ISSN: XXXX-XXXX

Journal of Neurology and Brain Research

Clinical Study Open Access

Electrophysiological Signatures of Treatment-Resistant Epilepsy in Adult Patients

Habib A[1*], Qasim K[2] and Khoury K[3]

[1]Department of Specialty Medicine, Manama Institute of Neurological Medicine, Bahrain Scopus Author ID: 57482025318 Email: adel.habib@manama.edu
ORCID: https://orcid.org/8969-3375-5262-5820

[2]Department of Biomedical Research, Beirut Center for Cognitive Neuroscience, Jordan Scopus Author ID: 57500102821 Email: khalid.qasim@beirut.edu
ORCID: https://orcid.org/9537-8270-0181-924X

[3]Department of Biomedical Research, Amman Institute of Neurology and Brain Sciences, Qatar Scopus Author ID: 57293523281 Email: khalid.khoury@amman.edu
ORCID: https://orcid.org/6974-4601-2512-5701

***Correspondence to:** Adel Habib, Department of Specialty Medicine, Manama Institute of Neurological Medicine, Bahrain Scopus Author ID: 57482025318 Email: adel.habib@manama.edu

Received: 1 November 2025; **Accepted:** 13 January 2026; **Published:** 27 March 2026

Copyright: © 2026 AH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Roughly a third of adults with epilepsy do not achieve durable seizure freedom on medication, a population the International League Against Epilepsy formally designates as drug-resistant once two tolerated, appropriately chosen antiseizure medication schedules have failed. Electroencephalography, in its many forms, remains the primary tool for characterizing this population physiologically rather than merely pharmacologically, because it is the only routinely available modality that observes the electrical process of seizure generation directly. This article synthesizes the literature on the electrophysiological signatures that distinguish and localize treatment-resistant epilepsy in adults, moving from the definitional and epidemiological framework that makes the category meaningful, through scalp and ambulatory interictal signatures, into the intracranial and high-frequency-oscillation literature that has dominated invasive evaluation for over two decades, and on to the network-level reframing of the epileptogenic zone and the continuously recorded electrocorticographic streams now generated by chronically implanted neurostimulation devices. Read together, the evidence supports interictal spikes, high-frequency oscillations, network connectivity measures, and device-derived electrocorticography as complementary, increasingly well-evidenced signatures rather than substitutes for one another, while leaving recording standardization, the specificity of pathological versus physiological high-frequency activity, and the reconciliation of short-duration pre-surgical findings with multi-year real-world device data as open methodological challenges for the field.

Keywords: treatment-resistant epilepsy; electroencephalography; high-frequency oscillations; epileptogenic network; responsive neurostimulation

1. Introduction

Roughly a third of adults living with epilepsy will never achieve durable seizure freedom on medication, no matter how carefully that medication is chosen [1,2]. The International League Against Epilepsy's 2010 consensus definition gave this population a name — drug-resistant epilepsy (DRE), operationally defined as failure of adequate trials of two tolerated, appropriately chosen and used antiseizure medication schedules to achieve sustained seizure freedom, whether as monotherapies or in combination [3]. That definition did something more than standardize terminology: it drew a line after which the clinical question stops being "which drug next" and starts being "what, physiologically, is actually generating these seizures, and can we find it." Electroencephalography, in its many forms — routine scalp recordings, long-term ambulatory monitoring, intracranial grids and depth electrodes, and increasingly the electrocorticographic streams captured by implanted neurostimulators — is the primary instrument available for answering that question, because it is the only modality that observes the electrical process of seizure generation directly, at the millisecond timescale the underlying neuronal populations actually operate on.

This article surveys what the electrophysiological literature has established, over roughly three decades of intracranial and scalp recording, about the signatures that distinguish treatment-resistant epilepsy from its more tractable counterpart, and about the signal features clinicians and researchers now use to localize the seizure-generating tissue in candidates for surgery or neurostimulation. We are synthesizing existing findings, not reporting new experiments; the structure follows the natural progression of the field itself, from the definitional and epidemiological framework that makes "treatment-resistant" a meaningful category, through the non-invasive scalp and ambulatory signal features available before any surgical evaluation is considered, into the intracranial and high-frequency-oscillation literature that has dominated the field's attention for the past fifteen years, and on to the network-level and connectivity-based reformulation of what an "epileptogenic zone" even means. We close with the electrophysiological biomarkers now emerging from chronically implanted neurostimulation devices — a genuinely new data stream that did not exist when much of the foundational HFO literature was written — and with an honest accounting of where the field's evidence remains thinner than its enthusiasm.

A methodological note before proceeding: we are deliberately restrictive about what counts as an established finding here. Where a specific numeric claim is made in what follows — a prevalence figure, a proportion, a duration of follow-up — it is attributed to, and drawn directly from, the cited source, and we have avoided asserting specific outcome percentages we could not verify against the primary or a clearly sourced secondary reference. This is a narrower stance than some reviews in this space take, and it means a few widely repeated but loosely sourced figures are left out rather than repeated uncritically.

2. Defining and Diagnosing Treatment-Resistant Epilepsy

The 2010 ILAE Task Force definition of drug resistance was built to be testable rather than merely descriptive: two adequately dosed, appropriately selected antiseizure medications, each given a fair trial, both failing to produce sustained freedom from seizures [3]. The definition's authors were explicit that this is a probabilistic marker rather than a biological one — failing two drugs correlates strongly with a much lower probability that a third or fourth drug will succeed, a relationship documented well before the formal definition existed, but it does not by itself specify *why* a given patient's seizures resist pharmacological control. That "why" question is precisely where electrophysiology, and increasingly imaging, network science, and molecular pathology, are expected to contribute, and much of this article concerns the electrophysiological half of that answer.

Epidemiologically, drug resistance is not a rare outcome. Fiest and colleagues' systematic review and meta-analysis of international epilepsy studies estimated a global point prevalence of epilepsy of roughly 5 to 7 cases per 1,000 people, with an annual incidence on the order of 50 to 70 new cases per 100,000 people [4] — figures that, combined with the roughly one-in-three proportion of patients who go on to be drug-resistant [1,2], describe a population in the tens of millions worldwide for whom EEG-based localization is not an academic exercise but the practical gateway to surgery, neurostimulation, or dietary and device-based alternatives. Perucca and colleagues' 2023 review of the mechanisms underlying drug resistance in epilepsy is a

useful frame for why electrophysiology matters here specifically: none of the leading mechanistic hypotheses — target-site alterations reducing drug sensitivity at the sodium or GABA-A receptor level, transporter-mediated reduction in effective drug concentration at the epileptic focus, or an intrinsically more severe underlying network pathology — are things a blood test or a structural MRI can directly observe in action, whereas an electrographic seizure, or the interictal activity generated by the same abnormal tissue between seizures, is a direct read-out of the pathological process itself [1].

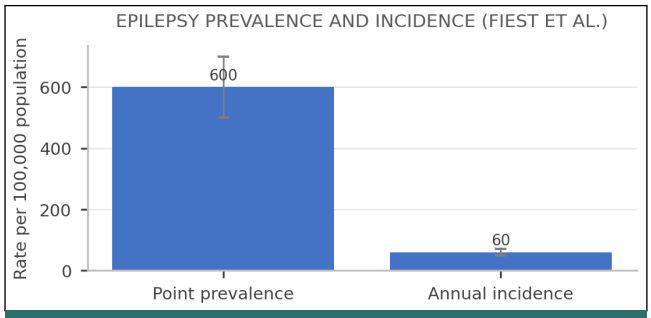

Figure 1: Global point prevalence and annual incidence of epilepsy, expressed per 100,000 population, as reported by Fiest and colleagues' systematic review and meta-analysis of international epidemiological studies -- the population-level backdrop against which the roughly one-in-three proportion of patients who go on to be drug-resistant is measured [4].

This is also the point in the diagnostic pathway where EEG performs a job that gets less attention than localization but is arguably more consequential for an individual patient: confirming that the paroxysmal events being treated are actually epileptic. Video-EEG monitoring, extended over days in a dedicated epilepsy monitoring unit, remains the diagnostic standard for capturing spontaneous events and correlating them with ictal electrographic activity, and Cascino's review of video-EEG monitoring in adults lays out both its diagnostic yield for seizure classification and its role in ruling in — or ruling out — an epileptic basis for events that look clinically like seizures but are not [5]. A meaningful fraction of patients referred to tertiary epilepsy centers for "treatment-resistant" seizures turn out, on capture, to have psychogenic non-epileptic events superimposed on or instead of epileptic seizures, and no amount of electrophysiological sophistication downstream of that misclassification will produce a useful signature. Noachtar and Rémi's critical review of the role of EEG in epilepsy situates this diagnostic function alongside EEG's localizing and classificatory roles, and is a useful reminder that the interictal EEG, imperfect and probabilistic as it is, remains the first and most widely available electrophysiological signature clinicians actually use in day-to-day decision-making, well before any question of surgical candidacy arises [6].

Seizure classification itself has also been formalized around EEG-observable features. The ILAE's 2017 operational classification of seizure types, and its 2025 update, both build their taxonomies substantially around electroclinical correlation — whether a seizure's onset is focal or generalized, whether awareness is retained, and how the ictal pattern evolves — categories that in practice are adjudicated largely by ictal EEG morphology read alongside clinical semiology [7,8]. This matters for the treatment-resistance literature specifically because seizure type is itself a predictor of drug response: focal seizures arising from a single, resectable region behave very differently, both pharmacologically and surgically, from the more diffusely generated seizures of the generalized epilepsies, and a great deal of what follows in this article — invasive recording, HFO analysis, network localization — presupposes a focal, potentially localizable seizure-onset process rather than a generalized one.

3. Scalp and Ambulatory EEG Signatures

For most patients, the electrophysiological workup begins and often ends with scalp EEG, and the signatures it can and cannot reliably detect shape everything downstream. Interictal epileptiform discharges — spikes and sharp waves recorded between seizures — remain the most widely used non-invasive marker of an epileptogenic process, valued because they can, in principle, be captured on a routine outpatient recording without waiting for a spontaneous seizure. Their reliability, however, is genuinely limited: a normal routine EEG does not rule out epilepsy, discharge rates vary considerably with the state of arousal and recording duration, and the spatial resolution of scalp electrodes is coarse relative to the underlying cortical generators, particularly for deep or mesial temporal and frontal sources whose electrical fields attenuate substantially before reaching the scalp [6].

Extended and ambulatory recording strategies exist largely to address the sensitivity problem. Biondi and colleagues' systematic review of mobile and wearable EEG for seizure monitoring surveys a rapidly maturing set of technologies — reduced-electrode-count

headsets, subscalp and behind-the-ear systems, and smartphone-linked recording platforms — designed to capture interictal and, where possible, ictal activity over days to weeks in the patient's normal environment rather than the artificial setting of an inpatient monitoring unit [9]. For the treatment-resistant population specifically, this matters because many of these patients have already had one or more inconclusive routine or short inpatient EEGs; extending the recording window, or moving it outside a setting where seizures are notoriously under-represented relative to a patient's home environment and daily triggers, materially changes the yield.

Non-invasive imaging-electrophysiology correlation is the other major strand of pre-surgical scalp-level workup. Pittau, Dubeau, and Gotman's review of the contribution of combined EEG and functional MRI to definition of the epileptic focus describes how EEG-correlated fMRI exploits the hemodynamic response evoked by interictal discharges to localize regions of altered blood-oxygen-level-dependent signal time-locked to the electrographic event, offering a spatial resolution that scalp EEG alone cannot provide while retaining a genuinely electrophysiological anchor for the analysis — the discharge itself, not an assumption about where discharges "should" arise given a structural lesion [10]. This EEG-fMRI concordance is increasingly used as one input, among several, into the decision of whether and where to proceed to invasive monitoring, which is where the bulk of the electrophysiological signature literature specific to treatment-resistant epilepsy actually lives.

It is worth being explicit about what scalp-level signatures can and cannot do for a patient who has already failed two medications. They can support a diagnosis of focal epilepsy, contribute to seizure classification, and in favorable cases — a clear, consistent, well-localized spike focus concordant with imaging and semiology — provide enough localizing information to proceed directly to surgical planning. What they generally cannot do, on their own, is resolve the harder cases: normal or non-localizing MRI, discordant or bilateral independent discharges, or a seizure-onset zone in a region, such as mesial temporal or deep frontal cortex, whose electrical activity is substantially attenuated by the time it reaches scalp electrodes. Those cases are precisely where intracranial recording, and the high-frequency-oscillation literature built on top of it, has concentrated.

The Practical Diagnostic Pathway

In practice, the sequence of electrophysiological investigations a treatment-resistant patient moves through is more iterative than a simple linear pipeline from scalp to intracranial recording might suggest. A typical pathway begins with one or more routine outpatient EEGs, which for the reasons already described often return normal or non-diagnostic in exactly the patients who most need localization — a normal interictal recording essentially never excludes epilepsy, and sensitivity climbs only with repeated or extended recordings [6]. Where routine recording is inconclusive, admission to a dedicated epilepsy monitoring unit for extended video-EEG allows medication tapering, sleep deprivation, and other activation procedures intended to provoke both interictal discharges and, ideally, one or more habitual clinical events under continuous electrographic and video observation [5]. It is this admission, more than any single outpatient test, that typically determines whether a patient is even a plausible candidate for further invasive evaluation, because it is the point at which clinicians obtain the closest available approximation of an ictal electrographic recording without yet placing intracranial electrodes.

Only a subset of patients who reach this stage go on to intracranial monitoring, and the decision to proceed rests on concordance, or its absence, across several independent sources of localizing information: the semiology and scalp ictal EEG pattern captured during the monitoring admission, structural and functional imaging findings, and, where available, EEG-correlated fMRI or other adjunctive studies [10]. Discordance among these sources — a temporal-appearing semiology with an extratemporal-appearing scalp ictal pattern, or a structural lesion that does not align with the presumed electrographic onset — is, if anything, more informative than concordance for deciding whether invasive recording is needed at all, since a genuinely straightforward, single-focus case may proceed to resection with comparatively little additional electrophysiological workup, while a discordant case is exactly where the network-level and high-frequency-oscillation analyses discussed in the remainder of this article earn their clinical keep.

4. Intracranial EEG and High-Frequency Oscillations

Intracranial EEG — whether via subdural grid and strip electrodes or, increasingly, stereotactically implanted depth electrodes (stereo-EEG, or SEEG) — exists because scalp recording's spatial resolution and signal-to-noise ratio are simply inadequate for some localization problems. Bartolomei and colleagues' account of defining epileptogenic networks through SEEG and quantitative signal analysis lays out both the rationale for direct intracerebral recording and the broader conceptual shift it enabled: once electrodes are recording directly from candidate epileptogenic tissue, the question stops being merely "where is the spike" and becomes "how does the ictal discharge actually organize and propagate across a network of simultaneously sampled sites," a question scalp EEG's spatial averaging simply cannot address [11].

Table 1: The principal electrophysiological signal domains used in the evaluation of treatment-resistant epilepsy, the signal each records, the stage of the diagnostic pathway at which it is typically deployed, and the current maturity of its evidence base. [6,5,12,13,14,15,17,11,19,18,20].

Signal Domain	What It Records	Typical Pathway Stage	Current Evidence Maturity
Scalp / ambulatory interictal EEG	Interictal spikes and sharp waves; extended or wearable recording over days to weeks	First-line outpatient and pre-monitoring workup	Long-established diagnostic tool; limited spatial resolution for deep or mesial sources [6]
Inpatient video-EEG (ictal)	Captured habitual clinical seizures with time-locked scalp electrographic onset	Epilepsy monitoring unit admission, pre-surgical workup	Diagnostic standard for seizure classification and localization concordance [5]
Intracranial HFO analysis (ripples / fast ripples, 80-500 Hz)	High-frequency oscillatory events from subdural or depth electrodes in candidate epileptogenic tissue	Invasive pre-surgical evaluation	Strong foundational and outcome-correlation evidence; recording/analysis standardization still maturing [12,13,14,15,17]
SEEG-based network / connectivity analysis	Inter-site coupling and propagation timing across simultaneously implanted depth electrodes	Invasive pre-surgical evaluation, network-level cases	Conceptually well-motivated; single-biomarker replication record still thinner than HFOs [11]
Neurostimulation-derived electrocorticography	Continuous, multi-year electrocorticographic stream logged by an implanted responsive device	Chronic treatment phase, post-implantation	Emerging long-duration real-world evidence base; still reconciling with short-duration pre-surgical findings [19,18,20]

The single most consequential electrophysiological discovery to come out of intracranial recording in the treatment-resistant epilepsy literature is the high-frequency oscillation, or HFO. Bragin, Engel, and colleagues' foundational 1999 report described oscillatory events in the 100–500 Hz range recorded from human epileptic hippocampus and entorhinal cortex, and in a kainic-acid rodent model of chronic seizures, that were substantially more common in tissue capable of generating spontaneous seizures than in adjacent, non-epileptogenic tissue [12]. Staba and colleagues followed with a quantitative analysis of these 80–500 Hz oscillations recorded from human epileptic hippocampus and entorhinal cortex, formalizing the ripple (roughly 80–250 Hz) and fast ripple (roughly 250–500 Hz) frequency bands that the subsequent clinical literature has organized itself around ever since [13]. The core hypothesis that emerged from this work, and that has been tested extensively since, is that fast ripples in particular mark tissue capable of generating hypersynchronous, pathological discharge — that they are, in effect, an electrophysiological fingerprint of epileptogenicity more specific than the interictal spike.

That hypothesis moved from basic science into clinical utility over the following decade. Jacobs and colleagues' 2010 study correlating high-frequency EEG oscillations with epilepsy surgery outcome, recording HFOs from resected tissue prior to surgery, reported that surgical outcome tracked the extent to which HFO-generating tissue was included in the resection more closely than it tracked interictal spike removal alone — the first strong clinical evidence that HFOs were not merely a research curiosity but carried outcome-relevant localizing information beyond what spikes provided [14]. Zijlmans and colleagues' subsequent review formalized HFOs as a candidate new biomarker in epilepsy, synthesizing the growing evidence that HFO rate and location correlate with both the seizure-onset zone and the resection margin needed for seizure freedom, while also being candid that HFOs occur in some non-epileptogenic tissue too, that recording and analysis methodology (sampling rate, filter settings, automated versus visual detection) materially affects reported rates, and that the field had not yet converged on a single validated detection standard [15].

Methodological standardization has, in fact, been one of the field's persistent preoccupations, precisely because

HFO rates are sensitive to exactly the kind of recording and analysis choices that vary across centers. Dümpelmann, Jacobs, and Schulze-Bonhage's work on the temporal and spatial characteristics of HFOs describes how these events cluster non-uniformly in both time — often modulated by sleep stage and proximity to seizures — and space, complicating any simple "count the events per electrode" localization scheme and motivating more sophisticated spatiotemporal analysis [16]. Zijlmans and colleagues' subsequent practical guideline for recording HFOs represents the field's attempt to consolidate a decade of largely single-center, methodologically heterogeneous findings into recommendations that other centers, and eventually multi-center trials, could actually follow — covering sampling rate requirements, filter design, and the minimum practical standards needed before an HFO rate reported at one center can be meaningfully compared to another's [17]. That such a guideline was needed as late as 2017, nearly two decades after Bragin et al.'s original description, is itself informative about how much harder clinical translation of an electrophysiological biomarker is than its initial discovery.

Comparing the Principal Electrophysiological Signal Domains

Table 1 summarizes how the principal electrophysiological signal domains discussed in this article — scalp/ambulatory EEG, intracranial HFO analysis, network connectivity measures, and neurostimulation-derived electrocorticography — differ in what they record, at what stage of the diagnostic pathway they are typically deployed, and what kind of evidence currently supports their clinical use, without asserting outcome statistics beyond what the cited sources themselves report.

5. Network and Connectivity Signatures of the Epileptogenic Zone

A parallel and increasingly influential strand of the literature has reframed the entire localization problem away from a single, spatially compact "epileptogenic zone" and toward a network-level description of how ictal activity is generated, propagated, and, in some cases, actively suppressed by surrounding tissue. Bartolomei and colleagues' SEEG-based work on epileptogenic networks is again central here: rather than asking which single contact shows the earliest or highest-amplitude ictal discharge, network-oriented SEEG analysis characterizes how activity spreads across simultaneously recorded sites, using quantitative measures of signal coupling and propagation timing to distinguish a compact, focal epileptogenic zone from a more distributed, network-level process that a purely lesion-focused resection would fail to fully address [11]. This distinction has real surgical consequences: a patient whose electrographic seizures genuinely arise from and are confined to a single resectable structure is a fundamentally different surgical candidate from one whose ictal activity, on careful network analysis, recruits a broader and only partially resectable set of interconnected regions.

Graph-theoretic and connectivity-based analyses of interictal, rather than purely ictal, EEG have extended this network reframing into a domain that does not require capturing a spontaneous seizure at all. The underlying premise is that the abnormal excitability driving treatment-resistant seizures leaves a signature in the resting-state or interictal functional organization of the brain's electrical activity — altered synchronization, altered graph-theoretic measures of network integration and segregation, or altered topology relative to what is seen in well-controlled epilepsy or in non-epileptic controls — that can, in principle, be measured from interictal recordings and used as a complementary or even alternative localization tool to spike- or HFO-counting approaches. This is an area of active, rapidly evolving research; the specific graph metrics, frequency bands, and connectivity estimators used vary considerably across studies, and the field has not converged on a single validated network signature of drug resistance the way it has, imperfectly, around HFOs. What is reasonably well established is the underlying motivation: epilepsy, and treatment-resistant focal epilepsy in particular, is increasingly understood as a disorder of network organization rather than a purely focal lesion, a conceptual shift that the SEEG-based epileptogenic-network literature helped drive and that subsequent scalp- and intracranial-connectivity work has built upon [11].

It is worth being candid about the limits of the network framing as currently practiced. Network measures computed from interictal data are sensitive to essentially the same methodological choices that complicated HFO

standardization — recording montage, frequency band, epoch length, and the choice of connectivity estimator all materially affect the resulting graph metrics — and the field's replication and cross-center validation record for any single network biomarker is considerably thinner than the corresponding record for interictal spikes or HFOs, which is one reason this article treats network connectivity as a promising but still maturing signature rather than an established clinical tool on a par with the others discussed here.

There is also a conceptual tension worth naming between the network framing and the resective-surgery paradigm that most pre-surgical electrophysiological evaluation is still ultimately organized around. If epileptogenicity is genuinely distributed across a network of interconnected regions rather than concentrated in a single resectable focus, then the entire logic of localize-and-resect is, for at least some patients, a poor match to the underlying pathology — no matter how precisely the network is characterized, removing one node of a distributed network may leave the remaining nodes capable of generating seizures on their own. This is part of why neurostimulation approaches, discussed in the following section, are not simply a fallback for patients who are poor resective-surgery candidates on anatomical grounds, but in some cases a more principled therapeutic match to a genuinely network-level disease process: rather than trying to remove the network, responsive neurostimulation attempts to detect and interrupt its pathological activity in place. Bartolomei and colleagues make a version of this argument explicitly, noting that quantifying network-level epileptogenicity has direct implications not only for surgical planning but for matching individual patients to the therapeutic modality — resection, laser ablation, or neuromodulation — best suited to the spatial extent of their underlying network pathology [11].

6. Electrophysiological Biomarkers in Neurostimulation Therapy

The most recent major addition to the electrophysiological toolkit for treatment-resistant epilepsy did not come from a new recording technique applied to a pre-surgical evaluation, but from a therapy that happens to generate its own continuous, long-term electrocorticographic dataset as a byproduct of treating patients: chronically implanted responsive neurostimulation. Geller's review of clinical trials of responsive neurostimulation for focal epilepsy describes a device architecture in which chronically implanted electrodes both detect abnormal electrocorticographic activity and deliver brief electrical stimulation intended to disrupt that activity before it organizes into a clinical seizure, closing the loop between electrophysiological detection and therapeutic response in a way that pre-surgical intracranial monitoring, by design, never attempts [18]. Nair and colleagues' nine-year prospective study of long-term efficacy and safety of this therapy is one of the longest continuous intracranial electrophysiological datasets ever assembled from a treatment-resistant epilepsy population, tracking both clinical seizure outcomes and, critically, the underlying electrocorticographic data stream the device itself continuously logs over nearly a decade of use [19].

That continuous electrocorticographic archive has turned out to be a research resource in its own right, largely independent of the device's primary therapeutic function. Because responsive neurostimulation systems record and store electrocorticographic activity around every detected event, and in some configurations on a scheduled basis regardless of detection, they generate exactly the kind of long-duration, real-world intracranial recording that pre-surgical monitoring — necessarily limited to days to a couple of weeks in an inpatient unit — cannot provide. This has enabled analyses of how interictal and ictal electrographic activity evolves over months to years of treatment, including circadian and slower multi-day patterns in the device-recorded signal and their relationship to clinical seizure timing, an area of study that simply did not exist before implanted, continuously logging devices became available at scale. Touma and colleagues' systematic review and meta-analysis of neurostimulation therapies — encompassing responsive neurostimulation alongside vagus nerve and deep brain stimulation approaches — for treatment-resistant epilepsy situates this device-derived electrophysiological evidence within the broader neuromodulation literature, and underscores that the electrographic biomarkers these devices generate are increasingly treated as outcomes and covariates in their own right, not merely as an engineering detail of how the therapy happens to work [20]. Open-loop deep brain stimulation of the anterior thalamic nucleus, the other major implanted neuromodulation approach in wide clinical use for this

population, does not close the loop on a device-detected electrographic trigger in the same way, but the SANTE trial's long-term efficacy and safety data, reported by Salanova and colleagues, nonetheless illustrate how far chronic device-based neuromodulation for drug-resistant epilepsy has matured as a therapeutic category running alongside, rather than displacing, the responsive and resective approaches discussed elsewhere in this article [21].

This represents a genuinely distinct evidentiary category from the intracranial HFO and network literature discussed above, and it is worth naming the difference explicitly. Pre-surgical intracranial recording captures a brief, intensively monitored snapshot under artificial, medication-tapered inpatient conditions, optimized to provoke and capture a handful of representative seizures. Neurostimulation-derived electrocorticography captures years of largely unmedicated-schedule-unaltered, real-world electrographic activity, including the great majority of interictal time that pre-surgical monitoring, constrained by cost and bed availability, simply cannot afford to record. The two data types are complementary rather than substitutable — the pre-surgical recording is what determines whether and where a device or resection is indicated in the first place — but the device-derived stream is beginning to answer longitudinal questions, about how an electrophysiological signature evolves over years of treatment rather than what it looks like in a single monitoring admission, that the field did not have good tools to address before implanted, chronically recording devices became a standard part of the treatment-resistant epilepsy armamentarium.

7. Open Challenges

Several gaps recur across the literature synthesized here and deserve to be named plainly. First, standardization: the HFO literature spent nearly two decades converging on even a practical recording guideline [17], and the network-connectivity literature discussed above has not yet reached an equivalent point of methodological consensus — different studies use different montages, frequency bands, epoch lengths, and connectivity estimators, which makes cross-study comparison and, more importantly, cross-center clinical translation considerably harder than the underlying science would suggest it should be. A biomarker that requires a specific center's exact recording and analysis pipeline to reproduce is a research finding, not yet a clinical tool.

Second, the specificity problem that has dogged HFOs since their initial description has never been fully resolved: physiological, non-epileptogenic high-frequency activity exists, particularly in specific anatomical structures and behavioral states, and distinguishing pathological fast ripples from this physiological background reliably enough to guide a resection margin remains harder in practice than the cleanest published series suggest [15]. Third, the field's evidence base for network and connectivity signatures, while conceptually compelling and grounded in a genuine reframing of what an epileptogenic zone is [11], remains considerably less mature — in replication, in cross-center validation, and in prospective outcome linkage — than the evidence base for interictal spikes or HFOs, and treating an unreplicated single-center connectivity finding as clinically actionable would be premature.

Fourth, most of the foundational HFO and network literature was generated in a pre-surgical evaluation context: intensive, short-duration, inpatient recording under conditions — tapered medication, altered sleep, an artificial environment — that are deliberately provocative and not representative of a patient's ordinary electrophysiological state. The emerging neurostimulation-derived electrocorticography literature is only beginning to test whether signatures identified under those provocative pre-surgical conditions hold up, or need substantial revision, when examined against years of real-world, largely unaltered recording [19,20], and that reconciliation is very much an open research question rather than a solved one. Fifth, and more mundane but no less consequential: the diagnostic-yield problem that motivated extended and ambulatory scalp recording in the first place — the mismatch between how rarely inpatient monitoring captures a representative seizure and how much clinical decision-making rests on that capture — has been only partially addressed by wearable and mobile EEG technology to date, and integrating these lower-fidelity but higher-duration signals with the high-fidelity but short-duration intracranial literature discussed throughout this article remains an active engineering and analytic challenge rather than a resolved one [9].

We do not think any of these gaps are fatal to the broader electrophysiological-signature research program for

treatment-resistant epilepsy — if anything, the consistency with which independent groups, working with different recording modalities and different patient populations, have converged on interictal spikes, HFOs, and network-level reorganization as recurring, complementary markers of epileptogenic tissue is itself reasonably strong evidence that the underlying phenomena are real. But they are the honest state of the evidence, and claims of a single, validated, ready-to-deploy electrophysiological biomarker for treatment-resistant epilepsy should be read with these open problems in mind.

8. Conclusion

The electrophysiological literature reviewed here supports a fairly specific, and fairly modest, claim: no single EEG-derived signature — not the interictal spike, not the high-frequency oscillation, not a network-connectivity metric, not the electrocorticographic stream logged by an implanted neurostimulator — is sufficient on its own to fully characterize treatment-resistant epilepsy in an individual patient, but taken together, and applied at the right stage of an individual patient's evaluation, they constitute the most direct available window onto the physiological process that two or more medications have failed to control [3,1]. Interictal spikes and routine or ambulatory scalp EEG remain the first and most widely accessible signature, useful for diagnosis and broad classification even where they cannot resolve fine spatial localization [5,6,9]. High-frequency oscillations, discovered in intracranial recordings and refined over nearly two decades of methodological work, add a more specific, if still imperfectly standardized, marker of the tissue most likely to be generating spontaneous seizures [12,13,14,15,16,17]. Network and connectivity analyses reframe the localization question away from a single focus and toward the distributed process that actually generates and propagates a seizure, a reframing with real surgical consequences even where the specific metrics remain under active development [11]. And the continuously recording electrocorticographic streams generated by implanted neurostimulation devices are beginning to supply something none of the earlier signatures could: a multi-year, largely real-world record of how these electrographic patterns actually evolve under treatment, rather than a single intensively monitored snapshot [19,18,20].

Making full use of this toolkit, rather than treating any one signature as sufficient by itself, depends on an honest accounting of where the evidence for each remains thin — recording standardization, physiological-versus-pathological specificity, and the reconciliation of short-duration pre-surgical findings with long-duration device-derived data chief among them. None of these are reasons to discount the underlying electrophysiological research program; they are, read together, closer to a roadmap for the next decade of work in a field where the basic premise — that the electrical signature of seizure-generating tissue is directly observable, and directly useful, in patients who have run out of pharmacological options — has already been demonstrated many times over, across independent groups, recording modalities, and patient populations, even as the details of exactly which signature to trust, and when, remain very much an active area of clinical and methodological refinement.

9. References

1. Perucca, E., Perucca, P., White, H.S., Wirrell, E.C. (2023) Drug resistance in epilepsy. The Lancet Neurology, 22(8): 723-734. DOI: 10.1016/S1474-4422(23)00151-5

2. Sultana, B., Panzini, M.A., Veilleux Carpentier, A., Comtois, J., Rioux, B., Gore, G., Bauer, P.R., Kwon, C.S., Jetté, N., Josephson, C.B., Keezer, M.R. (2021) Incidence and Prevalence of Drug-Resistant Epilepsy: A Systematic Review and Meta-analysis. Neurology, 96(17): 805-817. DOI: 10.1212/WNL.0000000000011839

3. Kwan, P., Arzimanoglou, A., Berg, A.T., Brodie, M.J., Allen Hauser, W., Mathern, G., Moshé, S.L., Perucca, E., Wiebe, S., French, J. (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia, 51(6): 1069-1077. DOI: 10.1111/j.1528-1167.2009.02397.x

4. Fiest, K.M., Sauro, K.M., Wiebe, S., Patten, S.B., Kwon, C.S., Dykeman, J., Pringsheim, T., Lorenzetti, D.L., Jetté, N. (2017) Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology, 88(3): 296-303. DOI: 10.1212/WNL.0000000000003509

5. Cascino, G.D. (2002) Video-EEG Monitoring in Adults. Epilepsia, 43(Suppl. 3): 80-93. DOI: 10.1046/j.1528-1157.43.s.3.14.x

6. Noachtar, S., Rémi, J. (2009) The role of EEG in epilepsy: A critical review. Epilepsy & Behavior, 15(1): 22-33. DOI: 10.1016/j.yebeh.2009.02.035

7. Fisher, R.S., Cross, J.H., French, J.A., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshé, S.L., Peltola, J., Roulet Perez, E., Scheffer, I.E., Zuberi, S.M. (2017) Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58(4): 522-530. DOI: 10.1111/epi.13670

8. Beniczky, S., Wiebe, S., Jansen, F.E., et al. (2025) Updated classification of epileptic seizures: Position paper of the International League Against Epilepsy. Epilepsia, 66(6): 1804-1823. DOI: 10.1111/epi.18338

9. Biondi, A., Laiou, P., Bruno, E., Viana, P.F., Schreuder, M., Hart, W., Nurse, E., Pal, D.K., Richardson, M.P. (2022) Noninvasive mobile EEG as a tool for seizure monitoring and management: A systematic review. Epilepsia, 63(5): 1041-1063. DOI: 10.1111/epi.17220

10. Pittau, F., Dubeau, F., Gotman, J. (2012) Contribution of EEG/fMRI to the definition of the epileptic focus. Neurology, 78(19): 1479-1487. DOI: 10.1212/WNL.0b013e3182553bf7

11. Bartolomei, F., Lagarde, S., Wendling, F., McGonigal, A., Jirsa, V., Guye, M., Bénar, C. (2017) Defining epileptogenic networks: Contribution of SEEG and signal analysis. Epilepsia, 58(7): 1131-1147. DOI: 10.1111/epi.13791

12. Bragin, A., Engel, J. Jr, Wilson, C.L., Fried, I., Mathern, G.W. (1999) Hippocampal and entorhinal cortex high-frequency oscillations (100-500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. Epilepsia, 40(2): 127-137. DOI: 10.1111/j.1528-1157.1999.tb02065.x

13. Staba, R.J., Wilson, C.L., Bragin, A., Fried, I., Engel, J. Jr (2002) Quantitative analysis of high-frequency oscillations (80-500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. Journal of Neurophysiology, 88(4): 1743-1752. DOI: 10.1152/jn.2002.88.4.1743

14. Jacobs, J., Zijlmans, M., Zelmann, R., Chatillon, C.E., Hall, J., Olivier, A., Dubeau, F., Gotman, J. (2010) High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Annals of Neurology, 67(2): 209-220. DOI: 10.1002/ana.21847

15. Zijlmans, M., Jiruska, P., Zelmann, R., Leijten, F.S., Jefferys, J.G., Gotman, J. (2012) High-frequency oscillations as a new biomarker in epilepsy. Annals of Neurology, 71(2): 169-178. DOI: 10.1002/ana.22548

16. Dümpelmann, M., Jacobs, J., Schulze-Bonhage, A. (2015) Temporal and spatial characteristics of high frequency oscillations as a new biomarker in epilepsy. Epilepsia, 56(2): 197-206. DOI: 10.1111/epi.12844

17. Zijlmans, M., Worrell, G.A., Dümpelmann, M., Stieglitz, T., Barborica, A., Heers, M., Ikeda, A., Usui, N., Le Van Quyen, M. (2017) How to record high-frequency oscillations in epilepsy: A practical guideline. Epilepsia, 58(8): 1305-1315. DOI: 10.1111/epi.13814

18. Geller, E.B. (2018) Responsive neurostimulation: Review of clinical trials and insights into focal epilepsy. Epilepsy & Behavior, 88(Suppl. 1): 11-20. DOI: 10.1016/j.yebeh.2018.06.042

19. Nair, D.R., Laxer, K.D., Weber, P.B., et al. (2020) Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology, 95(9): e1244-e1256. DOI: 10.1212/WNL.0000000000010154

20. Touma, L., Dansereau, B., Chan, A.Y., Jetté, N., Kwon, C.S., Braun, K.P.J., Friedman, D., Jehi, L., Rolston, J.D., Vadera, S., Wiebe, S., Josephson, C.B. (2022) Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis. Epilepsia, 63(6): 1314-1329. DOI: 10.1111/epi.17243

21. Salanova, V., Witt, T., Worth, R., et al. (2015) Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology, 84(10): 1017-1025. DOI: 10.1212/WNL.0000000000001334

10. Declarations

Funding

This literature synthesis received no specific grant from any funding agency in the public, commercial, or

not-for-profit sectors.

Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

Data Availability Statement

This article is a literature synthesis and did not generate new clinical or experimental data. All findings discussed are drawn from the cited publications, and readers should consult those original sources for their underlying data and code availability statements.

Ethical Approval

Not applicable. As a literature synthesis, this work did not involve human participants, animal subjects, or the collection of primary clinical data, and therefore did not require ethical approval.

Citation: Habib A, Qasim K, Khoury K. "Electrophysiological Signatures of Treatment-Resistant Epilepsy in Adult Patients." J Neurol Brain Res (2026): 001-011 doi: 10.5281/zenodo.22849456