

Review Article

Responsive Neurostimulation for Bitemporal Epilepsy: Seizure Outcomes and Device-Related Complications

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Abstract

Background: Bitemporal epilepsy, with independent seizure onsets from both mesial temporal structures, excludes most patients from curative resection.

Objective: To synthesize evidence on responsive neurostimulation (RNS) for bitemporal epilepsy, covering seizure outcomes, comparison with resective and ablative alternatives, and device-related complications.

Methods: Narrative review of pivotal RNS trials, long-term follow-up studies, bitemporal-specific cohorts, comparative surgical series, and safety analyses.

Findings: Long-term RNS cohorts show seizure reduction growing over time, from roughly 44% at one year to 75% or more by nine years, with bilateral implants performing comparably to unilateral placement. Bitemporal-specific series report meaningful reduction, some seizure-free. Complications, chiefly infection and lead issues, affect a minority of implants.

Conclusions: RNS offers a durable, non-resective option for bitemporal epilepsy, with a favorable long-term trajectory and acceptable safety, though seizure freedom remains less common than after unilateral resection.

Keywords: Responsive neurostimulation; Bitemporal epilepsy; Mesial temporal lobe epilepsy; Drug-resistant epilepsy; Device complications

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Introduction

Drug-resistant epilepsy, defined by the International League Against Epilepsy as failure of two appropriately chosen and tolerated antiseizure medication trials to achieve sustained seizure freedom, affects roughly one-third of people with epilepsy [1]. For unilateral mesial temporal lobe epilepsy, resective surgery is well established, with a landmark randomized trial demonstrating markedly superior seizure freedom compared with continued medical therapy [2]. Epilepsy more broadly remains a common and heterogeneous neurological disorder with substantial associated morbidity [3].

Bitemporal epilepsy is a distinct and more difficult clinical problem. In this pattern, video-EEG and intracranial monitoring show independent seizure onsets from both mesial temporal regions, either synchronously or asynchronously across recordings, so that resection of either side alone risks leaving an unresected epileptogenic focus while bilateral resection carries an unacceptable risk of severe amnestic syndrome [4]. A systematic review of epilepsy surgery in patients with bilateral temporal lobe seizures found that outcomes after unilateral resection guided by presumed asymmetry are inconsistent and substantially worse than in unilateral disease, while bilateral resection is rarely performed because of the memory risk [5]. Chronic ambulatory intracranial recording enabled by implanted responsive devices has itself clarified how often apparently unilateral cases are, in fact, bitemporal, with long-term electrocorticography reclassifying a meaningful proportion of patients initially thought to have unilateral onset [6]. Newer long-term intracranial EEG series confirm that lateralization confidence in suspected bitemporal cases often requires many months of ambulatory recording rather than a brief inpatient admission [7].

Historically, patients with this pattern were counseled that surgery offered little advantage over continued antiseizure medication, leaving vagus nerve stimulation or repeated medication trials as the only options despite persistent disabling seizures. The emergence of an implantable device capable of independently sensing and treating two separate epileptogenic zones changed this calculus, reframing bitemporal disease from a surgical dead end into a population for whom a specific, mechanistically appropriate device therapy exists. This review draws together the trial evidence, bitemporal-specific cohorts, comparative surgical literature, and safety data needed to place that therapy in context.

For these patients, responsive neurostimulation (RNS)

offers a non-resective alternative that can be tailored to bilateral disease. This review synthesizes evidence on the device, its seizure and cognitive outcomes when applied to bitemporal epilepsy, how those outcomes compare with resective and ablative alternatives, the device-related complications reported in the literature, and the criteria used to select bitemporal patients for this therapy.

The RNS Device and Rationale for Bitemporal Placement

The responsive neurostimulation system evolved from early closed-loop feasibility work showing that continuous electrocorticographic analysis could trigger stimulation that reduced seizure frequency in a small early cohort [8]. The commercialized RNS System couples a cranially implanted neurostimulator with up to two leads, most often placed as bilateral mesial temporal depth electrodes in bitemporal disease, allowing independent detection and stimulation at each seizure focus without requiring a single lateralizing decision [9]. Because the device both records and treats, it functions simultaneously as a long-term diagnostic tool and a therapeutic implant, a dual role that has proven especially valuable when the underlying question is not simply how to treat seizures but which side, or whether both sides, generate them [10].

Seizure Outcomes

The double-blind randomized pivotal trial first established that responsive stimulation reduced seizures significantly more than sham stimulation in adults with focal drug-resistant epilepsy [11]. The open-label extension through two years confirmed a progressive, rather than static, benefit, with median seizure reduction reaching roughly 44% at one year and continuing to improve through the second year of treatment [12]. Extended follow-up through the long-term treatment study showed sustained and deepening response, and post-hoc analyses found no significant difference in efficacy between patients with mesial temporal and

neocortical onsets [13]. The most mature data, a nine-year prospective analysis, reported a median seizure reduction that rose from about 44% in year one to roughly 75% by year nine, with a growing proportion of patients achieving prolonged seizure-free intervals over time [14]. A recent postapproval study extended these safety and efficacy signals into a real-world population followed for three years, corroborating the durability seen in the original pivotal cohort [15].

Table 1: Key studies of responsive neurostimulation (RNS) outcomes relevant to bitemporal and mesial temporal lobe epilepsy [11,12,13,14,16,20,15].				
Study	Design	Population	Follow-up	Key seizure outcome
Morrell 2011	Double-blind RCT	Focal drug-resistant epilepsy	12 weeks blinded	Significant reduction vs sham stimulation
Heck 2014	Pivotal trial, open-label extension	Focal drug-resistant epilepsy	2 years	Median reduction ~44% (yr 1) to higher by yr 2
Bergey 2015	Long-term treatment study	Focal drug-resistant epilepsy	Up to 3+ years	Sustained, deepening response; MTLE = neocortical
Nair 2020	Nine-year prospective analysis	Focal drug-resistant epilepsy	9 years	Median reduction ~75% by year 9
Geller 2017	Multicenter cohort	Medically intractable MTLE	Variable	Reduction comparable to mixed RNS cohorts
Kokoszka 2021	Single-center series	Confirmed bilateral TLE	Variable	Meaningful reduction; some seizure-free
Eliashiv 2026	Postapproval real-world study	Drug-resistant focal epilepsy	3 years	Efficacy and safety consistent with pivotal data

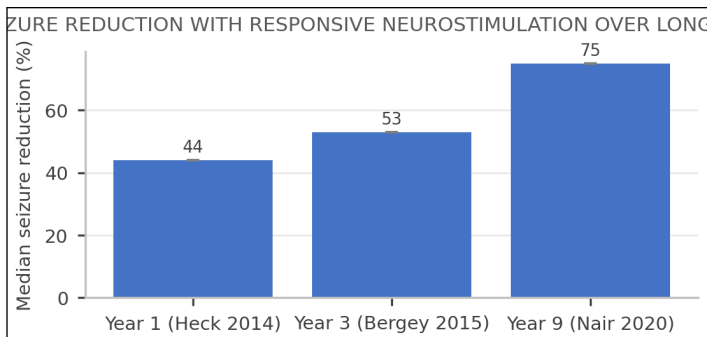


Figure 1: Median seizure reduction with responsive neurostimulation over long-term follow-up in the RNS System pivotal and long-term treatment cohorts: 44% at year 1 [12], 53% at year 3 [13], and 75% at year 9 [14].

Focusing specifically on mesial temporal lobe epilepsy, a multicenter analysis of patients implanted with RNS at one or both mesial temporal regions found seizure reduction comparable to, and in some analyses exceeding, that seen in mixed cohorts, alongside evidence that chronic electrocorticographic data could itself refine lateralization during treatment [16]. A meta-analysis pooling neuropsychological and neurobehavioral outcomes across RNS studies found stable or improved cognitive and mood measures over follow-up, reassuring given the bilateral mesial temporal placement inherent to bitemporal treatment [17]. Dedicated cognitive analyses within the pivotal cohort similarly found that RNS targeted to mesial temporal structures did not produce the verbal memory decline associated with unilateral dominant-side resection, an important distinction for bitemporal candidates who could not otherwise be offered resection at all [18]; a companion commentary emphasized that this cognitive safety, rather than seizure freedom alone, is central to how bitemporal patients and clinicians should weigh RNS against continued medical therapy [19].

A series specifically targeting the mesial temporal white matter in patients with confirmed bilateral temporal lobe epilepsy reported clinically meaningful reduction in disabling seizures across nearly all treated patients, with

some achieving sustained seizure freedom, using independent bilateral leads and detection algorithms tuned separately to each hemisphere [20]. A practical advantage repeatedly emphasized in this literature is that the two leads can be programmed, adjusted, and re-optimized independently as chronic recordings accumulate, so that a hemisphere responding poorly to an initial detection or stimulation setting can be retuned without disturbing therapy on the other side, a flexibility no single-target resective or ablative procedure can offer. Taken together, these bitemporal-specific data support RNS as an effective, if not typically curative, option in a population that otherwise has no surgical pathway to seizure freedom.

Comparison with Resective and Ablative Alternatives

Anterior temporal lobectomy remains the benchmark for unilateral mesial temporal lobe epilepsy, producing seizure freedom in a majority of well-selected patients [2], but this benchmark does not transfer to bitemporal disease. Older resection series in patients with bilateral temporal seizures reported markedly lower seizure-free rates than unilateral cohorts, with recurrence often arising from the untreated contralateral focus [4], a finding echoed in the broader systematic review of bilateral temporal surgery outcomes [5].

Minimally invasive ablative alternatives have been explored primarily for unilateral disease. Stereotactic laser amygdalohippocampotomy achieves seizure outcomes roughly comparable to open resection with a shorter recovery and a different complication profile, but published series remain concentrated in unilateral or single-target cases [21], and the prospective multicenter single-arm study of laser ablation for mesial temporal lobe epilepsy similarly enrolled patients amenable to a single ablation target [22]. The randomized ROSE trial comparing stereotactic radiosurgery with open resection

likewise addressed unilateral mesial temporal epilepsy, finding radiosurgery an effective but slower-acting alternative to lobectomy [23]. None of these focal, one-sided interventions is designed to address bilaterally independent epileptogenic zones, which is precisely the gap RNS fills by allowing simultaneous bilateral coverage without committing to a single surgical target [24]. This distinction matters clinically: a patient whose intracranial monitoring shows convincing bilateral independence is, by the logic of the resective and ablative literature above, a poor candidate for any of these unilateral procedures regardless of how refined the technique becomes, whereas the same bilateral-independence finding is the specific indication that makes RNS appropriate.

Table 2: Resective, ablative, and radiosurgical alternatives considered for mesial temporal lobe epilepsy, and their applicability to bitemporal disease [2,4,5,21,22,23].			
Modality	Target	Typical population	Applicability to bitemporal disease
Anterior temporal lobectomy	Unilateral mesial temporal focus	Unilateral MTLE	Poor outcomes if applied unilaterally in bitemporal cases
Bilateral resection	Both mesial temporal foci	Rarely attempted	High risk of severe amnesic syndrome
Stereotactic laser amygdalo hippocampotomy	Single mesial temporal target	Unilateral MTLE	Not designed for bilateral independent foci
Stereotactic radiosurgery (ROSE trial)	Single mesial temporal target	Unilateral MTLE	Slower-acting; single-target design
Responsive neurostimulation	Both mesial temporal foci independently	Bitemporal MTLE	Designed for bilateral independent treatment

Device-Related Complications

Safety data from the pivotal and long-term RNS cohorts describe hardware- and procedure-related adverse events, most commonly implant-site infection and lead-related complications, occurring in a minority of patients and rarely requiring permanent device removal [14]. A comparative single-center series found complication rates for RNS numerically similar to those for vagus nerve

stimulation, at approximately 15-18%, suggesting the RNS risk profile is broadly in line with other implanted neuromodulation devices rather than distinctly higher [25]. Lead configuration also appears to matter: a comparison of strip versus depth leads found differences in seizure outcome and lead-related complication patterns between the two configurations, information directly relevant to planning bilateral mesial temporal depth implants for bitemporal disease [26]. The recent postapproval study's interim safety results, drawn from a larger and more heterogeneous real-world population than the pivotal trial, reported complication rates consistent with prior premarket data, supporting the generalizability of the device's safety profile [15]. For bitemporal implants specifically, the presence of two independent lead systems roughly doubles the number of implanted contacts and connector sites relative to a unilateral implant, and clinicians managing these patients should anticipate a correspondingly higher cumulative hardware burden even though per-lead complication rates do not appear to differ from unilateral placements. Explantation for infection, when required, has generally been followed by successful reimplantation once the infection resolved, so an early hardware complication does not typically foreclose continued RNS therapy.

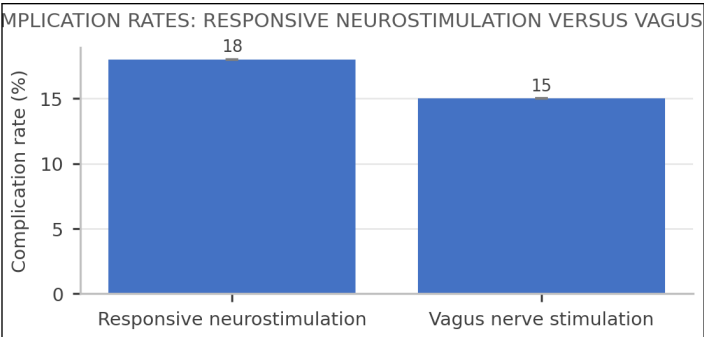


Figure 2: Reported complication rates across comparative and lead-configuration studies of implanted neurostimulation for epilepsy: RNS versus vagus nerve stimulation, 18% versus 15% [25].

Patient Selection

Selecting bitemporal patients for RNS depends on rigorous localization. Chronic ambulatory electrocorticography has shown that a substantial fraction of patients initially thought to have unilateral onset instead demonstrate bilaterally independent seizures once recorded over weeks to months, meaning candidacy determinations based on brief inpatient monitoring alone risk misclassification [6]; longer-duration intracranial recordings reinforce that confident lateralization in suspected bitemporal cases can require extended observation [7]. Practical selection criteria described in the bitemporal RNS literature include confirmed or strongly suspected independent bilateral mesial temporal onset on invasive monitoring, insufficient asymmetry to justify unilateral resection, and a clinical or neuropsychological profile in which bilateral resection would pose unacceptable memory risk [20]. A recent focused review of bitemporal epilepsy's diagnostic and treatment paradigms similarly frames RNS as the preferred option once bilateral independence is established, reserving resection for cases with clear lateralizing dominance [27]. In practice, this means the presurgical pathway for a suspected bitemporal patient increasingly runs through staged or extended intracranial evaluation aimed specifically at quantifying, rather than merely detecting, bilateral independence, since the degree of asymmetry — not simply its presence — determines whether unilateral resection, RNS, or a combination approach is most appropriate. Multidisciplinary epilepsy surgery conferences reviewing these cases benefit from having both structural imaging and chronic electrographic data before committing to a device strategy, since MRI-based hippocampal asymmetry alone correlates imperfectly with electrographic independence.

Conclusion

Bitemporal epilepsy leaves most patients without a resective pathway to seizure freedom, and pivotal and

long-term RNS studies, together with bitemporal-specific series, show that responsive neurostimulation provides a durable, growing seizure-reduction benefit when applied bilaterally, alongside neuropsychological outcomes more favorable than bilateral resection would allow. Device-related complications are real but generally manageable without permanent explantation, and appear comparable to other implanted neuromodulation devices. Comparative resective, ablative, and radiosurgical series confirm that none of these unilateral-target interventions substitutes for RNS's capacity to treat bilaterally independent foci simultaneously. Careful, often prolonged, intracranial characterization of laterality remains the foundation of appropriate patient selection, and continued long-term and comparative-effectiveness data will further clarify RNS's place in the bitemporal treatment algorithm.

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