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SHORT RESEARCH ARTICLE

The Efficacy, Safety, and Outcomes of Brain-responsive Neurostimulation (RNS® System) therapy in older adults

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Abstract

Objectives: The gold standard for the management of drug-resistant focal epilepsy (DRE) is resection of epileptogenic zone. However, some patients may not be candidates for resection. Responsive neurostimulation is approved in patients above 18 years of age for such patients. We aimed to investigate whether RNS outcomes and safety varied based on age.

Methods: We performed a single-center retrospective cohort study of patients with DRE who were treated with RNS between May 2008 and February 2020. We included patients who had been implanted with RNS for >6 months (N = 55), dividing them into older (N = 11) and younger adults (N = 44) depending on implantation age (≥50 and <50 years, respectively).

Results: Mean age at implantation in older adults was 54.9 ± 3.5 years. Seizure onset age, epilepsy duration, and comorbidities were significantly higher in older adults ($P < .01$). Stimulation parameters, treatment duration, and median seizure frequency reduction (76% in older vs 50% in younger adults) were statistically comparable between the two cohorts. Posttreatment, antiseizure medication burden was significantly decreased in older compared with younger adults ($P = .048$). Postoperative and delayed adverse events among older adults were mild. Compared with three younger adults, none of the older adults required device explantation due to surgical site infection.

Conclusion: Our study suggests that older adults treated with the RNS System achieve seizure outcomes comparable to younger adults with the additional benefit of a significant postimplantation medication reduction. With efficacy and safety similar to younger adults, brain-responsive neurostimulation was well-tolerated in older adults.

KEYWORDS

brain-responsive neurostimulation, epilepsy, older adults, RNS System

1 | INTRODUCTION

The responsive neurostimulation (RNS) system (NeuroPace, Inc) is a safe therapeutic option, providing long-term efficacy in seizure control for drug-resistant focal epilepsy(DRE) patients who are not candidates for surgical resection.[1-4] Average age of patients undergoing RNS therapy in the pivotal trial was ~30-35 years,[1-4] which is comparable with average age of epilepsy surgery in the United States.[5] Since we live in a rapidly aging society, it is important to evaluate the safety of treatment options among older adults. Recent evidence suggests epilepsy surgery outcomes in older adults, and the elderly are comparable with younger adults.[6,7] However, RNS System outcomes specific to older adults have yet to be analyzed. The purpose of our study is to investigate the efficacy, safety, tolerability, and outcome of RNS System in adults 50 years or older in comparison with younger adults.

2 | METHODS

2.1 | Study design and patient selection

Following IRB approval, we performed a single-center, retrospective study of all adult DRE patients managed with RNS System between 05/01/2008 and 02/29/2020 at Cleveland Clinic. Patients who had RNS System for at least 6 months were included. Patients who had the device for <6 months were excluded to diminish the impact of surgical manipulation on seizures ("implant effect").[8] Patients were divided into older and younger adults depending on age when device was implanted (≥50 years and <50 years, respectively).

2.2 | RNS system leads

Standard RNS System four-contact leads were utilized. Type of leads (depth, strips, or both), lead location, and stimulation parameters were determined based on review of electronic medical record or Patient Data Management System, an online RNS System database.

2.3 | Data collection and analysis

Data collected included age, sex, seizure type, age at seizure onset, age at RNS implantation, epilepsy duration at implantation, comorbidities at implantation (recorded using Charlson comorbidity index [CCI]),[9] pre-implant testing [MRI (lesional versus non-lesional), PET and MEG (positive versus negative), and ictal SPECT (unilateral versus bilateral)], intracranial EEG (subdural grids/strips vs. stereo-EEG therapy), recommendations made at patient management conference, prior resections, prior vagus nerve stimulation (VNS) treatment, anti-seizure medications (ASMs) at the time of RNS System implantation and at last follow-up, concurrent or subsequent surgical resections, device stimulation parameters, pre- and post-implantation seizure frequency and RNS System-related complications (including device explantation), if any.

The primary outcome was defined as the percentage change in patient-reported seizure frequency at the last clinic follow-up compared with pre-implant baseline. The pre-implant baseline seizure frequency was calculated as average monthly seizure frequency of the 12 months prior to RNS implantation. Patients with ≥50% reduction in seizure frequency at the last follow-up were classified as responders. Secondary outcomes included RNS System-related complications, subsequent surgical resections informed by the device's chronic ambulatory electrocorticography (ECoG) data, and changes in ASMs following RNS therapy. Mood outcomes (depression and anxiety) and quality of life (QOL) were analyzed by comparing baseline and most recent PHQ-9 (Patient Health Questionnaire-9), GAD2 (Generalized Anxiety Disorder-2), and QOLIE-10 (Quality of Life in Epilepsy-10) surveys, respectively. Cognitive outcomes were not included as most patients did not have post-RNS System neuropsychological testing.

2.4 | Statistical analysis

Qualitative variables were described as percentages and quantitative variables as mean plus standard deviation (SD) or median with range or interquartile range [Q1,Q3], as appropriate. Younger and older adults were compared using Chi-square, two-tailed Fisher's exact probability, and Mann-Whitney *U* test based on variable type and distribution. Alpha was set at $P < .05$ for statistical significance. Using multivariable linear regression (MLR) models, we analyzed the association of age at RNS System implantation [separate models for linear and dichotomized (<50 vs. ≥50) age parameterizations] with change in seizure frequency. We included covariates significantly different between the two cohorts in the univariate analysis (CCI) and the ones that could be clinically important prognostic factors: prior epilepsy surgery, intracranial electroencephalogram (icEEG), charge density, and stimulation duration. Age at epilepsy onset and epilepsy duration were not included due to multicollinearity concerns with the independent variable (age at implantation).

TABLE 1 Clinical Characteristics of patients and pre-RNS findings

Characteristic		Total study population (N = 55)	Older adults (n = 11)	Younger adults (n = 44)	Odds Ratio (95% Confidence Interval)	*P*-value
Sex: Female, N (%)		31 (56.4%)	7 (63.6%)	24 (54.5%)	1.46 (0.37-5.71)	.74
Age at RNS implantation in years (Mean ± SD)		35.1 ± 12.9	54.9 ± 3.5	30.2 ± 9.0	N/A	<.01
Age at seizure onset in years (Mean ± SD)		15.6 ± 11.6	23.2 ± 14.9	13.7 ± 10	N/A	.01
Duration of epilepsy in years (Mean ± SD)		19.5 ± 12.6	31.7 ± 15.9	16.5 ± 9.6	N/A	<.01
Pre-implant seizure frequency/Month (median)		9 (0.33-458)	25 (0.33-250)	8.75 (1-458)	N/A	.76
Charlson Co-morbidity Index (Mean ± SD)		0.44 ± 0.81	1.27 ± 1.27	0.23 ± 0.48	N/A	<.01
Charlson Co-morbidity index (range)		0-4	0-4	0-2	N/A	N/A
Pre-implant Cognitive Decline, N (%)		10 (18.2%)	4 (36.4%)	6 (13.6%)	3.6 (0.81-16.22)	.10
Pre implantation Mood Disorder, N (%)		38 (69.1%)	9 (81.8%)	29 (65.9%)	2.33 (0.45-12.17)	.47
Lesional MRI, N (%)		30 (54.5%)	5 (45.5%)	25 (56.8%)	0.63 (0.17-2.39)	.52
PET (N = 53)	Positive, N (%)	46 (86.8%)	11 (100%)	35 (83.3%)	4.86 (0.26-91.82)	.32
SPECT (N = 43)	Unilateral, N (%)	28 (65.1%)	3 (50.0%)	25 (67.6%)	0.48 (0.08-2.74)	.65
	Bilateral, N (%)	15 (34.9%)	3 (50.0%)	12 (32.4%)		
MEG (N = 36)	Positive, N (%)	30 (83.3%)	6 (100%)	24 (80.0%)	3.45(0.17-69.53)	.56
Prior resection, N (%)		17 (30.9%)	2 (18.2%)	15 (34.1%)	0.43 (0.08-2.25)	.47
Prior VNS, N (%)		14 (25.5%)	2 (18.2%)	12 (27.3%)	0.59 (0.11-3.14)	.71
Type of intracranial EEG (N = 49)[b]	SEEG or combination, N (%)[a]	36 (73.5%)	9 (100%)	27 (67.5%)	9.3(0.50-172.51)	0.09
	SDG/strips only, N (%)	13 (26.5%)	0 (0%)[c]	13 (32.5%)		
Therapy recommendations	RNS only, N (%)	41 (74.5%)	7 (64%)	34 (77%)	0.51 (0.12-2.12)	.44
	RNS or Others, N (%)	14 (25.5%)	4 (36%)	10 (23%)		
Epilepsy onset	Mesial Temporal, N (%)	20 (36%)	5 (45%)	15 (34%)	-	.68
	Neocortical, N (%)	25 (46%)	5 (45%)	20 (45%)		
	Both, N (%)	10 (18%)	1 (10%)	9 (21%)		

Abbreviations: MEG, Magnetoencephalogram; MRI, Magnetic Resonance Imaging; N/A, Not applicable; PET, Positron Emission Tomography; RNS, Brain-Responsive Neurostimulation; SDG, Subdural Grids; SEEG, Stereo Electroencephalography; SPECT, Single Photon Emission Computed Tomography; VNS, Vagus Nerve Stimulation.

[a]combination =Two separate intracranial evaluations with one of them being SEEG and one grids/strips.

[b]Forty-nine patients had intracranial monitoring prior to RNS System implantation, including 9 (81.8%) older adults and 40 (90.9%) younger adults [Odds ratio (OR) = 0.45 (95% CI =0.07 - 2.85), *P* =.59]. Of the remaining 6 patients, 2 were among the older adults group.

[c]None of the older adults underwent only subdural grid/strips electrodes.

3 | RESULTS

3.1 | Patient characteristics

Fifty-five patients (31 females; 56.4%) qualifying the study criteria were included. Eleven (20.0%) patients were ≥50 years old at the time of device implantation (older cohort). Clinical characteristics of these patients and comparison with younger adults are summarized in Table 1. Age at seizure onset and epilepsy duration were higher in older adults ($P \leq .01$). The oldest patient to undergo implantation was 60 years of age. Older adults had significantly more comorbidities at device implantation (CCI: 1.27 vs 0.23, $P < .01$). One younger adult had concurrent multiple subpial transections with device implantation.

Epilepsy etiologies for the two groups were comparable (Table S1). The groups did not differ by lead implantation sites, regions implanted, type of leads, stimulation duration, or stimulation parameters (Table 2).

3.2 | Seizure outcomes

RNS therapy was associated with a median seizure frequency reduction of 50% in the study population, which was higher (76%) in older adults, but not statistically different from younger adults who had a median seizure

TABLE 2 RNS system parameters and Seizure outcomes

Parameters		Total study population (N = 55)	Older adults (n = 11)	Younger adults (n = 44)	Odds ratio (95% confidence Interval)	*P*-value
Implantation site	Unilateral, N (%)	32 (58.1%)	5 (45.5%)	27 (61.4%)	0.52 (0.14-1.99)	.50
	Bilateral, N (%)	23 (41.8%)	6 (54.5%)	17 (38.6%)		
Region Implanted	Exclusively mesial temporal, N (%)	17 (30.9%)	5 (45.5%)	12 (27.3%)		.38
	Extra-mesial temporal, N (%)	25 (45.5%)	5 (45.5%)	20 (45.5%)		
	Mesial and extra-mesial N (%)	13 (23.6%)	1 (9.1%)	12 (27.3%)		
Lead placement	Depth only, N (%)	42 (76.4%)	10 (90.9%)	32 (72.7%)	3.75 (0.43-32.52)	.27
	Strip only or both (Strip +depth), N (%)	13 (23.6%)	1 (9.1%)	12 (27.3%)		
Post-operative CT finding of ICH, N (%)		1 (1.8%)	0 (0%)	1 (2.3%)	1.26 (0.05-33.04)	1.00
Median stimulation duration in months (range)		38 (6-144)	31 (9-68)	40 (6-144)	N/A	.19
Highest charge Density in $\mu C/cm^2$(Mean ± SD)		2.47 ± 1.25	2.24 ± 1.17	2.53 ± 1.28	N/A	.50
Highest charge density range ($\mu C/cm^2$)		0.1-6.1	0.1-4.6	0.5-6.1	N/A	N/A
Outcomes						
No. of ASMs at implantation (Mean ± SD)		2.82 ± 0.90	2.73 ± 0.79	2.84 ± 0.94	N/A	.72
No. of ASMs post-RNS (Mean ± SD)		2.92 ± 1.07	2.36 ± 1.03	3.07 ± 1.04	N/A	.048
Seizure Outcomes	≥50% seizure reduction, N (%)	30 (54.5%)	7 (63.6%)	23 (52.3%)	1.60 (0.41-6.25)	.74
	≥ 75% Reduction, N (%)	18 (32.7%)	6 (54.5%)	12 (27.3%)	3.20 (0.82-12.46)	.15
	Seizure-free, N (%)	8 (14.5%)	3 (27.3%)	5 (11.4%)	2.93 (0.58-14.79)	.33
Median seizure reduction (%; IQR)		50% (13-78.5)	76% (13-92.5)	50% (13.75-75)	NA	.43

Abbreviations: ASMs, Anti-seizure medications; CT, Computerized Tomography, ICH, Intra-cranial hemorrhage; IQR, Inter-quartile range; N/A, Not Applicable, SD: Standard deviation; RNS, Responsive Neurostimulation.

frequency reduction of 50% ($P = .43$; Table 2). The cohorts were comparable in responder rate, ≥75% seizure reduction, and seizure freedom at last follow-up. The responder rate was 54.5% (N = 30) for the entire cohort with 63.6% (N = 7) responder rate among older adults and 52.3% (N = 23) among younger adults. Eight of the 55 patients (14.5%) were seizure-free at the most recent follow-up, of whom 3 (27.3%) were older adults. Eighteen (32.7%) patients had at least 75% seizure reduction, and 6 (54.5%) of whom were older adults.

Variance in percentage change in seizure frequency compared with baseline was not significantly explained by MLR models using linear ($R^2 = 0.0572$, P-value = .18) or dichotomized ($R^2 = 0.0606$, P-value = .17) parameterization of implantation age.

3.3 | Secondary outcomes

Mean number of pre-implantation ASMs was comparable between the two cohorts (Table 2). After implantation, number of ASMs was increased in 12 (27.2%) patients, all among younger adults. Mean number of ASMs post-implantation was lower for older adults (2.36 vs 3.07, $P = .048$).

Eight patients (5 younger and 3 older adults) had post-operative adverse events (AEs). Among older adults, two had significant implant site pain and one had dizziness. Among younger adults, two had implant site swelling, one had cerebral edema, one had asymptomatic intracranial hemorrhage, and one had an implant site infection (ISI). All AEs were mild except ISI.

Delayed ISI was noted in 4 younger adults, leading to device explantation in 3. Additionally, 4 younger adults underwent device explantation during follow-up for reasons including lack of response (N = 2), non-compliance, and patient choice. No older adults had device explantation. Three patients had delayed frequent headaches, 2 among older and one among younger adults. One younger adult suffered sudden unexpected death in epilepsy (SUDEP).

Four younger adults had subsequent surgical resections (two right temporal lobectomy, one left temporal lobectomy, and one left inferior temporal gyrus resection) informed by longitudinal ECoG data obtained from RNS System. Two subsequently became seizure-free, and two achieved >50% seizure reduction. No older adults had concurrent or subsequent resections.

PHQ-9 for depression, GAD2 for anxiety, and QOLIE-10 for QOL changes after RNS System implantation were available in 45 (10 vs. 35), 34 (7 vs. 27), and 26 (6 vs. 20) older versus younger adult patients, respectively (Table S2). Baseline (pre-RNS System) and latest (post-RNS System) scores of these measures and their interval changes were comparable between the cohorts ($P > .1$).

4 | DISCUSSION

Using a single-center experience of 55 patients, we found that brain-responsive neurostimulation is an effective treatment in adults who undergo implantation at, or after, 50 years of age. With safety and efficacy outcomes comparable with younger adults, along with the additional benefit of significantly decreased ASM burden, our findings suggest that the RNS System should be considered in the rapidly growing older epilepsy population.

Average age of younger adults (30.2 ± 9.0 years) was comparable with patients in the pivotal trial.[1,3,4,10] Older adults (average age: 54.9 ± 3.5 years) had a significantly longer epilepsy duration (31.7 ± 15.9 years) at implantation. Median percentage reduction in seizure frequency was 76% among older adults, which was better than, but statistically comparable with, younger adults. Regression analysis showed no correlation between seizure frequency reduction and age at implantation, a finding that could be attributed to the relatively small number of 11 patients in the older cohort. Nonetheless, it is interesting that the percentage of seizure reduction in older adults after a median follow-up of only 31 months is comparable with the 9-year efficacy data from RNS System pivotal trial population.[4] These results indicate that despite being older, having more comorbidities, and a longer epilepsy duration than the typical younger adult population undergoing RNS therapy, older adults achieve a similar reduction in seizures arguably within a shorter treatment period. All other epilepsy-related factors, diagnostic evaluations, and stimulation parameters were comparable between the two cohorts and previous studies.[11-13]

There may be concerns of higher complications with depth electrodes in older adults. Depth electrodes were utilized in 10 (90.9%) of our older adults, none of whom had intracranial hemorrhage on post-operative CT as opposed to one younger adult. This finding suggests that depth electrodes should not be excluded in this population when clinically indicated.

Clinical trial data have shown that RNS System therapy does not adversely affect QOL or mood and may be associated with improvement in QOL.[1,4,14] Mood and QOL were not statistically different between our two cohorts. Even though the change in QOLIE-10 was not statistically significant, these scores did increase after initiating RNS System therapy, indicating a trend for improvement in QOL.

Mean number of ASMs prior to RNS System implantation was comparable with clinical trial patients.[1,3] Mean number of ASMs following device implantation was lower for older compared with younger adults. More than a quarter of younger adults, and none of the older adults, required addition of ASMs after device implantation. Older adults had a significant decrease in post-implantation ASM burden compared with younger adults and still showed a trend for a better, albeit not statistically significant, improvement in seizure control. These data illustrate that better seizure control in older adults is feasible with RNS System. Post-implantation changes in ASMs were not used as a covariate in the MLR model, as it is not a predictor of seizure reduction but rather an effect of the outcome. This finding is clinically relevant as polypharmacy among older adults is a major healthcare problem and ASM reduction may help mitigate cardiovascular and drug interaction risks associated with their use.[15]

There were no significant AEs from RNS System therapy in older adults despite their higher baseline CCI. This is a critical finding as the concern for neurosurgery-related complication risks may lead to withholding RNS System use in older adults. None of the AEs among older adults were severe, nor did they warrant device explantation. Overall, RNS System tolerability among this age group appears acceptable. The frequency of infections and device explantations in younger adults was comparable with RNS System pivotal trial experience.[1,3,4,10] However, it is unclear why these were less common in older adults. This may be due to the larger sample size of younger adults. Older adults are perhaps more disciplined in post-surgical wound care compliance by not picking on the implantation site, which is known to cause infection.[16]

Our study has several limitations. It is a single-center, retrospective study with a relatively small sample size of older adults. The terminology "older adult" may be controversial. While the elderly population is clearly defined, we have used a somewhat arbitrary cutoff of 50 years to denote patients, who underwent RNS System implantation later than the routinely reported experience in literature. However, we analyzed the association between percentage seizure reduction and age at device implantation as a linear predictor in the MLR analysis. Because seizure reduction related to electrode implantation alone can occur even without stimulation,[17] we sought to minimize this "implant effect"[8] by only including patients who had been implanted for ≥6 months. Arguably, the comparable outcomes among older adults could be secondary to a more conservative selection of these patients. However, both cohorts are similar in most negative prognostic factors for seizure outcome (non-lesional MRIs, inpatient intracranial evaluations, etc).

Our findings have significant implications for older adults with DRE who are RNS System candidates. Despite having more comorbidities, safety and efficacy of RNS System in the older cohort match younger adults. While over one-quarter of younger adults required addition of ASMs, older adults achieved comparable outcomes despite undergoing significant reduction of ASM burden compared with younger adults. In addition to the relevance of reducing polypharmacy in older adults, our findings indicate that a favorable response to RNS-based neuromodulation is achievable in older adults. Larger, multicenter studies are needed to confirm our findings. However, this study provides initial evidence that age should not be considered a barrier to offering brain-responsive neurostimulation therapy.

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CONFLICT OF INTERESTS

Dr Dileep Nair a consultant and speaker for NeuroPace, Inc All other authors declare no conflicts of interest relevant to this study. We confirm that we have read the Journal's position on issues involved in ethical publications and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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