FULL-LENGTH ORIGINAL RESEARCH

Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy

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Summary

Objective: Responsive neurostimulation decreases the frequency of disabling seizures when used as an adjunctive therapy in patients with medically refractory partial-onset seizures. The effect of long-term responsive neurostimulation on neuropsychological performance has not yet been established.

Methods: Neuropsychological data were collected from subjects participating in the open-label arm of a randomized controlled trial of responsive neurostimulation with the RNS® System. Primary cognitive outcomes were the Boston Naming Test (BNT) and Rey Auditory Verbal Learning (AVLT) test. Neuropsychological performance was evaluated at baseline and again following 1 and 2 years of RNS System treatment. Follow-up analyses were conducted in patients with seizure onset restricted to either the mesial temporal lobe or neocortex.

Results: No significant cognitive declines were observed for any neuropsychological measure through 2 years. When examined as a function of seizure onset region, a double dissociation was found, with significant improvement in naming across all patients ($p < 0.0001$), and for patients with neocortical seizure onsets ($p < 0.0001$) but not in patients with mesial temporal lobe (MTL) seizure onsets ($p = 0.679$). In contrast, a significant improvement in verbal learning was observed across all patients ($p = 0.03$), and for patients with MTL seizure onsets ($p = 0.005$) but not for patients with neocortical onsets ($p = 0.403$).

Significance: Treatment with the RNS System is not associated with cognitive decline when tested through 2 years. In fact, there were small but significant beneficial treatment effects on naming in patients with neocortical onsets and modest improvements in verbal learning for patients with seizure onsets in MTL structures. These results suggest that there are modest cognitive improvements in some domains that vary as a function of the region from which seizures arise.

KEY WORDS: Epilepsy, Brain stimulation, Naming, Memory.

Persons with epilepsy are at risk for cognitive disability and decline, and the cognitive effects of treatment are an important component in evaluating overall effectiveness. Many antiepileptic drugs (AEDs) have adverse cognitive effects,[1–3] and although epilepsy surgeries offer the potential for great benefit in select patients with intractable partial-onset seizures, they carry risks for cognitive decline in areas specific to the region of brain resected or disconnected, depending on the pathologic-functional status of the tissue included in resection.[4–10]

Responsive neurostimulation using the RNS® System (NeuroPace, Mountain View, CA, U.S.A.) is a U.S. Food

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Key Points

- Treatment with responsive neurostimulation was not associated with cognitive decline over time
- There were modest cognitive improvements in naming and memory that varied as a function of the region from which seizures arose.
- There was no relationship between cognitive outcome and change in seizure frequency

and Drug Administration (FDA)–approved adjunctive treatment for medically intractable disabling partial-onset seizures in adults with one or two seizure foci. This treatment provides stimulation to the epileptogenic region in response to detection of physician-selected electrographic activity, which usually represents interictal epileptiform activity preceding the onset of electrographic seizures. A randomized controlled trial (RCT) in patients with intractable partial seizures demonstrated a statistically significant reduction in seizures in patients treated with responsive neurostimulation compared to sham stimulation controls.[11] These patients showed a 41.5% seizure reduction in the active stimulation group and a 9.4% reduction in the sham control in the final month of the blinded period ($p = 0.008$, generalized estimating equation [GEE]).[11] The observed median percent reduction in disabling seizures during the open-label period was 44% at 1 year and 53% at 2 years ($p < 0.0001$).[12] Median percent seizure reductions in excess of 60% were sustained at 3–6 years of follow-up.[13]

Neurostimulation has been associated with neuropsychological changes specific to the region and condition being treated. Patients treated for Parkinson's disease with stimulation of the subthalamic nuclei or globus pallidus have experienced declines in verbal fluency.[14,15] Patients with Alzheimer's disease who were treated with stimulation of the anterior fornix experienced slowing rates of decline and some improvements in memory.[16] Patients with intractable partial seizures treated with scheduled deep brain stimulation (DBS) of the anterior nucleus of the thalamus did not show evidence of neuropsychological declines, although there were spontaneous complaints of poorer memory and mood.[17] Thus, in addition to demonstrating safety, an additional study goal was to determine whether cognitive risks varied according to the cortical region from which seizures arose and to which responsive neurostimulation was delivered.

Methods

A double-blind, randomized, sham-stimulation controlled study was conducted across 32 comprehensive epilepsy centers in the United States. The intent of the study was to establish the safety and efficacy of the RNS® System as an adjunctive treatment for adults with medically intractable and disabling partial-onset seizures arising from one or two seizure foci. A prespecified secondary safety endpoint included neuropsychological function during the open-label period.

The RNS System (NeuroPace, Inc.) provides targeted responsive neurostimulation via a cranially implanted programmable neurostimulator connected to 1 or 2 depth and/or subdural cortical strip leads. Leads are placed at 1 or 2 previously identified seizure foci, and each lead contains four electrode contacts (Fig. 1). The RNS Neurostimulator continuously senses electrocorticographic activity through the electrodes. It is programmed by the physician to detect specific patterns in the electrocorticogram (ECoG) and then to deliver brief stimulus pulses shortly after the detection. Recording and stimulation occur on the same electrodes. The physician adjusts detection and stimulation parameters for each patient as needed for seizure reduction. The typical patient receives brief bursts (100–200 msec) of high-frequency stimulation with a total cumulative stimulation time of <6 min a day.

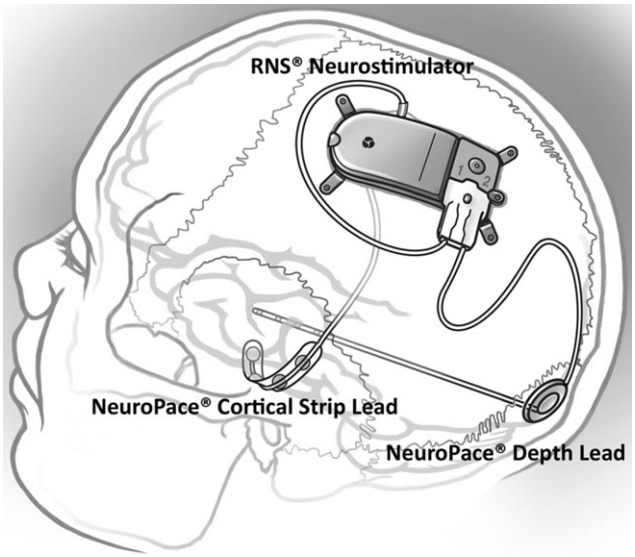

Figure 1.
Implanted RNS® Neurostimulator and NeuroPace® cortical strip and depth leads. The RNS System provides responsive neurostimulation to terminate abnormal electrographic activity. The neurostimulator is placed in a tray (or ferrule), which is seated within a craniectomy. The neurostimulator is flush with the skull, is extradural, and does not contact the brain. Within the neurostimulator, there are custom integrated circuits, a battery, and a connector assembly. The neurostimulator is connected to up to two leads: subdural cortical, depth, or a combination of the two. Each lead has four electrode contacts. The leads are placed at the seizure focus for that patient, which has been identified by standard tests to localize the seizure focus.

Detailed methods for the RNS® System randomized controlled trial are published elsewhere.[11,12] Patients in the trial were 18–66 years old and averaged three or more simple partial motor, complex partial, or secondarily generalized tonic–clonic seizures each month. All had inadequate seizure control with at least two AEDs. Seizure onset was localized to one or two foci using the standard procedures for localization at that investigational site. Patients with active psychosis, unstable major depressive disorder, or suicidal ideation in the previous year were excluded, but patients with a history of any of these or with a stable depressive disorder could be enrolled.

The neurostimulator and leads were implanted after a 3-month baseline. The neurostimulator was programmed to detect immediately. One month after implantation, patients were randomized one to one to receive active or sham stimulation in response to detections. Patients were followed in a double-blind fashion for 4 months, after which all patients received responsive neurostimulation for an 18-month open-label period. Neuropsychological data were collected at baseline and during the open label period at 1 and 2 years after implantation (Figure S1). The study protocol was approved by the institutional review boards of all participating investigational sites. All patients gave written informed consent. The study was registered on www.clinicaltrials.gov (NCT00264810).

Language and verbal memory were identified as the primary cognitive outcomes of interest, since declines in these areas are the most common risks following temporal lobectomy. Primary neuropsychological tests included the Boston Naming Test (BNT)[18]and the Rey Auditory Verbal Learning Test (AVLT).[19,20] Additional neuropsychological domains were analyzed as secondary outcomes to provide a comprehensive assessment of safety, and are presented in Table S1.

All neuropsychological tests were administered and scored by a neuropsychologist or a psychometrician at each participating site. Neuropsychological testing case report forms were reviewed by a blinded neuropsychologist (DWL) to determine whether scores were appropriate for inclusion in the analysis. Scores were identified for exclusion if evaluations were performed outside the per-protocol target date (>1 year prior to implantation for baseline or >4 weeks ± the per-protocol date for postimplantation data). In addition, data were excluded if case report forms included comments indicating that the score(s) were not considered to be valid (e.g., lack of task engagement or proximity of seizures to testing), if an incorrect form of the test was administered, or if the patient discontinued trial participation (Fig. 2).

To minimize practice effects, available alternate test forms were used for the AVLT. Form AB was utilized at baseline and 1 year, with form CD administered at year 2. The same test version was used at each time point for the BNT (Table S2).

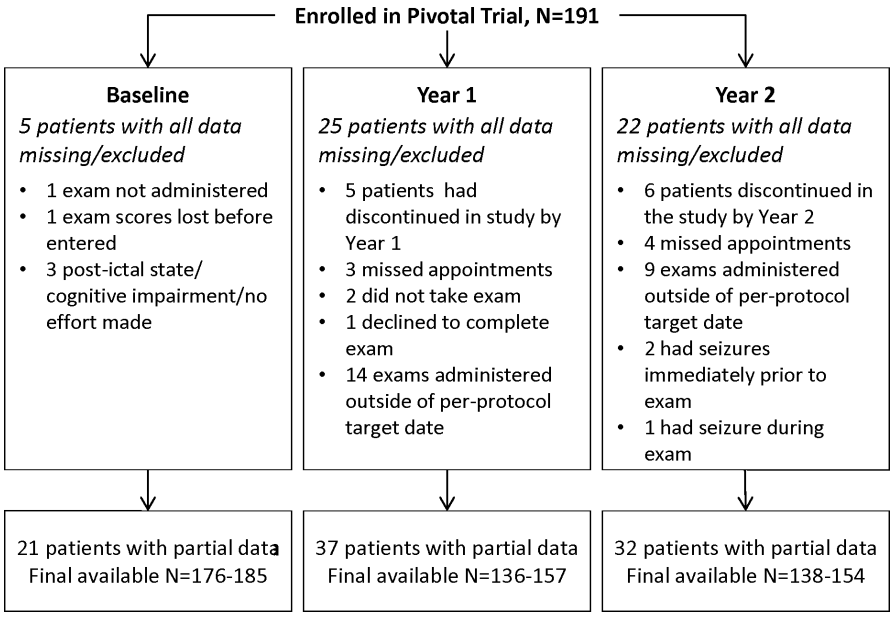

Figure 2.
Data exclusions. Detailed information on missing or excluded data at baseline, year 1, and year 2. Partial data collection occurred when an incorrect form was administered for the Rey Auditory Verbal Learning Test (AVLT), the Brief Visuospatial Memory Test - Revised (BVMT-R), or the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test, or if the patient was unable to complete the entire exam. This explains the range for sample sizes. The total number of subjects who had data for each test at each time point is available in Table S5.

The change in neuropsychological outcome measures from baseline through 2 years was assessed using the generalized estimating equation (GEE), an extension of generalized linear modeling that handles missing data and properly assigns significance to multiple correlated measurements.[21] A GEE model for change from baseline was used to generate estimates of change and the 95% confidence interval as well as the significance of change. The model included an intercept and estimated the change from baseline through 2 years.

Data from any subject who had a change from baseline score at year 1, year 2, or both, were included in the model. For the subset analyses to assess risks according to the region of seizure onset, separate GEE models were fit for patients with seizure onsets in mesial temporal lobe (MTL) structures and for those with neocortical seizure onsets. Although their data contributed to the overall results, subjects with onsets in both MTL structures and neocortical structures were excluded from the subset analyses by onset region because this group was too small to provide meaningful data when analyzed as a subset. Similarly, differences between groups with left- or right-sided seizure onsets were not examined separately in this study because of the low number of patients with exclusively left-sided or exclusively right-sided onsets.

Reliable change indices (RCIs) were used to identify patients with improvements or declines that cannot be attributed to practice effects or measurement error in the test–retest setting.[22,23] As is customary in the neuropsychological literature, 90% RCIs[20,23–29] were used for patient classification. Because the two versions (AB and CD) of the Rey AVLT are not equivalent,[28] a 3-point adjustment was made to the RCI threshold for the CD form of the AVLT Learning and a 1-point adjustment was made for the CD form of the AVLT Delayed Recall (Table S2).

Seizures were recorded in seizure diaries, and percent change in seizures was calculated by comparing the seizure rates in the last 3 months of year 1 and year 2 to the rate during the 3-month baseline. Missing days were not counted in the denominator (i.e., missing days were not imputed as days having no seizures). The relationship between the percent change in seizures and each test was assessed using both univariate and multivariate linear regression.

A given patient's antiepileptic drug (AED) change status was determined by looking at all changes made after the baseline period was over and up to the 1 year and 2 year time point. The most recent AEDs and doses in this window were compared to the AEDs and doses at baseline, and patients' AED change status was determined in this manner. Changes made <28 days before year 1 or year 2 were excluded from analysis. Changes relative to baseline were categorized for each patient as follows: (1) "Increased AEDs" if an AED was added or dose was increased by >25% with no AED discontinuations or dose decreases of >25%; (2) "Decreased AEDs" if an AED was discontinued or dose was decreased by >25% with no new AEDs or dose increases of >25%; (3) "Both Increased and Decreased" if there were new AEDs or dose increases as well as discontinued AEDs or decreases in dose; and (4) "No Change" if there were no dose changes of >25% and there were no new or discontinued AEDs. The relationship between the AED change category and the change in neuropsychological test score was assessed using an analysis of variance (ANOVA) model with change from baseline as the dependent and AED change category as the independent variable.

Results

Patient demographic and baseline characteristics are provided in Table 1. Of the 191 patients implanted in the

Table 1. Demographic and baseline characteristics of patients contributing to analysis (n = 175)

Characteristic	All subjects (n = 175)	MTL onsets[a] (n = 86)	Neocortical onsets[a] (n = 76)
	Mean ± SD (min–max) or % (n)		
Age in years	34.6 ± 11.6 (18–66)	37.3 ± 10.9 (18–60)	31.0 ± 10.9 (18–63)
Female	48% (84)	49% (42)	49% (37)
Duration of epilepsy (years)	20.4 ± 11.8 (2–57)	20.6 ± 12.8 (2–57)	20.1 ± 10.7 (4–47)
Number of AEDs at enrollment	2.8 ± 1.1 (0–8)	2.6 ± 1.1 (1–5)	3.0 ± 1.0 (1–6)
WRAT-3			
Arithmetic	82 ± 16 (44–127)	84 ± 14 (44–105)	78 ± 16 (44–120)
Reading	89 ± 17 (44–116)	88 ± 16 (44–113)	90 ± 17 (44–116)
Spelling	88 ± 17 (44–119)	87 ± 17 (44–115)	88 ± 178 (44–119)
Mean seizure frequency during preimplantation period (seizures/month)	34.5 ± 64.0 (3–338) median = 9.7	14.7 ± 26.5 (3–217) median = 7.0	60.3 ± 86.6 (3–338) median = 19.0
Number of seizure foci – two (vs. one)[a]	55% (96)	72% (62)	28% (21)
Prior therapeutic surgery for epilepsy[a]	33% (57)	13% (11)	51% (39)
Prior EEG monitoring with intracranial electrodes	58% (102)	41% (35)	76% (58)
Prior VNS	33% (58)	24% (21)	37% (28)

[a]Subjects with both mesial temporal (MTL) and neocortical onsets (n = 13) were not analyzed separately because the small *n* precludes meaningful subset analysis.

AEDs, antiepileptic drugs; WRAT-3, Wide Range Achievement Test 3; EEG, electroencephalography; VNS, vagus nerve stimulation.

Pivotal Trial, the patients who contributed to this analysis were those who had data at baseline and a score on a given cognitive assessment either at year 1, at year 2, or both (n = 175). Study participants had a long duration of epilepsy and were typically taking multiple AEDs. Approximately one third had previously been treated with a vagus nerve stimulator (VNS) and/or with focal resective epilepsy surgery. Seizure onset was localized to the MTL in 86 of the 175 patients; 72% (n = 62) of these had bilateral onsets. Seizures were localized to a neocortical region in 76 patients, the most common being frontal (n = 25) and lateral temporal (n = 25). Thirteen patients had seizures arising from both MTL and neocortical structures.

No significant group performance decline was detected on any neuropsychological outcome measure. Significant improvements were present for naming (BNT), with 23.5% of subjects demonstrating RCI improvements and 6.7% demonstrating declines (Tables 2 and 3). Similarly, there were statistically significant improvements in verbal learning on the AVLT, with 6.9% of subjects demonstrating RCI improvements and 1.4% demonstrating declines. There was a trend toward significant improvement on delayed AVLT recall (p = 0.07), with no suggestion of performance change for delayed AVLT recognition (p = 0.30).

When examined as a function of seizure-onset zone, a significant improvement was observed in naming (BNT) in patients with neocortical seizure onsets that was not present in patients with seizures of MTL onset (Fig. 3). This pattern was also seen in RCI analysis of individual patients (Table 3). In contrast, there was a significant overall memory improvement (AVLT Learning) for patients with MTL seizure onsets that was not present in the patients with neocortical seizure onsets. Although not statistically significant, there was a trend for improvement on delayed AVLT recall in the patients with MTL seizure onsets (p = 0.08), with no suggestion of a similar change in the neocortical group (p = 0.20).

To examine whether this regional effect was confounded by prior epilepsy surgery, the analysis was repeated only in those patients who had not had previous resections for treatment of epilepsy (75/86 MTL patients, 37/76 neocortical patients). This subgroup of patients showed the same pattern; significant improvements in naming were seen in neocortical patients (p < 0.0001) but not in MTL patients (p = 0.49), and significant improvements in memory were seen in MTL patients (0.008) but not in neocortical patients (p = 0.73). To investigate whether changes in seizure frequency influenced cognitive outcomes, BNT and AVLT change scores were correlated with the percent change from baseline seizure frequency. There was no significant relationship between cognitive outcome and change in seizures (Figure S2). Because no patients were seizure-free over the entire follow-up, it was not possible to examine the cognitive outcomes in seizure-free patients.

Most patients were on multiple antiepileptic drugs (AEDs), and in the open-label period, often more than one AED was changed by the physician at the same time. This precluded the possibility of examining the effect of any specific AED on cognitive outcome, but the relationship between AED change status (Increased, Decreased, Both Increased and Decreased, and No Change) and cognitive outcome was assessed. The ANOVA found no significant relationship between AED change status and cognitive outcome (Table S3).

Table 3. Percent of subjects with 90% RCI changes at 2 years

Neuropsychological measure	N	% with decline	% with no change	% with improvement
Boston Naming Test				
All patients	149	6.7%	69.8%	23.5%
MTL	72	9.7%	73.6%	16.7%
Neo	65	3.1%	64.6%	32.3%
AVLT learning				
All patients	145	1.4%	91.7%	6.9%
MTL	71	0.0%	91.5%	8.5%
Neo	62	3.2%	90.3%	6.5%
AVLT delayed recall				
All patients	147	0.7%	92.5%	6.8%
MTL	72	0.0%	95.8%	4.2%
Neo	63	0.0%	92.1%	7.9%

AVLT, Rey Auditory Verbal Learning Test.

Discussion

Treatment with targeted responsive neurostimulation assessed over 2 years was not associated with adverse cognitive effects in patients with medically intractable partial-onset seizures. In contrast, there was a modest cognitive benefit with responsive neurostimulation that was related to

Table 2. Primary scales, change from baseline through 2 years, GEE-modeled estimates

Test	Average change	Standard error	Lower 95% CL	Upper 95% CL	p-Value
Boston Naming Test	1.1759	0.2866	0.6143	1.7376	**<0.001**
AVLT Learning	1.3031	0.5871	0.1525	2.4538	**0.03**
AVLT Delayed Recall	0.3280	0.1792	−0.0233	0.6793	0.07
AVLT Recognition	0.1791	0.1734	−0.1608	0.5189	0.30

AVLT, Rey Auditory Verbal Learning Test; CL, confidence limit.

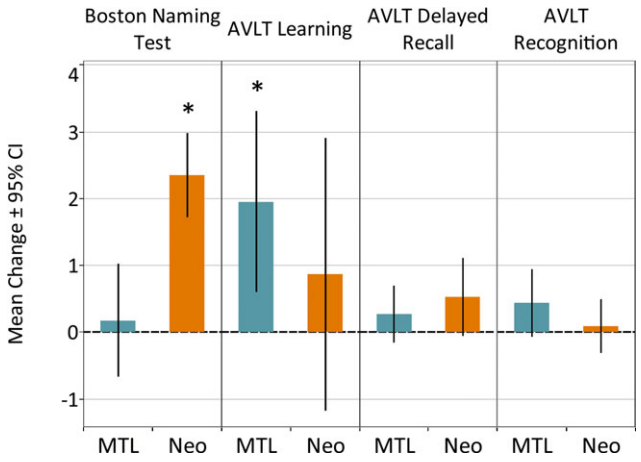

Figure 3.

Primary outcomes, change from baseline through 2 years by region of seizure onset. Bars represent the GEE-modeled average change from baseline naming and memory function at 2 years for MTL and neocortical patients. Error bars represent the 95% confidence interval. An asterisk (*) denotes a statistically significant change ($p < 0.05$) from baseline. An increase in score is in the direction of improvement. AVLT, Rey Auditory Verbal Learning Test; MTL, mesial temporal lobe; Neo, neocortical.

the region from which seizures arose and to which responsive neurostimulation was delivered. Naming performance on the BNT improved in patients with seizures arising from the neocortex, but not in the MTL group, and there were small verbal memory improvements in patients with MTL seizure onsets that were not observed in neocortical patients. This is an important observation given the cognitive side effects of some AEDs and the presence of cognitive decline with DBS stimulation of the subthalamic nuclei or of the globus pallidus for Parkinson's disease.[14,15]

When characterizing RCI improvements by individual subjects at the 2-year endpoint, approximately one of every three patients with neocortical seizure onsets and one of every six patients with seizures of MTL onset demonstrated naming improvement, suggesting a reliable improvement for these study participants. The improvement in verbal learning in patients with seizures of MTL onset was observed in a smaller percentage of patients (neocortical = 6.5%; MTL = 8.5%), and can be interpreted as a signal that responsive neurostimulation has the potential to favorably impact impaired memory function, although this bears further study.

The magnitude of beneficial effect on the group level was modest, and the average BNT improvements in the neocortical group and average AVLT improvements in the mesial temporal group were smaller than the critical value to infer reliable change on the individual subject level. The double dissociation observed serves primarily to provide empirical evidence that neurostimulation techniques may ultimately provide therapeutic benefit, and to conceptually support future studies directed explicitly at establishing and optimizing neurostimulation parameters to enhance cognition.

The improvements in some aspects of cognitive function cannot be attributed simply to practice effects from repeated neuropsychological assessments. Although there was not an untreated control group that allowed for an empirically derived estimate of practice effects from repeated neuropsychological assessments, the double dissociation between naming and verbal memory that varied as a function of the seizure-onset region indicates that performance improvements were unlikely to simply be practice effects. Practice effects are expected to occur at equal magnitudes in all clinical groups with comparable overall status, such as those that were observed for design fluency and block design performance (Table S4). In contrast, patients with neocortical seizure onsets improved on naming but not verbal memory, and patients with MTL seizure onsets improved on memory but not naming, indicating that practice effects were not the explanation for performance changes over time. These findings require replication but suggest potential cognitive therapeutic benefit associated with responsive neurostimulation. It is unclear if these effects are due to a direct positive effect on the stimulated structures or to modulatory reductions in the adverse effects of seizures or interictal discharges.

Cognitive outcomes were not attributable to changes in seizure frequency. However, whether there would be different results in patients who become seizure-free could not be addressed with these data. Although most patients experienced a substantial reduction in seizures, no patients were seizure-free for the entire 2-year follow-up period. Cognitive outcomes at 2 years did not appear to be associated with changes in AEDs. Unfortunately, there is insufficient information to examine the relationship to specific AEDs or AED combinations.

There is increasing evidence that electrical stimulation as a therapy for partial-onset epilepsy is not accompanied by the same types of cognitive side effects seen with epilepsy surgery. Neither responsive neurostimulation (reported here) nor scheduled stimulation[30] has been associated with cognitive declines, although these treatments are relatively novel and greater insight will be gleaned with longer term data and new cohorts. Similarly, cognitive decline has not been reported for direct stimulation of the presumed seizure focus (reported here), of other nodes in the seizure circuit,[30] or of the vagus nerve.[31]

Although it is not known why scheduled and responsive stimulation have different effects on cognition, it is possible that the shorter amount of time for which a patient is stimulated could contribute to the differences seen in the results of these studies. Responsive stimulation was delivered for <5 min per day on average compared to approximately 240 min per day with scheduled stimulation.[14,15] It is also possible that because the stimulation is closed-loop rather

than open-loop, stimulation preferentially interrupts pathologic, rather than healthy brain function. Moreover, this study used focal stimulation of cortical brain areas, whereas in the studies in which declines were seen, patients received stimulation in the thalamus and the internal globus pallidus.[14,15] These subcortical structures are more likely to have diffuse cortical targets, and stimulation could therefore have a broader impact on cortical function. However, because Parkinson's disease is a degenerative disorder, it is difficult to directly compare the cognitive outcomes for DBS in Parkinson's to responsive neurostimulation for epilepsy.

Cognitive impairment is a well-recognized comorbidity of medically intractable partial seizures. Cognitive disability in this patient population is multifactorial; it is related to the underlying pathophysiology of that individual's epilepsy, the acute and chronic effects of seizures, the effects of antiepileptic medications, and the effects of comorbid depression. Therapies for partial-onset seizures must consider not only the impact on seizure frequency and severity, but also the impact on cognition. Cognitive side effects related to specific types of AEDs and epilepsy surgeries are well understood.[5–10] However, the cognitive effects of targeted responsive neurostimulation have not been previously investigated. This series provides evidence that adults with frequent, intractable, partial onset seizures treated with responsive neurostimulation are not at increased risk for developing cognitive dysfunction, and that some aspects of cognition may be improved. Further investigation is needed to define the potential cognitive benefits of treating partial-onset seizures with responsive neurostimulation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Trial design and timing of neuropsychological evaluations.

Figure S2. No correlation between change in cognitive outcome and change in seizures.

Figure S3. Secondary outcomes, change from baseline through 2 years by region of seizure onset.

Table S1. Secondary outcomes, GEE estimated change from baseline through 2 years.

Table S2. Test forms and RCI cutoffs.

Table S3. No significant relationship between AED change status and cognitive outcome.

Table S4. Secondary outcomes, percent of subjects with 90% RCI changes at 2 years.

Table S5. Observed changes from baseline, by region of seizure onset (page 1 of 2).