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Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation

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ABSTRACT

Purpose: The primary efficacy and safety measures from a trial of responsive neurostimulation for focal epilepsy were previously published. In this report, the findings from the same study are presented for quality of life, which was a supportive analysis, and for mood, which was assessed as a secondary safety endpoint.
Methods: The study was a multicenter randomized controlled double-blinded trial of responsive neurostimulation in 191 patients with medically resistant focal epilepsy. During a 4-month postimplant blinded period, patients were randomized to receive responsive stimulation or sham stimulation, after which all patients received responsive neurostimulation in open label to complete 2 years. Quality of life (QOL) and mood surveys were administered during the baseline period, at the end of the blinded period, and at year 1 and year 2 of the open label period.
Results: The treatment and sham groups did not differ at baseline. Compared with baseline, QOL improved in both groups at the end of the blinded period and also at 1 year and 2 years, when all patients were treated. At 2 years, 44% of patients reported meaningful improvements in QOL, and 16% reported declines. There were no overall adverse changes in mood or in suicidality across the study. Findings were not related to changes in seizures and antiepileptic drugs, and patients with mesial temporal seizure onsets and those with neocortical seizure onsets both experienced improvements in QOL.
Conclusions: Treatment with targeted responsive neurostimulation does not adversely affect QOL or mood and may be associated with improvements in QOL in patients, including those with seizures of either mesial temporal origin or neocortical origin.

1. Introduction

Persons with epilepsy face challenges beyond the direct effects of seizures. Epilepsy therapy trials typically consider change in seizure frequency to be the primary indicator of effectiveness. However, counting seizures does not adequately reflect other important treatment effects on a patient's life experience, and increasingly, characterization of treatment effectiveness in epilepsy includes quality of life (QOL) and emotional health. In the present report, quality of life and mood were assessed in subjects participating in a randomized, double-blind, multicenter, controlled trial of a responsive neurostimulator for the treatment of medically intractable partial-onset seizures.

Targeted responsive stimulation using a cranially implanted neurostimulator (RNS® System, NeuroPace, Mountain View, CA) was recently approved by the FDA for the adjunctive treatment of medically intractable frequent partial-onset seizures in adults with one or two seizure foci [1,2]. The programmable neurostimulator continuously senses electrocorticographic activity through depth and/or cortical strip leads placed at the seizure focus or foci and delivers responsive stimulation when physician-specified electrocorticographic patterns are detected. Treatment with the RNS System reduced the frequency of medically intractable disabling partial-onset seizures in adults, and the safety of the implant procedure and responsive stimulation therapy was acceptable compared with comparable procedures. Here, the findings from that study are presented for quality of life, which was a supportive effectiveness analysis in the trial, and for mood, which was assessed as a secondary safety endpoint.

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2. Methods

2.1. Randomized, double-blind, multicenter, controlled trial

Eligible subjects were 18–70 years old; had 3 or more simple partial motor, complex partial, or secondarily generalized tonic–clonic seizures on average each month; had seizures which failed to substantially improve with at least 2 antiepileptic medications; and had seizures coming from 1 focus or 2 foci as identified using the standard procedures for localization at that investigational site. Patients with an active psychosis, an unstable major depressive disorder, or suicidal ideation in the previous year were excluded, but patients with a prior history of any of these, or with a stable depressive disorder, could be enrolled.

After a 3-month baseline, subjects were implanted with the responsive neurostimulator and leads, and detection was enabled. One month after implantation, subjects were randomized 1:1 to receive stimulation in response to detections (treatment group) or to continue detection without stimulation (sham group) for another 4 months (blinded period). Thereafter, all subjects received responsive stimulation through the end of the two-year study (open label period).

2.2. Behavioral surveys

Quality of life and mood surveys were administered during the baseline period, at the end of the blinded period, and at 1 year and 2 years during the open label period. Surveys were reviewed by a neuropsychologist blinded to randomization. Data were excluded from the analysis if the administration date of the survey was more than 6 weeks from the per protocol visit date or if the survey was missing ≥15% of the items. Differences between the treatment group and the sham group were assessed using 2-sample *t*-tests. Differences from baseline were assessed using paired *t*-tests.

Quality of life was assessed using the Quality of Life in Epilepsy Inventory — 89 (QOLIE-89) scoring manual [3]. QOLIE-89 scores were analyzed for all subjects who took the QOLIE-89 at both baseline and per protocol time points of interest. Because the QOLIE-89 generates 17 primary scale scores and an overall QOLIE-89 score as well as 4 derived subscales for Epilepsy-Targeted, Cognitive, Mental Health, and Physical Health [4] were analyzed to limit multiple comparisons. Subscale scores were not calculated if any of the primary scale scores were missing. Quality of life was characterized as meaningfully changed based upon difference scores of 5 or more points in t-score, which is equivalent to a change of 0.5 standard deviations [5].

Current symptoms of depression were assessed using the Beck Depression Inventory [6] and the Profile of Mood States [7]. The criterion for moderately severe symptoms of depression was a BDI-II score ≥ 20. Suicidality was assessed for all subjects who answered question 9 on the BDI-II, whether or not the BDI-II survey was otherwise complete. Response options were as follows: {0} I don't have any thoughts of killing myself; {1} I have thoughts of killing myself, but I would not carry them out; {2} I would like to kill myself; and {3} I would kill myself if I had the chance. Patients were categorized as endorsing suicidality if their response to question 9 on the BDI-II was greater than {0}.

2.3. Analysis of relationship of QOL to mood, seizures, and changes in antiepileptic drugs

Seizures were recorded in seizure diaries. The percent change in seizures was calculated by comparing the seizure rates in the last 3 months of the blinded period, year 1, and year 2 with the rate in the 3-month baseline. The relationship between the percent change in seizures, change in the QOLIE-89 overall score, and change in the BDI-II total scores was assessed using both univariate linear regression and multivariate linear regression.

For analysis of changes in antiepileptic drugs (AEDs), changes made in the 3 months leading up to the year 2 time point (relative to baseline) were categorized for each subject as follows: Increased AEDs if an AED was added or if dose was increased by >25% and there were no AED discontinuations or dose decreases of >25%; Decreased AEDs if an AED was discontinued or if dose was decreased by >25% and there were no new AEDs or dose increases of >25%; Both Increased and Decreased AEDs if there were new AEDs and/or dose increases as well as discontinued AEDs and/or decreases in dose; and No Change if there were no dose changes of >25% and there were no new or discontinued AEDs. The relationship between AED change category, change in the QOLIE-89 overall score, and change in the BDI-II total score was assessed using both univariate linear regression and multivariate linear regression.

3. Results

3.1. Subject demographics

Subject demographics are presented in Table 1. There were no significant demographic differences between patients randomized to the treatment group and to the sham group. Subjects had a long duration of epilepsy, and most were taking multiple daily AEDs. Approximately one third of the sample had previously been treated with the vagus nerve stimulator (VNS) and/or epilepsy surgery, and approximately 60% had previously undergone implantation of intracranial electrodes for seizure localization. Seizure onset was in the mesial temporal lobe (MTL) in 95 of the 191 subjects; 69 of the 95 had bilateral MTL seizure foci. Seizure onset was neocortical in 81 subjects, with frontal (n = 27) and lateral temporal (n = 26) being the most common. Fifteen subjects had seizures arising from both MTL and neocortical structures.

3.2. Quality of life

At baseline, QOLIE-89 overall scores (Table 2) were significantly lower than the population norms for patients with epilepsy ($p < 0.001$, one-sample *t*-test) [4]. There was no difference between treatment and sham group scores on the QOLIE-89 at baseline. Both groups had statistically significant improvements in overall scores at the end of the blinded period, with no significant difference between the groups.

Quality of life continued to improve at years 1 and 2 of the open label period and remained significantly higher than at baseline (Fig. 1, Table 2). In order to test whether these results were due to a change in group composition, a constant cohort analysis was performed using

Table 1
Demographic and baseline characteristics of implanted subjects. Demographic characteristics of all implanted patients at the time of enrollment in the pivotal trial. SD = standard deviation; AEDs = antiepileptic drugs; EEG = electroencephalogram; VNS = vagus nerve stimulator.

Characteristics	All implanted patients (N = 191)
	Mean ± SD (min–max) or % (n)
Age in years	34.9 ± 11.6 (18–66)
Female	48% (91)
Duration of epilepsy (years)	20.5 ± 11.6 (2–57)
Number of AEDs at enrollment	2.8 ± 1.2 (0–8)
Mean seizure frequency during preimplant period (seizures/month)	34.2 ± 61.9 (3–338) median = 9.7
Seizure onset location — mesial temporal lobe only (vs. others)[a]	50% (95)
Number of seizure foci — two (vs. one)[a]	55% (106)
Prior therapeutic surgery for epilepsy[a]	32% (62)
Prior EEG monitoring with intracranial electrodes	59% (113)
Prior VNS	34% (64)

[a] Characteristics used as strata in randomization algorithm.

Table 2
Quality of life and mood outcomes. The Quality of Life in Epilepsy Inventory — 89 (QOLIE-89) overall score is the normalized t-score. Beck Depression Inventory — II (BDI-II) and Profile of Mood States (POMS) scores are total scores (see Supplementary Table 2 for POMS primary scale scores). Data were collected at the end of the 4-month randomized double-blinded period (BP). During the blinded period, the treatment group (Tx) received stimulation while the sham group (Sh) did not. After the blinded period, stimulation was turned on in all subjects (All). SD = standard deviation. p-Values in bold represent a statistically significant difference at $p < 0.05$.

			Baseline			Post		Change from baseline[a]		p[b]	p[c]
			n	Average	SD	Average	SD	Average	SD		
QOLIE-89 overall	Baseline	All	186	45.1	9.6	–	–	–	–	–	0.511
	BP	Tx	93	45.7	9.5	47.8	9.8	2.0	9.4	**0.040**	0.916
		Sh	87	44.9	9.7	47.1	10.2	2.2	9.4	**0.032**	
	Year 1	All	166	45.4	9.5	49.0	10.5	3.6	8.9	<**0.001**	–
	Year 2	All	154	45.3	9.9	49.3	10.3	4.0	10.4	<**0.001**	–
BDI-II	Baseline	All	187	11.0	8.4	–	–	–	–	–	0.704
	BP	Tx	94	10.5	8.4	9.2	7.9	−1.4	8.0	0.098	0.602
		Sh	89	10.9	8.1	9.9	10.3	−1.0	8.0	0.226	
	Year 1	All	169	10.5	8.0	9.0	9.8	−1.6	9.5	**0.036**	–
	Year 2	All	155	10.6	8.4	8.7	8.9	−1.9	8.8	**0.008**	–
POMS	Baseline	All	188	27.8	32.1	–	–	–	–	–	0.701
	BP	Tx	94	27.9	30.0	23.8	29.7	−4.1	31.3	0.204	0.493
		Sh	87	26.7	34.7	27.3	39.2	0.7	32.0	0.841	
	Year 1	All	168	26.9	31.8	22.3	34.6	−4.6	33.6	0.080	–
	Year 2	All	156	27.8	33.0	22.0	36.5	−5.8	35.1	**0.040**	–

[a] An *increase* in QOLIE-89 scores represents an improvement in quality of life, and a *decrease* in the BDI-II and POMS scores represents an improvement in mood.
[b] Comparison vs. baseline, paired *t*-test.
[c] Comparison between the treatment group and the sham group, two-sample *t*-test.

only those subjects who completed year 2. The results of this analysis confirmed that QOLIE-89 overall scores improved over time, even when the subject population was constant (Fig. 1, Supplementary Table 1). At the end of year 2, 44% of the subjects reported clinically meaningful improvements in QOL, and 16% reported declines (Table 3, Supplementary Table 1). When subjects with MTL seizure onsets and those with neocortical seizure onsets were analyzed separately, 41% of the subjects with MTL seizure onsets and 51% of those with neocortical seizure onsets reported clinically meaningful improvements in QOL. Sixteen percent of the subjects with MTL seizure onsets and 15% of the subjects with neocortical seizure onsets reported declines. There were statistically significant group improvements on every composite subscale (Epilepsy-Targeted, Cognitive, Mental Health, and Physical Health) at 1 year and 2 years after implant (Fig. 1). Subjects with MTL seizure onsets and subjects with neocortical seizure onsets had significant improvements in the Epilepsy-Targeted and Cognitive domains at year 1 and year 2. Subjects with seizures of neocortical onset additionally showed significant improvements on the Physical Health subscale at

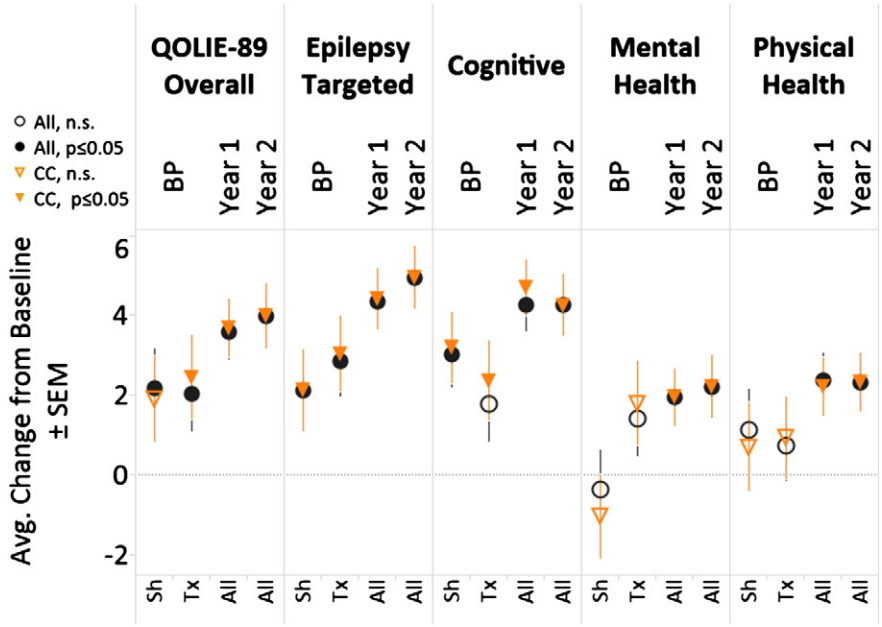

Fig. 1. Quality of life outcomes: QOLIE-89 overall scores and epilepsy-targeted, cognitive, mental health, and physical health composite subscales in all subjects and in a constant cohort. The primary scales of the QOLIE-89 can be grouped into 4 composite subscales. The epilepsy-targeted scale addresses seizure worry, health discouragement, medication effects, and work/driving/social function. The cognitive scale addresses language, memory, and attention/concentration. The mental health scale addresses overall quality of life, energy/fatigue, emotional well-being, role limitations due to emotional problems, social support, and social isolation. The physical health scale addresses role limitations due to physical problems, pain, health perception, and physical function. Improvements are represented by increased t-scores. The constant cohort (CC) was composed of subjects who had QOLIE-89 scores at baseline and at 2 years (n = 154, see Supplementary Table 1). A filled data marker indicates a statistically significant improvement from baseline ($p < 0.05$, paired *t*-test). BP = blinded period; Tx = treatment group; Sh = sham group; SEM = standard error of the mean.

Table 3
Percent of subjects with clinically meaningful changes in quality of life. Change from baseline QOLIE-89 overall score was considered clinically meaningful if the magnitude of the difference was ≥5 points. This 5-point change represents 0.5 standard deviations from the expected population mean score. BP = blinded period; Tx = treatment group; Sh = sham group; MTL = mesial temporal lobe.

			N	% of subjects with		
				Improvement	No change	Decline
All subjects	BP	Tx	93	37%	44%	19%
		Sh	87	39%	38%	23%
	Year 1	All	166	38%	49%	13%
	Year 2	All	154	44%	40%	16%
MTL onset[a]	BP	Tx	45	44%	38%	18%
		Sh	41	41%	34%	24%
	Year 1	All	79	38%	47%	15%
	Year 2	All	76	41%	43%	16%
Neocortical onset[b]	BP	Tx	41	32%	49%	20%
		Sh	38	37%	42%	21%
	Year 1	All	73	38%	51%	11%
	Year 2	All	65	51%	34%	15%

[a] Subjects with seizure onsets in the mesial temporal lobe only.
[b] Subjects with seizure onsets in neocortical areas only.

year 1 and on the Mental and Physical Health subscales 2 years after implant (Supplementary Fig. 1).

3.3. Mood

Mood was assessed as an additional safety endpoint in the trial. Patients who were actively suicidal were excluded from enrollment. At baseline, 16% of subjects had moderately severe symptoms of depression, and 10% endorsed suicidality (as assessed by the BDI-II). There were no baseline differences in treatment and sham group scores on either the BDI-II or the POMS mood inventories (Table 2). In addition, neither group had significant changes at the end of the blinded period compared with baseline, and there was no difference between groups. Furthermore, there were no adverse changes in the BDI-II score or in the POMS score at years 1 and 2. The percentage of subjects with moderately severe symptoms of depression or suicidality remained stable (Fig. 2). Two subjects committed suicide — one subject was being treated with responsive stimulation and one was not. Both had a history of depression, and one had a history of suicidality prior to enrollment. Subjects with complete BDI-II data for all time points were analyzed to look for consistent declines or improvements. Of the 148 subjects with complete BDI-II data, 5 subjects had scores that continued to decrease (improve) across each time point, whereas 3 subjects had scores that continued to increase across each time point.

There were no differences in the POMS total score until year 2 (avg. improvement = −5.8, SD = 35.1, p = 0.040), though statistically significant improvements were seen on the primary scales for fatigue (avg. = −0.98, SD = 6.02, p = 0.037) and tension (avg. = −1.33, SD = 6.85, p = 0.013) at year 1 and for confusion (avg. = −0.83, SD = 4.72, p = 0.029), fatigue (avg. = −1.56, SD = 6.25, p = 0.002), and tension (avg. = −1.67, SD = 6.88, p = 0.003) at year 2. The results for the POMS are depicted in Table 2, and primary scales are depicted in Supplementary Table 2.

3.4. Relationship of QOL to mood, seizures, and changes in antiepileptic drugs (AEDs)

Both univariate and multivariate regression analyses showed a clear relationship between improvement on the QOLIE-89 overall scores and decreases in the BDI-II total score (i.e., improvements in mood) at both 1 year and 2 years (p < 0.0001, both methods, both time points). The relationship between percent change in seizures and QOLIE-89 scores, however, appeared to be inconsistent. There was a statistically significant relationship at 1 year (univariate, p = 0.007; multivariate, p < 0.0001), which was weaker at 2 years (univariate, p = 0.143; multivariate, p = 0.425). Changes in AEDs did not predict changes in QOLIE-89 scores (univariate, p = 0.265; multivariate, p = 0.343) or changes in BDI-II scores (univariate, p = 0.523; multivariate, p = 0.515).

4. Discussion

Quality of life (QOL) and mood are often affected by epilepsy, particularly in patients with poorly controlled seizures. Quality of life encompasses not only physical health but also social and psychological well-being and functional status in daily life such as employment, education, and driving. Mood is one important predictor of QOL.

As expected with this sample of patients with frequent and disabling partial-onset seizures, many had poor QOL; scores at baseline were lower than scores of those with moderate epilepsy [4]. Treatment with responsive stimulation was associated with both group and individual improvements in overall QOL and in Epilepsy-Targeted and Cognitive domains. There were no declines in the group scores for overall QOL or for any of the composite subscales. Furthermore, patients with MTL epilepsy and patients with seizures of neocortical onset were equally likely to experience improvements in overall QOL.

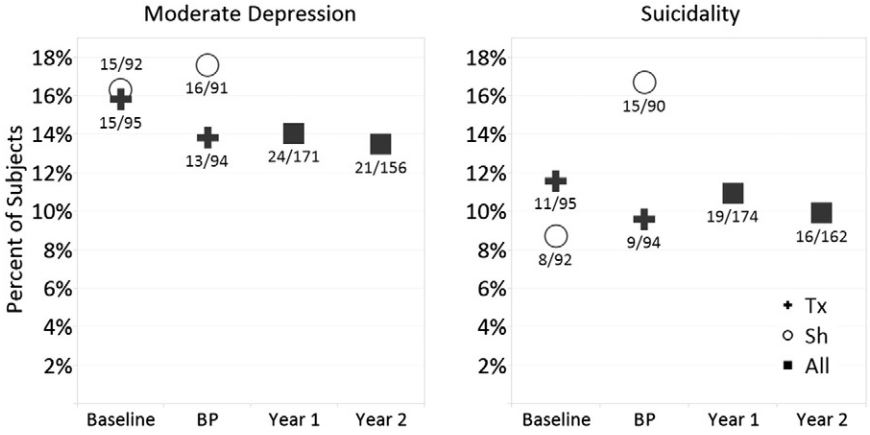

Fig. 2. Rates of depression and suicidality. Rates of depression and suicidality did not increase over the course of the trial. Subjects were classified as reporting moderate depression if they scored ≥20 on the BDI-II and were considered as endorsing suicidality based on their answer to question 9 of the BDI-II (see Section 2.2). The percent of subjects meeting each criterion is plotted in the figures above, and each data marker is labeled with the n patients meeting the threshold/n patients in the sample at that time point. BP = blinded period; Tx = treatment group; Sh = sham group.

Changes in quality of life were assessed in 31 patients with pharmacoresistant focal seizures who were being treated with vagus nerve stimulation (VNS) [8]. These patients were followed for one year, and the improvements in QOL were similar in magnitude to those seen at one year in this study. There were no significant changes in depression in subjects being treated with VNS.

Patients who are candidates for an anterior temporal lobectomy can anticipate an improvement in QOL that is substantially higher than that in patients with continued medical management [8–11]. Patients with MTL epilepsy treated with targeted responsive neurostimulation had improvements in overall QOL and composite subscales that generally surpassed those reported with continued medical management, although these were generally less than improvements reported after mesial temporal lobectomy [8–10]. The patients with MTL epilepsy in this trial, however, were *not* candidates for temporal lobectomy, and treatment with targeted responsive stimulation resulted in improvements in QOL that would not have been possible with previous medical management therapies.

Mood is an important determinant of the QOLIE-89 overall score [12–15]. In the present study, QOLIE-89 scores were more highly correlated with mood than with changes in seizures, a pattern similar to that seen in prior studies. However, improvements in QOL and mood were not explained by changes in AEDs; patients who had increases in AEDs reported similar changes in QOL and mood to those who had decreases or no change in AEDs.

Patients with medically intractable epilepsy are at risk of depression and suicidality, especially patients such as the ones who participated in this study, who have more severe and more frequent seizures [16–18]. The expected prevalence of depression in persons with medically intractable seizures treated at epilepsy centers is as high as 50% [16,19–23]. Sixteen percent of the subjects in the present study met the criteria for moderate depression at baseline. There was no increase in the prevalence of depression with initiation of treatment or over the 2 years of the trial. In fact, the changes in the BDI-II and POMS total scores, while modest, are in the direction of improvement and indicate that there is not an increased risk of mood issues in this already vulnerable population.

Ten percent of the subjects in this study endorsed suicidality at baseline. This is not higher than the prevalence of suicidality of 19% reported in persons with medically intractable epilepsy admitted to an inpatient video-EEG monitoring unit [24]. Treatment with responsive neurostimulation did not change the overall number of patients with suicidal thoughts or intent over the course of the study. Of the two subjects who committed suicide, one subject was being treated with responsive stimulation and one was not. Both had a history of depression, and one had a history of suicidality prior to enrollment, which have been identified in the literature as risk factors for completed suicide. Patients with epilepsy are three times more likely to have a completed suicide than persons without epilepsy, and the presence of a mood disorder increases the risk by 32-fold [25,26]. This underscores the need for constant vigilance for indications of suicidality in all patients with epilepsy, particularly in those with depression and/or a past history of suicidality [27].

This randomized controlled trial of targeted responsive neurostimulation for intractable partial seizures provides evidence for a treatment-related improvement in QOL without an adverse effect on mood. The changes in QOL do not appear to be the results of changes in seizure frequency or AEDs. However, one limitation of this study was that since subjects were on multiple medications that were adjusted according to best medical practice, a more detailed analysis of the relationship between specific AEDs and QOL or mood was not possible. Nevertheless, the sustained improvements in overall QOL and the specific domains of improvement suggest that the favorable effects are related to treatment with responsive neurostimulation. This hypothesis can be explored in future trials and in studies of the mechanism of action of responsive stimulation.

5. Conclusion

Treatment with targeted responsive neurostimulation does not pose risks to QOL or mood and may be associated with improvements in overall QOL and in Epilepsy-Targeted and Cognitive domains in patients, including those with seizures of mesial temporal and of neocortical origin.

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