

# Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy



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**Supplemental data  
at Neurology.org**

## ABSTRACT

**Objective:** To report long-term efficacy and safety results of the SANTE trial investigating deep brain stimulation of the anterior nucleus of the thalamus (ANT) for treatment of localization-related epilepsy.

**Methods:** This long-term follow-up is a continuation of a previously reported trial of 5- vs 0-V ANT stimulation. Long-term follow-up began 13 months after device implantation with stimulation parameters adjusted at the investigators' discretion. Seizure frequency was determined using daily seizure diaries.

**Results:** The median percent seizure reduction from baseline at 1 year was 41%, and 69% at 5 years. The responder rate ( $\geq 50\%$  reduction in seizure frequency) at 1 year was 43%, and 68% at 5 years. In the 5 years of follow-up, 16% of subjects were seizure-free for at least 6 months. There were no reported unanticipated adverse device effects or symptomatic intracranial hemorrhages. The Liverpool Seizure Severity Scale and 31-item Quality of Life in Epilepsy measure showed statistically significant improvement over baseline by 1 year and at 5 years ( $p < 0.001$ ).

**Conclusion:** Long-term follow-up of ANT deep brain stimulation showed sustained efficacy and safety in a treatment-resistant population.

**Classification of evidence:** This long-term follow-up provides Class IV evidence that for patients with drug-resistant partial epilepsy, anterior thalamic stimulation is associated with a 69% reduction in seizure frequency and a 34% serious device-related adverse event rate at 5 years.

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## GLOSSARY

**ANT** = anterior nucleus of the thalamus; **CI** = confidence interval; **DBS** = deep brain stimulation; **LSSS** = Liverpool Seizure Severity Scale; **QOLIE-31** = 31-item Quality of Life in Epilepsy; **SAE** = serious adverse event; **SANTE** = Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy; **SUDEP** = sudden unexpected death in epilepsy; **VNS** = vagus nerve stimulation.

Approximately 3 million people in the United States have epilepsy and approximately 30% remain resistant to medical treatment. Some of these patients are candidates for resective surgery.<sup>1,2</sup> For those who are not surgical candidates, or who continue to have seizures after surgery, neuromodulation may offer a viable therapeutic option. Several pilot studies,<sup>3-6</sup> and recent trials including the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial<sup>7</sup> and a trial of responsive cortical stimulation,<sup>8</sup> have demonstrated reduction in seizures. The SANTE trial in 110 subjects with localization-related epilepsy found that seizures were significantly reduced by stimulation.<sup>7</sup> We now report the 5-year efficacy and safety outcomes of this trial.

**METHODS** The SANTE trial<sup>7</sup> utilized a design with a 3-month baseline, 1-month postoperative recovery, followed by 3 months of double-blind treatment randomized to 5 V or 0 V of stimulation, then an open-label conversion of all subjects to 5-V stimulation for 9

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SANTE Study Group coinvestigators and contributors are listed on the *Neurology*® Web site at Neurology.org.

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additional months. The long-term follow-up reported here began at 13 months and continued for an additional 4 years. The primary research question was whether seizure frequency continued to improve over time with open-label anterior thalamic stimulation.

Subjects were 18 to 65 years old with at least 6 partial or secondarily generalized seizures per month who had failed at least 3 antiepileptic drugs (AEDs) because of lack of efficacy. Subjects with IQ <70, inability to complete neuropsychological testing, or progressive neurologic deficits were excluded. Subjects were seen every 6 months in addition to daily diary collection and monthly telephone contact. Efficacy analyses were performed on the 109 subjects randomized in the original study. One subject who was implanted but not randomized is included for safety analyses only. The outcome measures included efficacy (seizure diary), Liverpool Seizure Severity Scale (LSSS), and 31-item Quality of Life in Epilepsy (QOLIE-31). Safety was addressed by adverse event collection and neuropsychological measures.

**Standard protocol approvals, registrations, and patient consents.** This study was approved by all study center institutional review boards, and subjects provided written informed consent before participation. The study is registered on clinicaltrials.gov, identifier NCT00101933.

**Statistical analysis.** The required sample size was determined for the randomized portion of the study; no additional sample size requirements were associated with long-term follow-up. Device longevity was determined through Kaplan-Meier survival analysis, and sudden unexpected death in epilepsy (SUDEP) confidence intervals (CIs) were based on the Poisson distribution. Appropriate summary statistics are reported for all other measures. Change from baseline was tested using a paired *t* test or Wilcoxon signed rank test as appropriate. Statistical tests were examined for significance at the 0.05 level, with no adjustments for multiple comparisons. SAS software (version 9.2; SAS Institute, Cary, NC) was used for all analyses.

Seizure frequency reduction was determined via daily seizure diaries and is reported as percentage change from baseline. Sensitivity analyses were completed to show the robustness of the main analysis.

This long-term follow-up provides Class IV evidence that for patients with drug-resistant partial epilepsy, anterior thalamic stimulation is associated with a 69% reduction in seizure frequency and a 34% serious device-related adverse event rate at 5 years.

**RESULTS** The mean age was 36.1 years (range 18.2–60.9 years). The average number of years with epilepsy was 22.3 (range 2–60 years) and the median monthly seizure frequency during baseline was 19.5 (range 6–604). A total of 105 subjects entered the long-term follow-up phase beginning 13 months after implant (figure 1). There were 30 discontinuations in the long-term follow-up phase, including 5 deaths (1 each due to drowning, suicide, SUDEP, cardiac arrest, and liver cancer). SANTE subjects have received stimulation for 441 years of follow-up at 5 years and 623 years including all follow-up.

Between implant and year 5, 61 of the 110 implanted subjects added at least one AED that was not present at baseline. Each subject could have added more than one AED. Medications added were lacosamide (28 subjects), pregabalin (24), levetiracetam (8),

lamotrigine (7), clonazepam (6), and 15 others in 4 or fewer subjects. A similar reduction in seizure frequency was seen for subjects who had at least one medication added vs those subjects who did not add medications (figure e-1 on the *Neurology*® Web site at Neurology.org). Not surprisingly, subjects with less improvement were more likely to add a medication. Over most of the follow-up, however, the curves of improvement were parallel, such that subjects who added medicines did not improve faster than those who did not. No significant link was detected for using a specific medication and seizure improvement. Most subjects continued to take medications; when looking at changes relative to the previous year, 6 to 8 subjects per year were on a decreased number or dosage of AEDs at the year 1 to 5 visits.

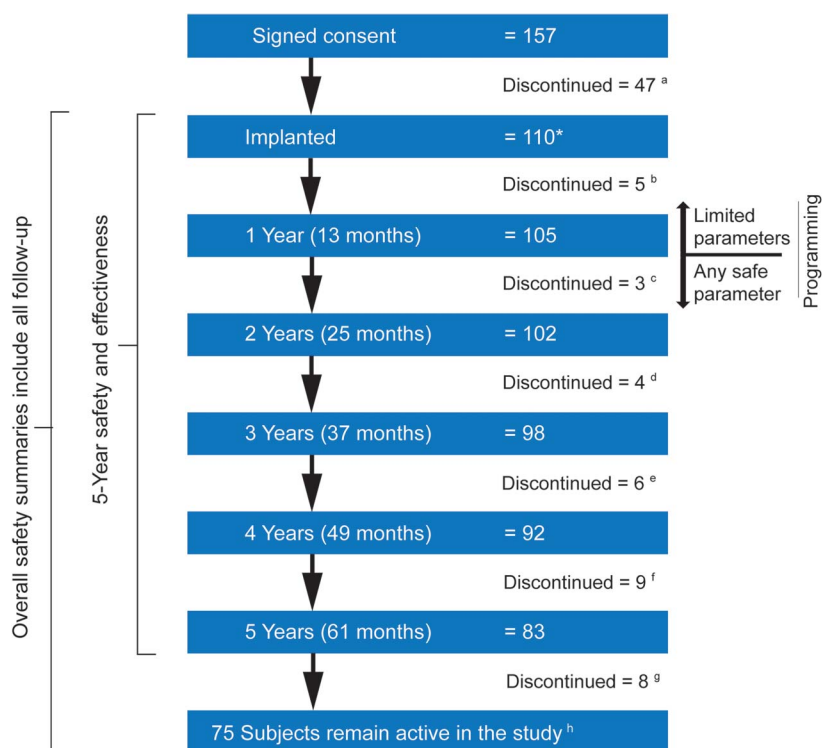
Neurostimulator battery life is directly related to stimulation parameters (parameters shown in table e-1), which varied over time and across subjects. Half of the subjects needed their first battery replacement after an average of 35.0 months (2.9 years). No formal statistical analysis of stimulation parameters was performed to identify the most efficacious parameters, as parameters were not assigned experimentally. Stimulation parameters for responders and nonresponders at year 2 to 5 were compared using descriptive statistics. However, no trend was found to favor any one stimulation parameter. Some investigators judged that rapid cycling and higher amplitude in some subjects appeared to improve outcome, although numbers were small.

**Long-term follow-up efficacy.** Figure 2 shows the seizure frequency change from baseline at 1 to 5 years for subjects with at least 70 days of diary entries. The median change from baseline was 41% at 1 year and 69% at 5 years ( $p < 0.001$  for both). Sensitivity analyses shown in the figure demonstrate the robustness of the results. The cohort that completed diaries for every annual visit until the last observation (constant cohort) showed a gradual seizure frequency reduction with median reduction from baseline of 49% at 1 year and 69% at 5 years ( $n = 74$ ,  $p < 0.001$  for both). Figure 3 shows the distribution of individual responses to treatment at 5 years. The responder rate was 43% at 1 year ( $n = 99$ ) and 68% at 5 years ( $n = 59$ ).

Each subject identified a seizure type as the “most severe” at the initial baseline visit. Using subjects who experienced at least one most severe seizure during baseline with at least 70 days of diary, seizure reductions for the most severe seizure type were 39% at year 1 ( $n = 74$ ) and 75% at year 5 ( $n = 42$ ) ( $p < 0.001$  for year 1–5).

**Seizure freedom.** In the 5 years after implant, 16% (17/109) of randomized subjects reported a

**Figure 1** Participant timeline



The number of subjects who completed, or discontinued before, each visit is indicated in the figure. Reasons for discontinuation between phases are as follows. <sup>a</sup>Preimplant discontinuations: have been described in detail by Fisher et al.<sup>7</sup> <sup>b</sup>One year: device explant (4: implant site infection in 2 subjects, discomfort, involuntary muscle contractions); SUDEP (1). <sup>c</sup>Two years: device explant (2: implant site infection, therapeutic product ineffective); drowning (1). <sup>d</sup>Three years: device explant (3: anxiety, cognitive disorder, meningitis); withdrawal of consent (1). <sup>e</sup>Four years: device explant (4: therapeutic product ineffective in 2 subjects, psychotic disorder, undesirable change in stimulation); completed suicide (1); physician choice (1). <sup>f</sup>Five years: device explant (5: therapeutic product ineffective in 4 subjects, implant site infection); withdrawal of consent (2); SUDEP (1); physician choice (1). <sup>g</sup>More than 5 years: device explant (4: anxiety, convulsion, implant site infection, therapeutic product ineffective); withdrawal of consent (2); cardiac arrest (1); liver cancer (1). <sup>h</sup>Subjects have been followed through 6 (80 subjects), 7 (41), 8 (31), and 9 (6) years. \*One hundred nine of 110 implanted subjects were randomized, but all subjects continued to be followed. Statistical imputation is based on 109 randomized subjects.

seizure-free interval of at least 6 months and 6 subjects were seizure-free for more than 2 continuous years during that time. In addition, 6 subjects had 2 or more seizure-free intervals of at least 6 months. At the 5-year assessment, 11 subjects were seizure-free for at least 6 months.

**LSSS and QOLIE-31.** The mean improvement from baseline in the LSSS was 13.4 (n = 103) at 1 year and 18.3 (n = 81) at 5 years ( $p < 0.001$  for both, figure 4). The mean improvement from baseline in QOLIE-31 scores at 1 year was 5.0 (n = 102) and at 5 years was 6.1 (n = 80,  $p < 0.001$  for both, figure 4). The percentage of subjects experiencing at least a 5-point change from baseline in QOLIE-31 scores, which has been reported to be clinically significant,<sup>9</sup> was 46% at year 1 (n = 102) and 48% at year 5 (n = 80).

**Subgroup analysis.** Median seizure reduction was also determined for subgroups of subjects. Reduction by seizure onset zone was computed for temporal lobe seizures, frontal lobe seizures, and all other seizure onset zones. The median reduction for temporal lobe seizures was 44% at 1 year (n = 59,  $p < 0.001$ ) and 76% at 5 years (n = 33,  $p < 0.001$ ), and 53% at 1 year (n = 25,  $p = 0.001$ ) and 59% at 5 years (n = 17,  $p = 0.005$ ) for frontal lobe seizures. The remaining seizure onset locations experienced a median reduction of 34% at 1 year (n = 22,  $p = 0.012$ ) and 68% at 5 years (n = 13,  $p = 0.124$ ).

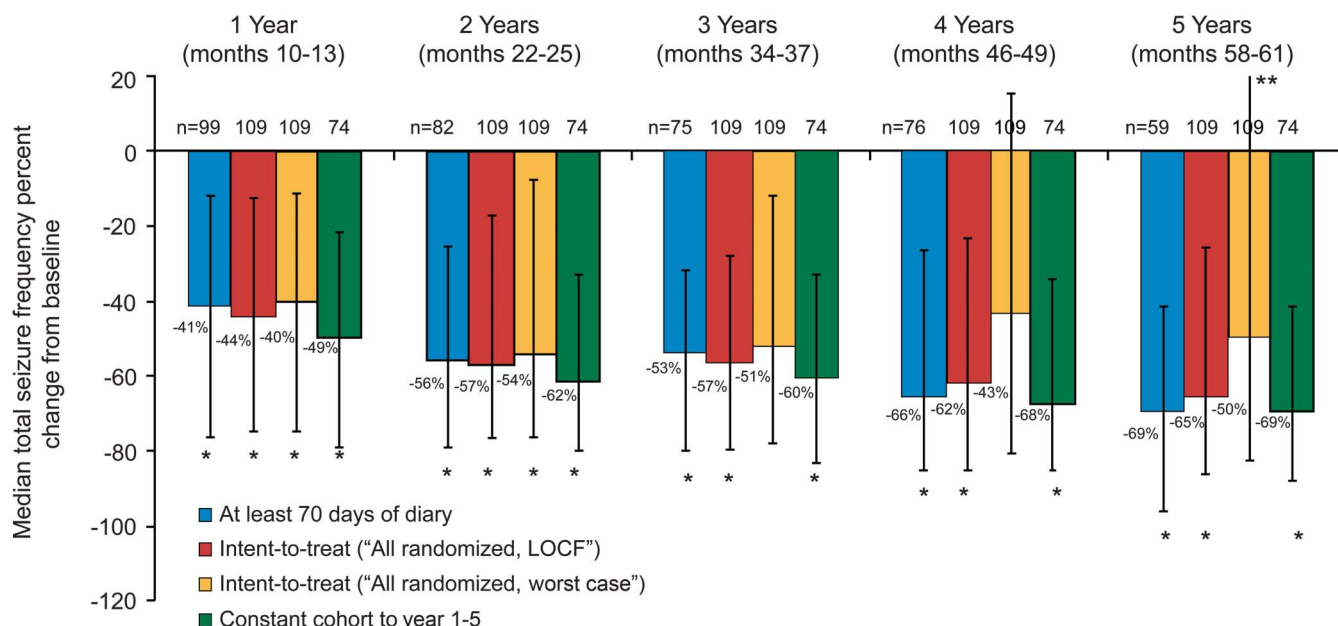
Previous vagus nerve stimulation (VNS) and history of resective surgery were also used to create subgroups. The median seizure reduction from baseline for subjects who previously tried VNS was 40% at 1 year (n = 45,  $p < 0.001$ ) and 69% at 5 years (n = 25,  $p < 0.001$ ), and 45% at 1 year (n = 54,  $p < 0.001$ ) and 69% at 5 years (n = 34,  $p < 0.001$ ) for those without prior VNS. Those subjects who underwent previous resective surgery had a median reduction of 53% at 1 year (n = 24,  $p < 0.001$ ) and 67% at 5 years (n = 14,  $p < 0.001$ ).

**Neuropsychological outcome.** Selected neuropsychological test results are presented in figure 5; the scores are expressed as composites across several tests within a given domain. There was a gradual improvement from baseline in several neuropsychological composites. Neuropsychological test composite scores showed statistically significant gains from baseline to 5 years including attention ( $p < 0.001$ ), executive function ( $p < 0.001$ ), depression ( $p = 0.039$ ), tension/anxiety ( $p = 0.027$ ), total mood disturbance ( $p = 0.0016$ ), and subjective cognitive function ( $p < 0.001$ ). Individual neuropsychological test scores are provided in table e-2.

**Device-related adverse events.** The most frequent device-related adverse events at any time after implantation were implant site pain in 23.6% (20.9% in 5 years), paresthesias including tingling, vibration, or shocking sensations at the stimulator implant site in 22.7% (22.7%), implant site infection in 12.7% (12.7%), therapeutic product ineffective in 10.0% (8.2%), discomfort in 9.1% (9.1%), lead(s) not within target in 8.2% (8.2%), sensory disturbance in 8.2% (8.2%), memory impairment in 7.3% (6.4%), implant site inflammation in 7.3% (7.3%), dizziness in 6.4% (6.4%), postprocedural pain in 6.4% (6.4%), extension fracture in 5.5% (4.5%), and neurostimulator migration in 5.5% (5.5%). Of the 14 subjects who experienced implant site infection, there were 17 events (3 subjects experienced 2 events) of infection. Of those, 5 led to full system explants and 4 led to partial system explants. None included osteomyelitis, meningitis, or infections of the brain.

**Figure 2** Percentage seizure reduction over time

Median and 25th and 75th percentiles around the median



The graph shows seizure reduction for those subjects who had at least 70 days of diary in the 3 months before each annual visit (blue bars) as well as sensitivity analyses allowing diaries as short as 28 days, and using either last observation carried forward (red bars) or a worst case (100% worsening from baseline, yellow bars) data imputation methodology for subjects with fewer than 28 diary days. Also shown is seizure reduction for those subjects who had at least 28 days of diary in the 3 months before each and every annual visit, elucidating whether, in the most diary-compliant subgroup of subjects, seizure reductions change over time (constant cohort, green bars). \*Wilcoxon signed-rank,  $p < 0.001$ ; \*\*25th percentile bar extends to 100% since more than 25% of 109 subjects were imputed to or had greater than 100% median percent change in total seizure frequency from baseline.

**Device-related serious adverse events.** Overall, 39 of the 110 implanted subjects (35.5%) had a device-related serious adverse event (SAE) in the study (33.6% in 5 years), with the majority occurring in the first few months following implant. After the blinded phase, 13.6% experienced an SAE. The most frequent SAEs reported any time after implant were implant site infection in 10.0% (10.0% in 5 years) and lead(s) not within target in 8.2% (8.2% in 5 years), with all others reported in 1.8% or less.

**Other adverse events. Depression.** Depression events were reported in 37.3% (32.7% in 5 years) at some time after implant. Three events in 3 subjects were considered device-related. Of the 41 subjects who reported depression, 66% had a history of depression.

**Suicide.** After implantation, 11.8% (13 subjects) (8.2% in 5 years) reported at least one instance of suicidal ideation. One subject committed suicide approximately 4 years after implant, not judged by the site investigator or data monitoring committee to be device-related. Ten of the 13 subjects, including the one who completed suicide, had a history of depression. Causes for suicidal ideation were multifactorial and none of the episodes of suicidal ideation were considered by the treating physician to be device-related.

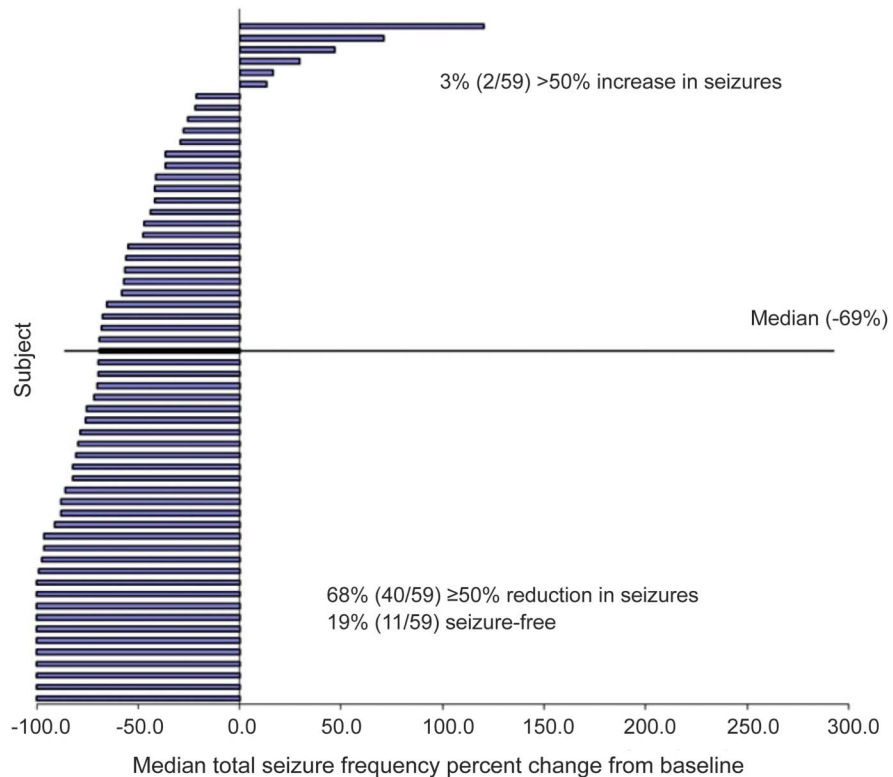
**Memory impairment.** Memory impairment was reported in 27.3% of subjects at some time after implant (25.5% in 5 years). None of the events were considered serious. Of the 30 subjects who had an adverse event of memory impairment, 50% had a history of memory impairment. Approximately a third of memory impairment events were confirmed with a change from baseline in neuropsychological testing. It did not appear that memory impairment was related to seizure control or to any particular stimulation parameter.

Status epilepticus occurred in 7 subjects (6.4%) during the study. Four of the 7 events were nonconvulsive in nature. Six of the 7 subjects required hospitalization for their status epilepticus. Three of the 7 events occurred in subjects who were not receiving stimulation.

**Sudden unexpected death in epilepsy.** To evaluate the SUDEP rate, the 7 deaths during the study were considered. None were considered by the investigator or data monitoring committee to be device-related. One probable SUDEP occurred in the baseline phase, and 2 definite and 1 possible SUDEP occurred after implant, none occurring after 5 years. The remaining 3 deaths were due to suicide, cardiorespiratory arrest, and liver cancer. Including



**Figure 3** Distribution of individual subject response to treatment



The graph shows the by-subject distribution of total seizure frequency percent change from baseline at 5 years for subjects who had at least 70 days of diary in the 3 months before the year 5 visit. Negative values indicate a seizure frequency reduction compared with baseline.

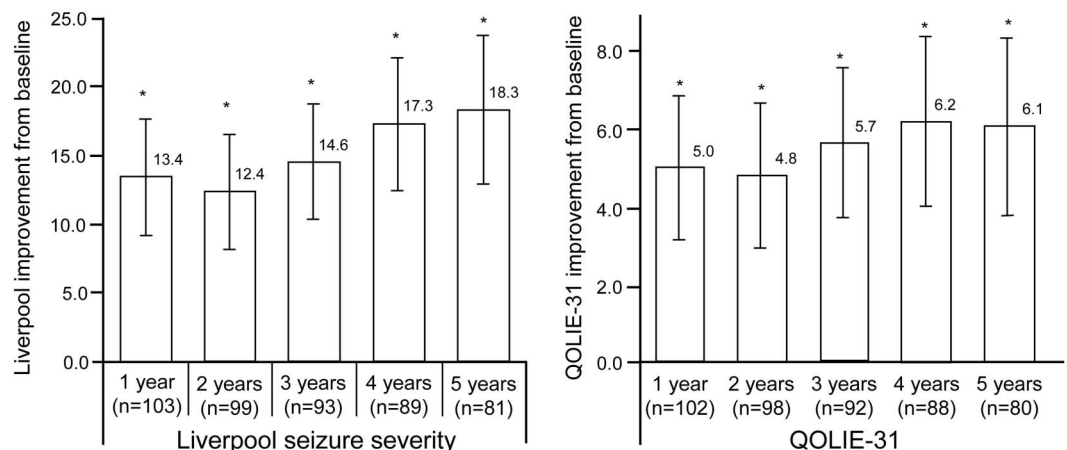
the pilot studies, SUDEP rate of definite/probable SUDEP was 2.9 per 1,000 patient-years (95% CI: 0.3, 10.4), which is lower than published SUDEP rates as high as 9.3 per 1,000 patient-years in epilepsy surgical candidates.<sup>10</sup> The SUDEP rate

excluding subject follow-up after 5 years is 3.9 per 1,000 patient-years (95% CI: 0.5, 14.01).

**DISCUSSION** Long-term deep brain stimulation (DBS) for epilepsy showed a sustained and statistically

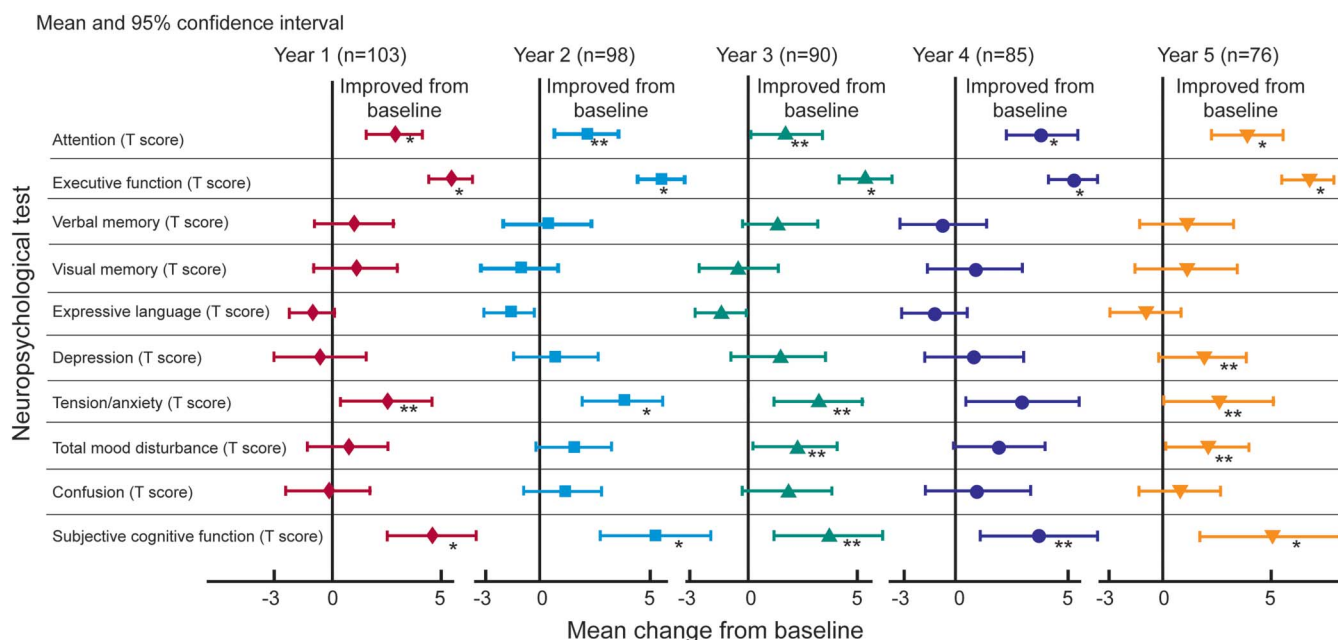
**Figure 4** Seizure severity and quality of life

Mean and 95% confidence interval



The graph shows responses to the Liverpool Seizure Severity Scale and the 31-item Quality of Life in Epilepsy (QOLIE-31) scale for all subjects who completed the respective questionnaire at each annual visit. Higher values reflect improvement in both charts. A QOLIE-31 change of at least 5 points is considered clinically meaningful.<sup>9</sup> \*Paired t test,  $p < 0.001$ .

**Figure 5** Neuropsychological outcomes



The graph shows composited T scores across several neuropsychological tests within each given domain, over time. Positive values represent an improvement in each outcome. \* $p < 0.001$ , \*\* $p < 0.05$ , Wilcoxon signed-rank nonparametric test.

significant seizure frequency reduction from baseline after 1, 2, 3, 4, and 5 years of stimulation. Also showing significant improvement were responder rates, seizure severities, quality of life, and reductions in most severe seizures. Certain subgroups improved over baseline, including those with temporal or frontal seizure origin, those with or without prior VNS, and those with prior epilepsy surgery. Seizures originating in lobes other than frontal or temporal showed trends toward improvement, but small sample size and variability precluded achieving significance.

Several clinical markers improved in addition to seizure frequency. Five years after implantation, nearly half of the subjects experienced a clinically meaningful improvement in quality of life. Likewise, improvement of 18.3 in the LSSS at 5 years is in the range of changes considered to be clinically significant.<sup>11,12</sup>

Because all subjects received active stimulation at month 4, all subsequent evaluations were unblinded and compared with an earlier baseline, rather than with a parallel control group. We therefore cannot rule out factors other than the stimulation as the cause for the improvement. It is nonetheless encouraging that the benefits observed during the blinded phase did not diminish and in fact seemed to increase over time.

An obvious question is whether long-term results are better because those doing poorly discontinued from the trial. Even making a worst case assumption of 100% seizure increase in those discontinued, seizure frequency was still approximately 50% of baseline at 5 years. These data strongly suggest that

discontinuations for lack of efficacy do not account for much of the improvement over time. Medication changes, which were not analyzed in detail during the long-term follow-up phase, also could account for some improvement. Two points argue against this being a major effect. First, subjects had been tried on at least 3 AEDs before entry without major benefit. Second, medications were kept constant in almost all subjects from month 4 through month 13 of the trial, and improvement was evident during this phase. Furthermore, subjects treated with new medications and stimulation did not improve faster than those with stable medications and stimulation.

Steady improvement over several years of neurostimulation has been reported for both VNS and responsive neurostimulation.<sup>8,13</sup> Our results now add thalamic DBS to this list. It is interesting by way of contrast that DBS for Parkinson disease affects tremor and bradykinesia within minutes of initiation. The differences of location of stimulation and underlying disorder likely have a large role in this difference. The mechanisms of progressive improvement with neurostimulation are unknown.

Most adverse events associated with neurostimulation occur around the time of device implantation. As detailed in the randomized phase of the SANTE trial,<sup>7</sup> device-related implantation problems were reversible and as expected with this surgical procedure. The percentage of subjects in this study with implant site pain (most common device-related

adverse event) is consistent with rates reported for prospective DBS studies in Parkinson disease.<sup>14</sup> At 5 years after device implantation, there was a high subject retention rate of 75%, and 73% of subjects also indicated they were satisfied with the therapy, suggesting that stimulation was well-tolerated in this study population.

An interpretive difficulty arises because of the high prevalence of depression and memory problems in people with refractory epilepsy. Our follow-up included depression in 37.3% of subjects, memory impairment in 27.3%, status epilepticus in 6.4%, and suicidal ideation in 11.8%, with one suicide. However two-thirds of the subjects reporting depression had a history of depression, and half of the subjects reporting memory impairment had a history of memory impairment.

Prevalence of depression in people with epilepsy in community settings has been reported to range from 12% to 37%. A recent systematic review and meta-analysis of depression in 29,891 people with epilepsy showed an overall prevalence of active depression of 23.1%.<sup>15</sup>

Cognitive impairment has long been associated with intractable epilepsy. A study in 136 patients with refractory epilepsy found that “cognitive decline was severe and occurred across a wide range of cognitive functions.”<sup>16</sup> Favorable effects on cognition have also been reported for thalamic stimulation. A case series study<sup>17</sup> reported 9 patients with intractable epilepsy treated with continuous anterior nucleus of the thalamus (ANT) DBS who underwent cognitive testing before implantation and more than 1 year after surgery. The mean seizure reduction after DBS was 57.9% and was accompanied by favorable cognitive test results for verbal fluency tasks and a significant improvement in delayed verbal memory. The authors hypothesized that these improvements may be attributable to bilateral activation of fronto-limbic circuits during DBS.<sup>17</sup>

Some subjects reported mood and memory problems, but objective neuropsychological testing of the overall study group showed improved attention, executive function, depression, tension/anxiety, mood disturbance, and subjective cognitive function compared with baseline. It remains to be determined whether there are individual risk factors predisposing to emergence or worsening of depression and cognition during ANT stimulation.

Repeated electrical stimulation of the brain in animal models of epilepsy can produce kindling.<sup>18</sup> It is reassuring that no evidence of kindling and increasing seizures/status epilepticus over time was seen in the 5 years of our observation, although this does not rule out problems with neurostimulation beyond 5 years. However, 41, 31, and 6 subjects have been observed respectively at 7, 8, and 9 years with no evidence of

stimulation-linked seizures or increased rate of status epilepticus.

Despite limited understanding of the mechanisms of benefit for DBS in epilepsy, our observation is that long-term ANT DBS is well-tolerated and associated with a significant and sustained reduction in the frequency and severity of seizures in a very refractory patient population.

## AUTHOR CONTRIBUTIONS

V. Salanova: conception or study design, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content, acquisition of data. T. Witt: drafting or revising the manuscript for intellectual content, acquisition of data. R. Worth: drafting or revising the manuscript for intellectual content. T. Henry: conception or study design, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content, acquisition of data. R. Gross: drafting or revising the manuscript for intellectual content. J. Nazzaro: drafting or revising the manuscript for intellectual content. D. Labar: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. M. Sperling: drafting or revising the manuscript for intellectual content, acquisition of data. A. Sharan: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. E. Sandok: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. A. Handforth: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content, local study supervision or coordination. J. Stern: drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. S. Chung: drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. J. Henderson: drafting or revising the manuscript for intellectual content, acquisition of data. J. French: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. G. Baltuch: conception or study design, drafting or revising the manuscript for intellectual content, acquisition of data. W. Rosenfeld: drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. P. Garcia: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. N. Barbaro: drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. N. Fountain: drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. W. Elias: drafting or revising the manuscript for intellectual content, acquisition of data, local study supervision or coordination. R. Goodman: drafting or revising the manuscript for intellectual content. J. Pollard: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content, local study supervision or coordination. A. Tröster: conception or study design, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. C. Irwin: analysis or interpretation of the data, statistical analysis. K. Lambrecht: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. N. Graves: conception or study design. R. Fisher: conception or study design, drafting or revising the manuscript for intellectual content.

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## DISCLOSURE

V. Salanova has served on the speakers bureau for UCB Pharma, Lundbeck, Sunovion, and Supernus, has served as the Indiana University principal investigator for the NIH ROSE, Medtronic SANTE, NeuroPace, Visualase, and Eisai Perampnel trials, and Indiana University receives research grants from NIH, Medtronic, and NeuroPace. T. Witt reports no disclosures relevant to the manuscript. R. Worth has a patent pending on real-time seizure prediction algorithms. T. Henry reports no disclosures relevant to the manuscript. R. Gross has consulted for Medtronic, NeuroPace, Visualase, Boston

Scientific, Deep Brain Innovations, Duke University, Lilly, University of Alabama, and the National Football League, received travel support from Medtronic, NeuroPace, and the International Neuromodulation Society, provided expert testimony for Hanna, Campbell and Powell, received payment for lectures from Cornell Weill College of Medicine and Case Western, received payment for participation in data safety monitoring boards from St. Jude Medical, holds provisional patents relating to epilepsy treatment and optogenetic techniques, received payment for development of educational presentations from Visualase and Medtronic, and Emory University receives research support from Medtronic, NeuroPace, Visualase, NIH (R01 NS040894-06A1, 1R01NS079268, 1R01NS079757, 13-NIH-1001), CURE, American Epilepsy Society, and the Epilepsy Foundation. Dr. Gross serves as a consultant to Medtronic Inc. and receives compensation for these services. Medtronic develops products related to the research described in this paper. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. J. Nazzaro and D. Labar report no disclosures relevant to the manuscript. M. Sperling is a consultant for UCB Pharma, Accord Therapeutics, and electroCore, and receives research support from UCB Pharma, Sunovion, SK Life Sciences, Eisai, Lundbeck, Upsher-Smith, LCGH, Vertex Pharmaceuticals, Neuronex, and Visualase. A. Sharan serves on the advisory board for Medtronic, is a speaker for St. Jude Medical, receives grant support from St. Jude Medical, is the owner of Integrated Care Pharmacy, and is the founder of ICVrx, a company developing drug delivery technologies for epilepsy. E. Sandok reports no disclosures relevant to the manuscript. A. Handforth received research support from the International Essential Tremor Foundation, the Ralph M. Parsons Foundation, and Sonexa, Inc., and is receiving research support from Veterans Affairs. J. Stern has served on an advisory board for Sunovion, Upsher-Smith, Lundbeck, and UCB, has received lecturing honoraria from Sunovion, Lundbeck, UCB, Cyberonics, and GSK, and receives royalties from *MedLink Neurology*, McGraw-Hill, and Lippincott Williams & Wilkins. S. Chung receives grant support from Medtronic for the SANTE study, is a consultant for UCB, Accord Therapeutics, Upsher-Smith, SK Life Sciences, has received lecturing honoraria from Lundbeck, UCB, Eisai, and Sunovion, and receives research support from UCB Pharma, SK Life Sciences, Eisai, Lundbeck, and Upsher-Smith. J. Henderson is chair of the medical advisory board for Circuit Therapeutics, is a consultant for Nevro Corp, receives stock options for Circuit Therapeutics and Nevro Corp, and has received stock options from Proteus Biomedical for consulting activities. J. French serves as the president of The Epilepsy Study Consortium, a nonprofit organization, and NYU receives a fixed amount from the Epilepsy Study Consortium toward Dr. French's salary. The money is for work performed by Dr. French on behalf of The Epilepsy Study Consortium, for consulting, and clinical trial-related activities. Dr. French receives no personal income for these activities. Within the past year, The Epilepsy Study Consortium received payments from Biotie, Cyberonics, Eisai Medical Research, Entra Pharmaceuticals, GlaxoSmithKline, Icadex, Inc., Johnson & Johnson, Mapp Pharmaceuticals, Marinus, Neurotherapeutics, NeuroPace, NeuroVista Corporation, Ono Pharma USA, Inc., Lundbeck, Pfizer Inc., Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc./Schwarz Pharma, Upsher-Smith, Valeant, and Vertex. G. Baltuch reports no disclosures relevant to the manuscript. W. Rosenfeld receives research support from Pfizer, UCB Pharma, Eisai, Valeant, Medtronic, Lundbeck Pharmaceuticals, Sunovion Pharmaceuticals, Artemis, SK Life, and Upsher-Smith, is a consultant for UCB Pharma, Lundbeck Pharmaceuticals, and Supernus Pharmaceuticals, and serves on the speakers bureau for UCB Pharma, Lundbeck Pharmaceuticals, GlaxoSmithKline, Supernus Pharmaceuticals, Sunovion Pharmaceuticals, and Eisai. P. Garcia received research funding from Medtronic, UCB Pharma, and NIH (1U01NS058634-01A2 [Barbaro] and R01NS069779-01 [Starr]), and provided expert testimony in the following cases: *Watts v. University of Utah Medical Center*, *Golin v. Stanford*, *Barclay v. XE Services Inc.*, and *People v. Figg*. N. Barbaro received research support from NIH (National Institute of Neurological Disorders and Stroke) and Elekta. N. Fountain performs EEG interpretation in his clinical practice (10% effort), and the University of Virginia receives research support from UCB, SK Life Sciences, Sunovion, Medtronic, NeuroPace, and NIH for grants awarded to him. J. Elias was awarded grants, and the University of Virginia receives research support, from Focused Ultrasound Foundation and InSightec. R. Goodman

was on the scientific advisory board for Medtronic, Inc., and is currently on the neurosurgical advisory board for NeuroPace, Inc. J. Pollard served as a consultant to H. Lundbeck Inc., receives clinical trials support from GlaxoSmithKline, Vertex Pharmaceuticals, Medtronic, PI, Lundbeck, SK Biopharmaceuticals, Brain Sentinel, and Upsher-Smith Labs, and has ownership in Cognizance Biomarkers, LLC, which has no current market value and no relationship with Medtronic. A. Tröster receives honoraria and is on the scientific advisory boards of St. Jude Medical, Medtronic, Boston Scientific, and Theravance, receives royalties from Oxford University Press, and receives research support from Barrow Neurological Institute. C. Irwin holds stock options from Medtronic and is an employee of Medtronic. K. Lambrecht holds stock options from Medtronic and is an employee of Medtronic. N. Graves holds stock options from Medtronic, is a former employee of Medtronic, and holds several patents that may be related to this work. R. Fisher has been a consultant for Cyberonics, and receives no income or equity from Medtronic, but Stanford received a research grant from Medtronic. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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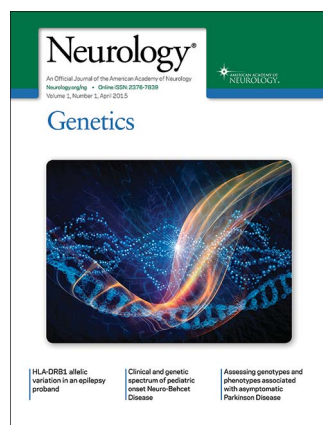
## REFERENCES

- Engel JJ, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 2012;307:922–930.
- Engel JJ. Another good reason to consider surgical treatment for epilepsy more often and sooner. *Arch Neurol* 2011;68:707–708.
- Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002;43:603–608.
- Lee KJ, Jang KS, Shon YM. Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. *Acta Neurochir Suppl* 2006;99:87–91.
- Lim SN, Lee ST, Tsai YT, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. *Epilepsia* 2007;48:342–347.
- Kerrigan JF, Litt B, Fisher RS, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia* 2004;45:346–354.
- 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.
- Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295–1304.
- 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* 2012;23:230–234.
- Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. *J Clin Neurophysiol* 1991;8:216–222.
- Baker GA, Currie NGT, Light MJ, Schneiderman JH. The effects of adjunctive topiramate therapy on seizure severity and health-related quality of life in patients with refractory epilepsy: a Canadian study. *Seizure* 2002;11:6–15.
- Bryant-Comstock L, Scott-Lennox J, Lennox R. Assessment of seizure severity with adjunctive lamotrigine therapy: results from a U.S. observational study. *Epilepsy Behav* 2001;2:152–157.
- Fisher RS. Therapeutic devices for epilepsy. *Ann Neurol* 2012;71:157–168.



14. Medtronic, Inc. Medtronic DBS Therapy for Parkinson's Disease and Essential Tremor Clinical Summary [online]. Minneapolis: Medtronic, Inc.; 2013. Available at: [http://manuals.medtronic.com/wcm/groups/mdtcom\\_sg/@emanuals/@era/@neuro/documents/documents/contrib\\_181407.pdf](http://manuals.medtronic.com/wcm/groups/mdtcom_sg/@emanuals/@era/@neuro/documents/documents/contrib_181407.pdf). Accessed August 1, 2014.
15. Fiest KM, Dykeman J, Patten SB, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology* 2013;80:590–599.
16. Thompson PJ, Duncan JS. Cognitive decline in severe intractable epilepsy. *Epilepsia* 2005;46:1780–1787.
17. 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;21:183–187.
18. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol* 1969;25:295–330.

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