 events. Of note, nearly all (29/33; 87.9%) depression AEs occurred during the first 2 years after implantation and led to reprogramming in four PwE and therapy suspension in one patient. Prior history of depression was affirmed by 11 of 28 PwE (39.3%). *Suicidality* (two ideations, two attempts, one completed) was reported in four PwE. Half of them were female and had a history of mood disorder. In addition, they had a mean age of 41.5 ± 9.0 years, a disease duration of 19.5 ± 10.8 years, a median baseline seizure frequency of 18.5 per month, and therapy with mean 2.5 ± 0.6 ASMs at implantation.

TABLE 3 Adverse events in ≥2% of all implanted subjects ($n = 179$) until 5-year follow-up.

Description	All adverse events (number of patients (%) [number of events])	Serious adverse events (number of patients (%) [number of events])
Total number of events	156 (87.2%) [655]	102 (57.0%) [222]
Deep brain stimulation (DBS)–related events	113 (63.1%) [225]	56 (31.3%) [75]
Procedure-related events	49 (27.4%) [73]	27 (15.1%) [32]
Device-related events	99 (55.3%) [185]	43 (24.0%) [57]
System component–related events	30 (16.8%) [39]	17 (9.5%) [20]
Program stimulation–related events	86 (48.0%) [153]	30 (16.8%) [40]
Memory impairment	20 (11.2%) [21]	3 (1.7%) [3]
Cognitive disorder	8 (4.5%) [8]	0 (0%) [0]
Seizure	19 (10.6%) [22]	11 (6.1%) [12]
Epilepsy	10 (5.6%) [11]	2 (1.1%) [2]
Depression	11 (6.1%) [13]	4 (2.2%) [4]
Device deployment issue	7 (3.9%) [7]	5 (2.8%) [5]
Device dislocation	6 (3.4%) [7]	6 (3.4%) [7]
Headache	7 (3.9%) [8]	1 (.6%) [1]
Anxiety	7 (3.9%) [9]	1 (.6%) [1]
Irritability	6 (3.4%) [6]	0 (0%) [0]
Implant site pain	6 (3.4%) [6]	1 (.6%) [1]
Psychotic disorder	5 (2.8%) [6]	3 (1.7%) [4]
Dizziness	4 (2.2%) [4]	1 (.6%) [1]
Non–DBS-related events	135 (75.4%) [430]	74 (41.3%) [147]
Death	NA	5 (2.8%) [5]

Remarkably, all four PwE had TLE. Five *deaths* occurred at 1.5–4.6 years post implantation due to suicide ($n = 1$), endocarditis ($n = 1$), possible ($n = 1$) or definite ($n = 2$) sudden unexpected death in epilepsy (SUDEP[21]) and were rated as non-DBS related. The incidence rate for SUDEP was 1.62 events for 1000 person-years.

Although it was not in the scope of the study, double stimulation with VNS and DBS did not lead to more frequent or different AEs compared to DBS only.

3.6 | Device performance

A total of 59 of 170 PwE (34.7%) had a least one device modification, with 19 PwE (11.2%) having lead modifications. The most frequent lead modification type was explantation with replacement. Seven device deficiencies in five FAS patients (2.9%) were reported from implantation to 5-year follow-up, including one extension damage, two lead damages, two electrical impedance issues, and two device malfunctions. Definitive device explantation was performed in eight PwE (4.5%) due to lead malposition ($n = 1$), dizziness ($n = 1$), infection ($n = 3$), or lack of seizure reduction ($n = 3$). Mean survival time to definitive explant was 41.0 months.

INS depletion occurred in 37 PwE (20.7%) at 45.0 ± 13.2 months post implantation, on average. Most of these PwE (33/37; 89.2%) were on cyclic mode with median stimulation settings similar to the SANTE parameters except of a higher median stimulation amplitude of 6 V (maximum 8 V).

3.7 | Other reported events

Five pregnancies have been reported in three patients during follow-up visits, including one reported AE of miscarriage unrelated to DBS therapy.

4 | DISCUSSION

The MORE 5-year follow-up provides, besides the SANTE reports,[6,7,11] the first multicenter long-term data on the clinical application of ANT-DBS therapy for people with drug-resistant focal epilepsy. It is unique in its observational design, allowing for an individualized ANT-DBS therapy implementation at the physicians' discretion and thereby reflects clinical routine. In contrast to shorter term follow-ups (<3 years), the up to 5-year, long-term observation further allowed analysis of the device performance, long-term tolerability of ANT-DBS, and the response time course.

Progressive reductions in the average monthly seizure frequency rates were observed, reaching a median reduction of 56% (CC, $n = 46$) at 5-year follow-up and a responder rate of 41% at last follow-up (FAS, $n = 170$) with most pronounced effects on FBTCS. Significantly better seizure outcomes were observed in people (1) with unifocal epilepsy, and (2) without history of resective surgery. Of note, therapy outcome was independent of age, gender, disease duration, prior VNS, and stimulation settings. Quality of life and BDI scores improved slightly over time, unrelated to the seizure frequency reduction rate. AEs occurred mainly during the first 2 years after implantation and encompassed the previously described range of epilepsy-associated events, cognitive and affective symptoms. Activa PC INS depletion occurred after an average of 3.8 years.

4.1 | Long-term efficacy

The MORE long-term evaluation confirms the previously reported gradual decrease in monthly seizure frequency rates under ANT-DBS therapy and carries on the trend of the 2-year evaluation.[10] However, the achieved overall seizure frequency reduction and responder rates slightly underscored the ones reported in the SANTE trial (5 year: 56% vs 69%; responder rate: 41% vs 68%).[7] The observed differences are most likely due to the lower number of people with unifocal epilepsy (MORE vs SANTE: 67% vs. 82%) and TLE (MORE vs SANTE: 39% vs 60%), who are by trend more likely to achieve favorable outcomes.[10] Of note, in the SANTE trial, PwE were exclusively implanted transventricularly. With the limitation that the subgroup of transventricularly implanted PwE was much smaller in the MORE registry than the SANTE trial, their outcome was comparable (MORE vs SANTE at 5 year follow-up: $n = 28$ vs $n = 74$; median seizure frequency reduction from baseline 62% vs 69%). Cohort characteristics including median baseline seizure frequency (MORE vs SANTE: 15.8 vs 19.5 per month), disease duration (23.1 vs 22.3 years), prior VNS (43% vs 44.5%), and prior resection (20% vs 24.5%) did not strikingly differ between both trials.[7] Furthermore, in SANTE, all implants were evaluated by an expert group and only PwE with MRI verified lead contacts bilaterally within the ANT were included in the study (nearly 10% were reimplanted).[6] The observational MORE, in contrast, had no preset surgical method or guided selection of lead contacts, potentially explaining the lower seizure reduction rates and more delayed therapy response compared to SANTE.

4.2 | Outcome modifiers

Up to now, the optimal patient selection, implantation, and stimulation setting remain an unanswered but urgent clinical question.[9,22] The multicenter approach allowed identification of positive outcome modifiers including unifocal epilepsy and negative history of epilepsy surgery. These PwE might be less severely affected and bear a higher potential for neuromodulation than people with multifocal epilepsies or prior surgery. However, the proposed association requires further evaluation. In epilepsy, unifocality and pretreatment seem to be even more relevant than age, as no age- or disease stage–dependent effects have been observed—in contrast to the EARLYSTIM trend in Parkinson's disease.[23] In line with the MORE 2-year evaluation, better outcomes were also observed in PwE without cognitive impairment and implantation at experienced centers. These parameters did not reach significance in the long-term follow-up—potentially due to the reduced sample size at 3- to 5-year follow-up.

Similar to the 2-year evaluation, current experts' clinical practice, and other long-term reports,[9,11,22] stimulation settings stayed close to the initial SANTE parameters and did not differ relevantly between response groups at last follow-up. Furthermore, clinical response was typically achieved within the first 2 years after implantation. Both could indicate that stimulation setting is less crucial for therapy success than candidate selection and surgical parameters. However, it remains to be elucidated whether systematic changes in the stimulation settings could convert non-responders into responders. Smaller-scaled studies did not reveal conclusive results for different stimulation approaches (for summary see, e.g., Fasano et al.[9]). Sufficiently powered subgroup analyses would be desirable to reveal the best stimulation settings for certain seizure-onset zones and seizure characteristics. Further analysis is also needed on the clinical importance of electrode placement within the ANT, the lamina, or neighboring thalamic nuclei, which requires a detailed MRI-based

analysis of the precise location of the active contacts and will be reported separately.

ANT-DBS therapy led to meaningful QOL improvement in about one third of the available PwE. No association was found, however, between seizure frequency reduction and measures of HRQOL or BDI scores and no difference was seen between response groups. This is likely due to the limited number of available data sets for the 4- and 5-year follow-up. However, the patients might also become more aware of their own disabilities and epilepsy associated limitations after a reduction of their seizure frequency, reflecting in unchanged HRQOL and BDI scores .[24]

4.3 | Safety and mortality

There were no unanticipated device- or therapy-related AEs. AEs occurred mainly within the first 2 years after implantation, were of moderate severity, and were typically easily resolvable. It is notable that suicidality occurred only in people with TLE, half of whom had a history of mood disorder. A number of reports emphasized that PwE have an up to 5-fold increased rate of death by suicidality compared to the general population, with highest rates in people with TLE and history of surgery.[25–27] The increased suicidality rate in TLE was attributed to the impairment of limbic regions leading to mood disturbance, aggression, and impulsivity. Of interest, suicides tended to occur once good seizure control was obtained in people with chronic TLE.[28,29] The so-called "burden of normalization" is highest in people with TLE, because they achieve the highest rates of seizure freedom after surgery and—by trend—also under ANT-DBS therapy.[7,9,11,30]

During the 5-year follow-up, five deaths occurred, none of which were considered to be related to the device or the therapy. This number is in line with the SANTE trial, which reported 5 deaths over 441 subject-years at 5-year follow-up.[7] The observed SUDEP rate of 1.6 per 1000 patient-years is also comparable to the one reported in the SANTE trial (2.1/1000 patient-years) and below the SUDEP rate expected in people with drug-resistant epilepsy (6–9/1000 patient-years).[11,31–33] The SUDEP risk is driven substantially by the frequency of FBTCS,[34,35] which are effectively reduced by ANT-DBS therapy. Altered thalamo-cortical coupling and increased vigilance, as well as repeated nocturnal arousal reactions under cyclic ANT-DBS, might constitute further protective factors.[36–39]

4.4 | INS longevity

Activa PC INS depletion occurred on average after 3.8 years, whereas an INS longevity of 2.9 years was reported for the Kinetra model in the SANTE trial using similar stimulation parameters.[11]

4.5 | Strengths and limitations

The international multicenter design of the registry ensured coverage of the geographic area where the therapy was available per CE mark, with large variety in health care systems, sociocultural environments, implantation techniques, and patient management strategies. As this was an observational study documenting clinical-routine use in a post-market environment, there was no control group. The registry protocol also allowed for a retrospective enrollment, which makes it prone to documentation and recall errors. Furthermore, seizure frequency is known to greatly fluctuate and thus the short baseline interval of 2 months bears the risk of reflecting an exceptionally good period and to consequently cover the true efficacy at long-term follow-up. Due to the consequently limited sample size at 2- to 5-year follow-up, the long-term follow-up results should be interpreted with caution. It was further optional to provide HRQOL and BDI data, which led to limited data sets and prohibited meaningful analyses. Other outcome parameters such as seizure severity, seizure duration, or duration of the postictal phase were not assessed at all and should be considered in future trials.

5 | CONCLUSION

ANT-DBS therapy is safe and effective also during long-term use up to 5 years. Candidate selection and patient management might be optimized based on the identified outcome modifiers, but the potential of different stimulation settings still needs to be explored. Clinical benefit increases over time and is accompanied by a low risk of typically moderate and reversible AEs, which manifest mainly during the first 2 years after implantation. The longevity of the Activa PC INS exceeded the one of Kinetra by about 1 year.

AUTHOR CONTRIBUTIONS

Elisabeth Kaufmann: Data collection, interpreted the data; drafted the manuscript. Jukka Peltola: Data collection, interpreted the data; drafted the manuscript. Albert J. Colon: Data collection, data analysis, critical revision of the manuscript. Kai Lehtimäki: Providing surgical treatment, surgical analysis, interpreted the data. Milan Majtanik: Providing surgical treatment, interpreted the data. Jürgen K. Mai: Surgical analysis, critical revision of the revised manuscript. Beata Bóné: Data collection, data analysis,

critical revision of the manuscript. Carla Bentes: Data collection, data analysis, critical revision of the manuscript. Volker A. Coenen: Interpreted the data, proofreading of the manuscript. Antonio Gil-Nagel: Analysis or interpretation of the data; drafting or revising the manuscript for intellectual content. Antonio J. Goncalves-Ferreira: Major role in recruiting and leading project; manuscript review. Philippe Ryvlin: Interpreted the data; revised the manuscript for intellectual content. Rod S. Taylor: Interpreted the data; revised the manuscript for intellectual content. Thomas C. Brionne: Designed the study, interpreted the data; revised the manuscript for intellectual content. Frans Gielen: Analyzed and interpreted the data; revised the manuscript for intellectual content. Shannon Song: Analyzed and interpreted the data; revised the manuscript for intellectual content. Paul Boon: Interpreted the data; revised the manuscript for intellectual content.

AFFILIATIONS

[1]Department of Neurology, Epilepsy Center, LMU University Hospital, LMU Munich, Munich, Germany
[2]Department of Neurology, Tampere University and Tampere University Hospital, Tampere, Finland
[3]Academic Center for Epileptology Kempenhaeghe/Maastricht UMC+, Maastricht, The Netherlands
[4]Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland
[5]MRX-Brain GmbH, Düsseldorf, Germany
[6]Department of Informatics, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany
[7]Department of Neuroanatomy, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany
[8]Medical School, University of Pécs, Pécs, Hungary
[9]Department of Neurosciences and Mental Health, Centro de Referência para a área de Epilepsia Refratária (Epicare Member), Hospital de Santa Maria- Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
[10]Faculdade de Medicina, Centro de Estudos Egas Moniz, Universidade de Lisboa, Lisbon, Portugal
[11]Department of Stereotactic and Functional Neurosurgery, Universitätsklinikum Freiburg, Freiburg, Germany
[12]Epilepsy Program, Neurology Department, Hospital Ruber Internacional, Madrid, Spain
[13]Department of Neurosurgery, Hospital Santa Maria Centro Hospitalar Lisboa Norte, Lisbon, Portugal
[14]Département des Neurosciences Cliniques, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[15]MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow, Glasgow, UK
[16]College of Medicine and Health, University of Exeter, Exeter, UK
[17]Clinical Department, Medtronic Internal Trading Sàrl, Tolochenaz, Switzerland
[18]Medtronic Bakken Research Center, Maastricht, The Netherlands
[19]Department of Neurology, Medtronic Operational Headquarters, Minneapolis, Minnesota, USA
[20]Department of Neurology, Ghent University Hospital—Ghent University, Ghent, Belgium

ACKNOWLEDGMENTS

Many thanks are due to the PwE who participated in the study as well as due to the following team members who supported the study and patient management, data collection, and documentation as well as data quality assurance: Gregory Beth, Jean Prather, Carine Van den Abeele, Karin Werner, Stefanie Gadeyne, Maaike Vierstraete, Timo Möttönen, Satu Hietala, Mrs. Michaela Steiner, PD Dr. Dr. Christian Vollmar, Dr. Katharina Ernst, PD Dr. Jan Mehrkens, Dr. Thomas Kinfe, Dr. Michael Weiss, Friederike Rautenberg, Jan Hubert, Dr. Marcel Heers, Dr. Victoria San Antonio, Dr. Nele Dammeier, Laszlo Halasz, György Perczel, Dr. Laszlo Entz, Mrs Sara Rinaldo, Denis Aiudi, Alessio Iacoangeli, Dr. Mauro Dobran, Dr. Maurizio Gladi, Dr. Claudia Passamonti, Dr. Alicja Kepinska-Wnuk, Dr. Elena Jiltsova, Charlotta Bergman, Lille-Mor Janson, Mrs. Savelkoul, Dr. Mathieu Lenders, Mrs. Janita Zwiers, Mr. Rene Bakker, Elise Reus, Mandy Nusse, Alexandra Tanis-Numan, Dr. Helena Rocha, and Dr. José Manuel Dias da Costa. Furthermore, we thank Chris Irwin, Abdallah Abouihia, and Kristie Wallace for the statistical support and Ariane Beaumann for her help with the publication process. MORE was sponsored by Medtronic, plc. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

MORE was sponsored by Medtronic, plc.

CONFLICT OF INTEREST STATEMENT

All authors participated in the MORE, which was sponsored by Medtronic. E.K. received speaker honoraria and financial compensation for travel expenses from Medtronic, UCB, and Eisai; and has participated in clinical trials for UCB and Precisis. J.P. has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for Arvelle, Novartis, LivaNova, Eisai, Medtronic, UCB, and GW-pharma. A.J.C. received speaker honoraria and compensation for travel costs from Medtronic. K.L. has business relationships with Medtronic. M.M. is data analyst and AI developer for MRX-Brain GmbH. J.K.M. is CEO of MRX-Brain GmbH. M.M. and J.K.M. have business relationships with Medtronic. A.R. received speaker honoraria from UCB. B.B. has received speaker honoraria from Medtronic, UCB Pharma, Richter Gedeon Nyrt, Biogen, Allergan, and Gerot Pharma; and received support for travel to

congresses from UCB, Allergan, Biogen, and Meditop Pharmaceuticals Ltd. C.B. reports that the Reference Centre for Refractory Epilepsy from Hospital de Santa Maria—Centro Hospitalar Lisboa Norte and received fees from Medtronic in January 2021 for the educational course: "Curso Luso Brasileiro DBS em Epilepsia". V.C. received honoraria for talks from Boston Scientific, USA; he has received grants for clinical trials (IITs) from Boston Scientific and Medtronic. He receives an ongoing collaborative grant from BrainLab (Munich, Germany) and is scientific advisor for CereGate (Hamburg) and Cortec (Freiburg). A.G.N. received grants or honoraria as speaker or advisory board from Bial, Biocodex, Eisai, Stoke Therapeutics, GW Pharma, Esteve, UCB Pharma, Zogenix, and Arvelle Therapeutics. A.J.G.F. declares Medtronic support for his participation in different scientific events including membership of the MORE Steering Committee. K.L. received speaker or consultancy fees from Medtronic. P.R. has received speaker or consultant fees from UCB Pharma, GW pharmaceutical, Eisai, Arvelle, LivaNova, and Medtronic. R.T. is a paid consultant for Medtronic. However, he received no payment associated with preparation/contribution to this manuscript. T.C.B., F.G., and S.S. are or were Medtronic employees. P.B. received speaker and consultancy fees from LivaNova, Medtronic, UCB Pharma, and Eisai.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Elisabeth Kaufmann https://orcid.org/0000-0002-7582-2215
Carla Bentes https://orcid.org/0000-0003-2399-7678
Antonio Gil-Nagel https://orcid.org/0000-0003-4515-0793
Philippe Ryvlin https://orcid.org/0000-0001-7775-6576

REFERENCES

1. Spindler P, Bohlmann K, Straub HB, Vajkoczy P, Schneider UC. Effects of vagus nerve stimulation on symptoms of depression in patients with difficult-to-treat epilepsy. Seizure. 2019;69:77–9. https://doi.org/10.1016/j.seizure.2019.04.001
2. Cook IA, Schrader LM, DeGiorgio CM, Miller PR, Maremont ER, Leuchter AF. Trigeminal nerve stimulation in major depressive disorder: acute outcomes in an open pilot study. Epilepsy Behav. 2013;28:221–6. https://doi.org/10.1016/j.yebeh.2013.05.008
3. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77:1295–304.
4. Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015;84:810–7. https://doi.org/10.1212/WNL.0000000000001280
5. Nair DR, Laxer KD, Weber PB, Murro AM, Park YD, Barkley GL, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. 2020;95:e1244–e1256. https://doi.org/10.1212/WNL.0000000000010154
6. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51:899–908. https://doi.org/10.1111/j.1528-1167.2010.02536.x
7. Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015;84:1017–25.
8. Bouwens van der Vlis TAM, Schijns OEMG, Schaper FLWVJ, Hoogland G, Kubben P, Wagner L, et al. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. Neurosurg Rev. 2018;42:287–96.
9. Fasano A, Eliashiv D, Herman ST, Lundstrom BN, Polnerow D, Henderson JM, et al. Experience and consensus on stimulation of the anterior nucleus of thalamus for epilepsy. Epilepsia. 2021;62:2883–98.
10. Peltola J, Colon AJ, Pimentel J, Coenen VA, Gil-Nagel A, Gonçalves Ferreira A, et al. Deep brain stimulation of the anterior nucleus of the thalamus in drug-resistant epilepsy in the MORE multicenter patient registry. Neurology. 2023;100:e1852–e1865. https://doi.org/10.1212/WNL.0000000000206887
11. Salanova V, Sperling MR, Gross RE, Irwin CP, Vollhaber JA, Giftakis JE, et al. The SANTÉ study at 10 years of follow-up: effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021;62:1306–17. https://doi.org/10.1111/epi.16895
12. Kaufmann E, Bötzel K, Vollmar C, Mehrkens JH, Noachtar S. What have we learned from 8 years of deep brain stimulation of the anterior thalamic nucleus? Experiences and insights of a single center. J Neurosurg. 2020;135:1–10. https://doi.org/10.3171/2020.6.JNS20695
13. Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia. 2007;48:1561–71.
14. Oh YS, Kim HJ, Lee KJ, Kim YI, Lim SC, Shon YM. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure. 2012;21:183–7. https://doi.org/10.1016/j.seizure.2011.12.003
15. Kim SH, Lim SC, Kim J, Son BC, Lee KJ, Shon YM. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: a 11-year, single center experience. Seizure. 2017;52:154–61. https://doi.org/10.1016/j.seizure.2017.10.009
16. Mai JK, Majtannik M, Paxinos G. Atlas of the human brain. 4th ed. London: Academic Press Inc.; 2015.
17. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58:531–42.
18. Grudzinski AN, Hakim Z, Coons SJ, Labiner DM. Use of the QOLIE-31 in routine clinical practice. J Epilepsy. 1998;11:34–47.

19. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care. 1992;30:473–83.
20. Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. Epilepsy Behav. Epilepsy Behav. 2012;23:230–4. https://doi.org/10.1016/j.yebeh.2011.12.023
21. Annegers JF, Coan SP. SUDEP: overview of definitions and review of incidence data. Seizure. 1999;8:347–52.
22. Kaufmann E, Bartolomei F, Boon P, Chabardes S, Colon AJ, Eross L, et al. European expert opinion on ANT-DBS therapy for patients with drug-resistant epilepsy (a Delphi consensus). Seizure. 2020;81:201–9. https://doi.org/10.1016/j.seizure.2020.08.015
23. Schuepbach W, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 2013;368:2037–8.
24. Tröster AI, Meador KJ, Irwin CP, Fisher RS. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure. 2017;45:133–41. https://doi.org/10.1016/j.seizure.2016.12.014
25. Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in the epilepsies: a meta-analytic investigation of 29 cohorts. Epilepsy Behav. 2005;7:305–10.
26. Bell GS, Gaitatzis A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: how great is the risk? Epilepsia. 2009;50:1933–42.
27. Barraclough BM. The suicide rate of epilepsy. Acta Psychiatr Scand. 1987;76:339–45.
28. Blumer D, Montouris G, Davies K, Wyler A, Phillips B, Hermann B. Suicide in epilepsy: psychopathology, pathogenesis, and prevention. Epilepsy Behav. 2002;3:232–41.
29. Wilson SJ, Bladin PF, Saling MM. The burden of normality: a framework for rehabilitation after epilepsy surgery. Epilepsia. 2007;48:13–6.
30. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005;128:1188–98.
31. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology. 2020;94:e419–e429.
32. Ficker DM. Sudden unexplained death and injury in epilepsy. Epilepsia. 2000;41:S7–S12.
33. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013;12:966–77.
34. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. Epilepsia. 2011;52:1150–9.
35. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet. 1999;353:888–93. https://doi.org/10.1016/S0140-6736(98)05114-9
36. Voges BR, Schmitt FC, Hamel W, House PM, Kluge C, Moll CKE, et al. Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. Epilepsia. 2015;56:e99–e103.
37. Bucurenciu I, Staack AM, Gharabaghi A, Steinhoff BJ. High-frequency electrical stimulation of the anterior thalamic nuclei increases vigilance in epilepsy patients during relaxed and drowsy wakefulness. Epilepsia. 2020;61:1174–82.
38. Sorokin JM, Davidson TJ, Frechette E, Abramian AM, Deisseroth K, Huguenard JR, et al. Bidirectional control of generalized epilepsy networks via rapid real-time switching of firing mode. Neuron. 2017;93:194–210. https://doi.org/10.1016/j.neuron.2016.11.026
39. Scherer M, Milosevic L, Guggenberger R, Maus V, Naros G, Grimm F, et al. Desynchronization of temporal lobe theta-band activity during effective anterior thalamus deep brain stimulation in epilepsy. NeuroImage. 2020;218:116967. https://doi.org/10.1016/j.neuroimage.2020.116967

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kaufmann E, Peltola J, Colon AJ, Lehtimäki K, Majtanik M, Mai JK, et al. Long-term evaluation of anterior thalamic deep brain stimulation for epilepsy in the European MORE registry. Epilepsia. 2024;65:2438–2458. https://doi.org/10.1111/epi.18003

APPENDIX

PARTICIPANTS OF THE MORE STUDY GROUP

Name	Highest academic degrees	Location	Contribution
Elisabeth Kaufmann	MD	Epilepsy Center, Department of Neurology, University Hospital, LMU Munich, Germany	Data collection, interpreted the data; drafted the manuscript
Jukka Peltola	MD, PhD	Department of Neurology, Tampere University and Tampere University Hospital, Tampere, Finland	Data collection, interpreted the data; drafted the manuscript
Albert J. Colon	MD, PhD	ACE Kempenhaeghe Heeze & Maastricht UMC, The Netherlands	Data collection, data analysis, critical revision of the manuscript
Kai Lehtimäki	MD, PhD	Department of Neurosurgery, Tampere University Hospital and Tampere University, Finland	Providing surgical treatment, surgical analysss, Interpreted the data
Milan Majtanik	MD, PhD	1. Department of Neurosurgery, Tampere University Hospital and Tampere University, Finland	Providing surgical treatment, Interpreted the data
Jürgen Konrad Mai	MD	1. MRX-Brain GmbH, Düsseldorf, Germany 2. Department of Neuroanatomy, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany	Surgical analysis, critical revision of the revised manuscript
Beata Bóné	MD, PhD	Medical School, University of Pécs, Pécs, Hungary	Data collection, data analysis, critical revision of the manuscript
Carla Bentes	MD, PhD	3. Centro de Referência para a área de Epilepsia Refratária (Epicare Member), Department of Neurosciences and Mental Health, Hospital de Santa Maria- Centro Hospitalar Universitário Lisboa Norte. Lisbon, Portugal 4. Centro de Estudos Egas Moniz, Faculdade de Medicina, Universidade de Lisboa. Lisbon, Portugal	Data collection, data analysis, critical revision of the manuscript
Volker A. Coenen	MD	Universitätsklinikum Freiburg, Department of Stereotactic and Functional Neurosurgery Freiburg, Germany	Interpreted the data, proof-reading the manuscript
Antonio Gil-Nagel	MD, PhD	Neurology Department, Epilepsy Program, Hospital Ruber Internacional, Madrid, Spain	Analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Antonio Gonçalves Ferreira	MD, PhD	Department of Neurosurgery, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal	Major role in recruiting and leading project; Manuscript review
Kai Lehtimäki	MD, PhD	Department of Neurosurgery, Tampere University Hospital and Tampere University, Finland	Providing surgical treatment, Interpreted the data
Philippe Ryvlin	MD, PhD	Département des Neurosciences Cliniques Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne, Switzerland	Interpreted the data; revised the manuscript for intellectual content
Rod S. Taylor	MSc, PhD	1. MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow 2. College of Medicine and Health, University of Exeter	Interpreted the data; revised the manuscript for intellectual content
Thomas C. Brionne	PhD	Medtronic Internal Trading Sàrl, Clinical Department, Tolochenaz, Switzerland	Designed the study, interpreted the data; revised the manuscript for intellectual content
Frans Gielen	PhD	Medtronic Bakken Research Center, Maastricht, The Netherlands	Analyzed and interpreted the data; revised the manuscript for intellectual content

Name	Highest academic degrees	Location	Contribution
Shannon Song	MS	Medtronic Operational Headquarters, Minneapolis, USA	Analyzed and interpreted the data; revised the manuscript for intellectual content
Paul Boon	MD, PhD	Department of Neurology Ghent University Hospital—Ghent University, Belgium	Interpreted the data; revised the manuscript for intellectual content
Abdallah Abouihia	MS	Medtronic Internal Trading Sàrl, Clinical Department, Tolochenaz, Switzerland	Designed the study, analyzed and interpreted the data; revised the manuscript for intellectual content
José Pimentel	MD, PhD	Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar, Universitário Lisboa Norte, Lisbon, Portugal	Major role in recruiting and following-up patients; drafted part of the manuscript; revised the manuscript for intellectual content
Linda Ackermans	MD, PhD	1. Departments of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands, 2. Academic Center for Epileptology Kempenhaeghe/ MUMC+, Maastricht, The Netherlands	Providing surgical treatment, discussing the data
Jacqueline Ardesch	MD	Stichting Epilepsie Instellingen Nederland (SEIN), Zwolle, The Netherlands	Site Principal Investigator and Revised the manuscript
Magdalena Bosak	MD	Department of Neurology, Jagiellonian University Medical College, Faculty of Medicine, Krakow, Poland	Major role in recruiting patients, patients follow-up, Major role in the acquisition of data
Jorge G. Burneo	MD, MSPH	Western University, London, Ontario, Canada	Patient enrolment as site Principal Investigator, Revised the manuscript
Clara Chamadoira	MD	Neurosurgery Department, Centro Hospitalar Universitário de São João, Porto, Portugal	Providing surgical treatment, reviewing planning and final electrode location data
Christian E. Elger	MD, PhD, FRCP	Department of Epileptology, University Hospital Bonn, Germany	Design and conceptualization of the study Revising the manuscript for intellectual content
Loránd Erőss	MD, PhD	National Institute of Clinical Neuroscience; Budapest, Hungary	Site Principal Investigator and performed surgery
Dániel Fabo	MD, PhD	Országos Idegtudományi Intézet/National Institute of Neurosciences; Budapest, Hungary	Site Investigator and Revised the manuscript
Howard Faulkner	FRCP, PhD	North Bristol NHS Trust, Bristol, UK	Major role in the acquisition of data and revising the manuscript for intellectual content
Jacek Gawlowicz	MD, PhD	Wojewodzki Szpital Specjalistyczny w Lublinie, Lublin, Poland	Principal Investigator Site
Alireza Gharabaghi	MD	Institute for Neuromodulation and Neurotechnology, Department of Neurosurgery and Neurotechnology, University of Tübingen, Tübingen, Germany	Major role in the acquisition of data, revised the manuscript
Maurizio Iacoangeli	MD, PhD	Università Politecnica delle Marche; Umberto I General University Hospital, Department of Neurosurgery, Ancona, Italy	Principal Investigator Site and Revised the manuscript
Jozsef Janszky	MD, PhD	Department of Neurology, Medical School, University of Pécs, Pécs, Hungary	Site Principal Investigator and Revised the manuscript
Soila Järvenpää	MD, PhD	Department of Neurology, University of Tampere and Tampere University Hospital	Data collection and patient follow-up
Kuan H. Kho	MD	Medisch Spectrum Twente (MST), Enschede, The Netherlands	Provided surgical treatment, data acquisition, reviewed manuscript

Name	Highest academic degrees	Location	Contribution
Eva Kumlien	MD, PhD	Dept. of Neuroscience, Uppsala University, Uppsala, Sweden	Site Principal Investigator and Revised the manuscript
Helmut Laufs	MD, PhD	Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Christian-Albrechts-Universität zu Kiel, Germany	Interpreted the data; revised the manuscript for intellectual content
Christian Lettieri	MD	Neurology and Clinical Neurophysiology Unit, "S. Maria della Misericordia" University-Hospital, Department of Neuroscience, Udine, Italy	Major role in the acquisition of data; revised the manuscript for intellectual content
Paulo Linhares	MD, PhD	1. Neurosurgery Department, Centro Hospitalar Universitário de São João, Porto, Portugal 2. Faculdade de Medicina, Universidade do Porto. Porto, Portugal	Providing surgical treatment, reviewing planning and final electrode location data
Soheyl Noachtar	MD	Epilepsy Center, Department of Neurology, University Hospital, LMU Munich, Munich, Germany	Revised the manuscript for intellectual content
Andrew Parrent	MD	Western University, London, Ontario, Canada	Revised the manuscript
Ekaterina Pataraia	MD	Department of Neurology, Medical University of Vienna, Austria	Recruiting patients, collecting data, patient follow-up and programming, revising manuscript
Nikunj K. Patel	MD FRCS(SN)	Southmead Hospital, North Bristol NHS Trust, Bristol, UK	Major role in the acquisition of data and interpretation revising the manuscript for intellectual content
Ana Rita Peralta	MD, MsC	1. Laboratory of EEG/Sleep, Department of Neurology, Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal 2. Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal	Major role in seeing patients (clinical and parameters) in every single visit and in reviewing the EEG
Attila Rácz	MD, PhD	Department of Epileptology, University Hospital Bonn, Germany	Major role in the acquisition of data Revising the manuscript for intellectual content
Alexandre Rainha Campos	MD	Department of Neurosurgery, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal	Major role in recruiting and following-up patients; providing surgical treatment, revised the manuscript for intellectual content
Ricardo Rego	MD	Neurophysiology Unit, Neurology Department, Centro Hospitalar Universitário de São João, Porto, Portugal	Major role recruiting patients, collecting data, patient follow-up and programming.
Riccardo A. Ricciuti	MD	Department of Neurosurgery, Viterbo Hospital, Viterbo (VT), Italy	Providing surgical treatment
Sabine Rona	MD, PhD	Epilepsy Unit, Department of Neurosurgery and Neurotechnology, University of Tübingen, Tübingen, Germany	Major role in the acquisition of data, revised the manuscript
Rob P. W. Rouhl	MD, PhD	1. Department of Neurology, Maastricht University Medical Centre+, Maastricht, The Netherlands 2. Academic Center for Epileptology Kempenhaeghe/ Maastricht UMC+, Maastricht, The Netherlands 3. School for Mental Health and Neurosciences, Maastricht University, Maastricht, The Netherlands	Role in acquisition of the data, revising the manuscript
Andreas Schulze-Bonhage	MD, PhD	University Hospital Freiburg, Freiburg, Germany	Site Principal Investigator and Revised the manuscript

Name	Highest academic degrees	Location	Contribution
Rick Schuurman	MD, PhD	Department of neurosurgery, Amsterdam University Medical Centers, Amsterdam, The Netherlands	Provided surgical treatment, revised the manuscript
Mathieu Sprengers	MD, PhD	Department of Neurology, Ghent University Hospital Ghent University Hospital—Ghent University	Major role in the acquisition of data
Albert Sufianov	MD	1. Federal Centre of Neurosurgery (Tyumen), Russia 2. I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia 3. Peoples' Friendship University of Russia (RUDN University), Moscow, Russia	Provided surgical treatment, Revised the manuscript
Yasin Temel	MD, PhD	Department Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands	Role in data acquisition, providing surgical treatment, discussing the data
Tom Theys	MD, PhD	UZ Leuven, Leuven, Belgium	Major role in the acquisition of data and revising the manuscript for intellectual content
Wim Van Paesschen	MD, PhD	1. Department of Neurology, UZ Leuven 2. Laboratory for Epilepsy Research, KU Leuven, Leuven, Belgium	Major role in the acquisition of data and revising the manuscript for intellectual content
Dirk Van Roost	MD, PhD	Department of Neurosurgery, Ghent University Hospital—Ghent University, Ghent, Belgium	Providing surgical treatment, revising the manuscript for intellectual content
Rui Vaz	MD, PhD	Neurosurgery Department (Head), Centro Hospitalar Universitário de São João, Porto, Portugal	Major role recruiting patients, coordination of surgical strategies.
Kristl Vonck	MD, PhD	Department of Neurology, Ghent University Hospital—Ghent University, Ghent, Belgium	Patient follow-up
Louis Wagner	MD	ACE Kempenhaeghe/Maastricht UMC, The Netherlands	Major role in acquisition of data, discussed and revised the manuscript
Jack Zwemmer	MD, PhD	Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands	Site Principal Investigator and Revised the manuscript.