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Early seizure spread and epilepsy surgery: a systematic review

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Abstract

Objective: A fundamental question in epilepsy surgery is how to delineate the margins of cortex that must be resected to result in seizure freedom. Whether and which areas showing seizure activity early in ictus must be removed to avoid post-operative recurrence of seizures is an area of ongoing research. While seizure spread dynamics in the initial seconds of ictus are often correlated with postoperative outcome, there is no consensus definition of early spread, nor is there a concise summary of the existing literature linking seizure spread to post-surgical seizure outcomes. The present study is intended to summarize the literature linking seizure spread to postoperative seizure outcome and provide a framework for quantitative assessment of early seizure spread.

Methods: A systematic review was carried out according to PRISMA guidelines. A Medline search identified clinical studies reporting data on seizure spread measured by intracranial electrodes, having at least 10 subjects and reporting at least 1-year postoperative outcome in the English literature from 1990 to 2019. Studies were evaluated regarding support for a primary hypothesis: Areas of early seizure spread represent cortex with seizure-generating potential.

Results: The search yielded 4562 studies. 15 studies met inclusion criteria. 7 studies supported the primary hypothesis. The methods and metrics used to describe seizure spread were heterogenous. The timeframe of seizure spread associated with seizure outcome ranged from 1 – 14 seconds, with large, well-designed, retrospective studies pointing to 3 – 10 seconds as most likely to provide meaningful correlates of postoperative seizure freedom.

Significance: The complex correlation between electrophysiologic seizure spread and the potential for seizure generation needs further elucidation. Prospective cohort studies or trials are needed to evaluate epilepsy surgery targeting cortex involved in the first 3–10 seconds of ictus.

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Ethical publication

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosures

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Keywords

seizure; seizure spread; epilepsy; seizure propagation; ictal spread

Introduction

Why do seizures involve one area of cortex and not the area immediately adjacent to it, or other heavily interconnected areas? This seems to represent a gradient of susceptibility to seizure involvement, where certain areas are more prone to seize than others. It is logical that areas more easily recruited by seizures may also be more likely to generate a seizure independently. Wherever seizures arise in persons with focal epilepsy may be termed ictogenic. For the purposes of this paper, the primary focus is on the cortex that, when removed, results in seizure freedom[1]. This is one of the classic notions of the epileptogenic zone[2, 3], the exact delineation of which remains an elusive goal of epilepsy surgeons and epileptologists alike. The tissue that is involved in a seizure at time t=0 (seizure onset) has the ability to give rise to seizures. However, does the cortex involved at seizure time t=(0+x) also have seizure generating potential? If so, where is the cutoff for x? How early in ictus does cortical involvement count as a marker of tendency to generate seizures? Answers to these questions are critical because a surgical cure for epilepsy depends on incorporation of all cortex that can generate seizures.

Different hypotheses have been generated to explain the routes to seizure freedom after surgery. The network hypothesis of epilepsy purports that different nodes in the same network may generate a seizure, which would appear as if produced from different onsets, when it is actually the same seizure network arising from any of its possible nodes[4, 5]. Clearly, not everywhere to which a seizure spreads throughout its entire course must be removed achieve seizure-freedom, otherwise no one whose seizures generalize would be cured through surgery. Surgical paradigms assume that the site of initial seizure activity is the best marker of cortex with seizure-generating potential. While not the only variable to consider, seizure's onset location[1] is a candidate for surgical resection or disconnection based on having shown the ability to generate seizures[2, 3, 6]. Such logic leads to the question: at what time during the course of a seizure does the area involved no longer represent cortex with seizure generating potential, but rather normal cortex pushed out of homeostasis past an otherwise physiologic seizure threshold?

Efforts to standardize definitions associated with the zones purported to have seizure generating potential have been proposed, such as the epileptogenicity index[7–9]. These represent a step in the direction of making the margins of seizure-generating cortex more tangible. However, the biology underlying seizure spread and ictogenicity remains largely unknown, despite the uncovering of a myriad of genetic and molecular contributions[10].

Recent work suggests that the early seconds of a seizure may be a sensitive marker of the areas which, if not included in resections, lead to postoperative seizure recurrence[11]. A simple marker, such as timing out the first 10 seconds of a seizure and mapping out the cortex involved to incorporate into resection, could provide powerful decision-making

capability. This review is aimed at summarizing the literature that is constructed in such a manner as to support or refute such a hypothesis.

Methods

Systematic review

A systematic review was carried out according to PRISMA guidelines. A Medline search was carried out for English literature publications from 1/1/1990 – 12/15/2019 found with the following search terms: ((seizure) OR (ictal)) AND ((spread) OR (propagation)) AND ((surgery) OR (resection)) AND (outcome). The predetermined inclusion criteria were 1) human studies including 10 or more patients, 2) intracranial EEG measure of (ictal) seizure spread, 3) a correlation of seizure spread with post-surgical seizure outcome, 4) at least 1 year follow for post-surgical seizure outcome. After the search was carried out, a first pass of titles was carried out to see which studies could be eliminated for obvious criteria such as non-human studies, duplicates, non-English literature, and clearly irrelevant subject matter. After this, the remaining abstracts were reviewed for meeting inclusion criteria. Those manuscripts not excluded by either title or abstract were subsequently reviewed in full for both inclusion criteria and data analysis.

Hypothesis evaluation

The primary hypothesis is as follows: *Areas of early seizure spread represent cortex with seizure-generating potential*.

In this paradigm, if all areas with seizure-generating potential are removed, patients will be seizure-free. The manuscripts that met inclusion criteria were evaluated as to whether they supported, offered indeterminate support, provided no support, or refuted this hypothesis. The heterogeneity of measures of seizure spread and methods of analysis prevented a meta-analysis that would be meaningful from a statistical perspective. The primary hypothesis has two notable implications, which can be summarized in two secondary hypotheses:

1. Including areas of early seizure spread in resections is associated with favorable seizure outcomes and, inversely, exclusion of areas of early seizure spread is associated with unfavorable seizure outcomes post operatively.
2. Seizures that spread rapidly and widely are unlikely to have areas of early involvement incorporated into resections, and thus are independently associated with unfavorable seizure outcomes postoperatively.

The secondary hypotheses are more readily testable clinically and are logical extensions of the primary hypothesis. The main criteria for evaluating whether a study supported the primary hypothesis involved whether the secondary hypotheses were tested.

Results

The Medline search yielded 4562 publications. The process of filtering for inclusion is presented visually in Figure 1. From these, 4284 studies were excluded from initial screening to not meet inclusion criteria, primarily through being unrelated subject matter,

not a human study, a duplicate study or non-English literature. From the remaining 278 studies, abstracts were reviewed, and 195 were excluded due to not meeting inclusion criteria, primarily due to lack of intracranial EEG data, non-human studies, having less than 10 subjects, or having insufficient (<1 year) of clinical follow-up. The 83 full length manuscripts remaining were reviewed in their entirety for meeting strict inclusion criteria. Studies from citations of these papers or those uncovered while cross-referencing these manuscripts were also investigated for inclusion. One prominent reason for exclusion was the lack of analysis of ictal EEG. Interictal high frequency oscillations were commonly the focus of analyses, while this review is limited to ictal seizure activity. In addition, measures of ictal EEG analysis that could be interpreted as spread, requiring both spatial and temporal components were required. 72 studies were excluded for not meeting these criteria, and 4 papers were found while cross-referencing included studies that met inclusion criteria. This left 15 studies included.

Table 1 summarizes the 15 studies that met inclusion criteria[11–25]. All of the studies were retrospective, either class II or III evidence. Subject numbers ranged from 15–177. 11 studies used data from subdural electrodes (SDE), alone or in combination with depth electrodes. 4 studies relied on SEEG or depth electrodes alone. 10 studies relied on adult patients, 1 on pediatric, 4 spanned age-groups.

Of 15 studies, 7 supported either primary or secondary hypotheses, 5 were indeterminate and 3 showed no support. No studies directly refuted primary or secondary hypotheses. Regarding the time-course for defining early seizure spread, 8 studies gave a cutoff in seconds for the time of ictus representative of early spread, to correlate with seizure outcome following epilepsy surgery. The timeframes of early seizure spread that correlated with surgical outcome ranged from <1 to 14s, with a median of 3s. Of the 8 studies with well-defined cutoffs for early or rapid seizure spread, 7 studies reported support of primary or secondary hypotheses. 4 studies supported the hypothesis*: including areas of early seizure spread in resections is associated with favorable seizure outcomes, and by contrast exclusion of areas of seizure spread is associated with unfavorable seizure outcomes post operatively*. While 6 studies (3 overlapping) supported the hypothesis: *seizures that spread rapidly are independently associated with unfavorable seizure outcomes postoperatively*.

Discussion

This hypothesis-driven systematic review highlights relevant clinical research regarding the implications of early seizure spread for surgical planning given its role as an independent predictor of surgical outcome. The inclusion criteria limited this study to those that could speak to the hypothesis—a*reas of early seizure spread represent cortex with seizure-generating potential*. This hypothesis is an idea already accepted *conceptually* by many epileptologists and epilepsy surgeons. However, the *quantitative* details of that hypothesis are consequential and there is as yet insufficient data to tease them out.

There is a lack of strict agreement on what the term “early” or “rapid” spread means. For example, 1, 3, 10, 14 seconds, as well as a proportional value (10% of ictus[25]), were all either proposed or uncovered empirically in the studies included[11, 13, 14, 18]. Likewise, the

overlap between the area from which seizure activity is seen to first arise at the onset of a seizure, and the area of cortex that must be resected in order to render a patient free of seizures[2–4, 26], is an ongoing topic of debate.

Tertiary referral centers for epilepsy tend to rely on interdisciplinary conferences where neurologists, surgeons, radiologists and others, come to a consensus agreement. The rates of seizure freedom reported at these centers suggest that there is something shared about these approaches that is valuable for outcomes. It is with this in mind that the present study was undertaken. Here, the focus is directed at the start of the seizure as representing at least in part, the area that when removed, is most likely to render a person seizure-free. Below selected studies that met inclusion criteria are discussed.

Included studies

Kim et al.[14] studied surgical outcomes for neocortical epilepsy in a cohort of 177 patients. This study comes as close as any, in retrospective fashion, to answering the question of how early in ictus we are to consider cortex involved as able to give rise to seizures. They divide the cohort of patients into those that received resections including only partial resection of the area involved in the first 3 s of ictus (group I), those that underwent resection of all electrodes involved in the first 3 s of ictus (group II) and those that underwent resection of all cortical areas involved in the first 5 s of ictus (group III).

The study found that both groups II and III had significantly greater proportion of seizure free outcomes (57% and 54% seizure free, respectively) than group I which did not resect all of cortex involved in the first 3 s of ictus (24% seizure free). They did not find a significant difference between groups II and III (3s vs 5s of ictal involved electrodes resected), suggesting that the first 3 s of ictus was the critical cut-off. This study represents strong support for the hypotheses of the present review.

Holtkamp et al.[16] studied intracranial EEG in frontal lobe epilepsy patients. One relevant finding of the study was that widespread onset—defined as onset in an area greater than 2 cm—was associated with unfavorable seizure outcome. Speaking more specifically to the notion of spread, latency to onset of spread >2cm from seizure onset zone was found to be on average 0.5 s in patients with recurrent seizures vs. 4 s in patients who were seizure free ($p=0.016$). In addition, spread to extrafrontal structures was found to be on average 6.5 s in patients in whom seizures recurred vs 17.5 s in those who were seizure free ($p=0.025$). Both of these measures support the hypothesis that faster spreading seizure activity early in ictus is a predictor of poor seizure outcome.

Andrews et al.[11] studied seizure spread directly. One method involved looking at the electrode(s) showing seizure onset and subsequently documenting the latency before spreading to an electrode 2 or more centimeters away. The cohort of patients whose seizures began to spread in 10 seconds or less were significantly more likely to have seizures recur after surgery. The second method involved quantifying seizure spread beyond surgical margins, using beta power on intracranial EEG as a surrogate marker for early seizure activity. Patients whose seizures recurred after surgery had significantly higher ictal beta-power outside surgical margins during the first 10 seconds of seizures. These findings

support the hypothesis that early seizure spread outside surgical margins in the first 10s portends seizure recurrence after surgery.

Weiss et al.[18] investigated early areas of phase-locked high gamma (PLHG) on intracranial EEG. The hypothesis of the study was that seizure activity could be distinguished from physiologic inhibitory responses to seizure activity by selecting for a high frequency, phase-locked electrodes. In essence, they try to distinguish pathologic seizure spread from the brain's physiologic response to the seizure activity. The study found that rates of good seizure outcome after surgery were improved when areas of early PLHG were included in resection. This was interpreted as support for the hypothesis that resecting areas of early seizure spread is associated with favorable seizure outcomes.

Wang et al.[24] took a graph theory approach to looking at seizure spread in temporal lobe epilepsy measured by SEEG. They found that when seizures propagated outside of the temporal lobe within 3s of seizure onset, patients were less likely to be seizure free. These results seem a rather clear support of early seizure spread being predictive of recurrent seizures.

Yang et al.[23] studied intracranial EEG predictors of seizure freedom in a cohort of MRI-negative frontal lobe epilepsy patients. The study reports that patients with recurrent seizures after surgery had on average shorter latency to onset of spread, which they defined as seizure activity ≥2cm away from the electrodes of seizure onset (1.4±2.9s in recurrent seizure group, vs 5.9±7.1s in seizure free group, P=0.016). They also found that patients with recurrent seizures had shorter latency of spread outside of the frontal lobe, supporting the hypotheses of this review.

Kutsy et al. 1999[13] report on patterns of intracranial EEG in neocortical epilepsy, associated with surgical outcome. They found that velocity of spread was related to surgical outcome. They divided patients into fast (<1s) and slow (>1s) spread, but also comment that essentially all the slow spread was >10s. Other nuances worthy of note are that spread to mesial temporal structures was not factored into the spread, as it was found in many of the patients and did not correlate with outcome. Their findings support the hypothesis that rapid spreading seizures are associated with poor outcome.

Limitations

A great many studies comment on one or another aspect of seizure spread[27–31]. However, it is much rarer that it is brought together with post-operative clinical outcome. There are undoubtedly studies that for reasons of search terms and indexing would likely meet criteria but have been overlooked by this systematic review. Indeed, even the search terms that narrow a systematic review to the area of focus, may have the effect of selecting preferentially studies that report the significance of these terms. It is difficult to account for the effects of such search and publication biases on a study such as this.

It should be noted that this study draws on broad search terms and may appear to discuss all medically refractory focal epilepsy as a monolith. However, the authors recognize that applying an early seizure-spread paradigm as a blanket surgical approach to all focal

epilepsy would be a gross oversimplification. For example, epileptic spasms in a pediatric population have been shown to propagate widely and quickly, sometimes within a few hundred milliseconds, and these patients often still attain seizure freedom without incorporating these spread sites[32, 33]. The diverse biologic perturbations that underlie epileptogenicity in different pathologies and populations will likely require focused investigations as opposed to broadly applied rules.

One reason for the heterogeneity of studies of seizure spread is large practice variation in intracranial studies. Not all areas of cortex can or should be recorded on every patient. Differences in sampling between SEEG and subdural grids also will affect how seizure spread can be measured and interpreted. of However, clinicians are limited in the places they can detect seizure spread by the areas from which they choose to sample. The seizure spread as shown in Figure 2 is the type of pattern for which broad temporal coverage would be necessary. Figure 2A and B depict focal ictal activity localized to mesial temporal structures for the entirety of the first 10 seconds of ictus. In contrast, Figure 2C and D depict the spread of seizure activity to the posterior superior temporal gyrus—which is spared in most standard anterior temporal lobectomies—within 10s of onset. One possible confounder of literature on resection of sites of early seizure spread is whether studies supporting such resections are confounded by selecting generally for larger resections. There is some evidence to support larger resections associated with seizure freedom at least in the temporal lobectomy literature[34], and quantifying the amount of cortex resected has been incorporated into outcomes analyses elsewhere in the epilepsy literature[35]. The studies identified in this work discuss extent of resection largely in terms referring to the degree of seizure onset zone[14] or perceived epileptogenic zone removed, as opposed to volumetric measures of resection. Disentangling these two notions would be a difficult endeavor and require more focused studies

Currently the work up for epilepsy surgery consists of multiple non-invasive imaging studies, that may reveal a structural epileptogenic lesion, sometimes obviating the need for invasive EEG studies. Lesion-guided epilepsy surgery does indeed already have favorable outcomes compared to MRI-negative epilepsy[36, 37]. In pediatric epilepsy, there are examples of scalp EEG with generalized findings in patients that nonetheless had favorable seizure outcomes with focal lobar resections[38]. The current study does not support discarding established routes of pre-operative epilepsy surgery work-up. Rather, here we illustrate possible supplementary analyses to aid in delineating surgical margins in cases where long-term invasive EEG studies have been deemed necessary.

Mechanisms linking seizure spread and epileptogenesis

The mechanisms of how a seizure begins, and how a seizure—once it has begun—spreads to other cortex, may involve different pro-epileptic cellular and network-wide variables.[10] Some of these mechanisms may be static, like mutations in ion channels, and some may be dynamic, like activity dependent concentration of chloride or glutamate[10, 39–41]. Part of the hypothesis of this study is that the cellular or network architecture that results in one area of cortex being recruited by a seizure before another is indicative of areas that either already

have the ability to generate seizures or indicative of areas that will gain the ability to generate seizures (pro-ictogenic).

Epileptogenic brain is not in a constant state of seizure, so there is likely some homeostatic mechanism balancing excitation and inhibition that is thrown off leading up to a seizure. Why an area involved early in a seizure would be more likely to *generate* a seizure depends on whether distinct mechanisms are at play to generate seizures versus propagate seizure activity. Epileptiform spikes on EEG or electrocorticography represent a gray zone in the conceptual framework of epileptogenicity, as they may be seen temporally and spatially distinct from seizures and their relationship with epileptic seizures is not fully understood[42–44]. Epileptiform spikes do not necessarily represent cortex that must be removed to attain seizure-freedom, because their resection is neither uniformly associated with, nor necessary for, favorable seizure outcome[45–47]. They are pointed out here to illustrate that there are areas of the brain producing epileptiform disturbances of cerebral activity exist distinct from the core seizure-generating cortex. Such areas offer an enigmatic link between seizure spread and seizure onset.

If spikes, or some other pro-epileptic influence, are produced by areas of an epileptic brain that may not otherwise produce seizures, then areas of seizure onset may not actually be independently seizure-producing per se. The seizure onset zone may instead represent the most susceptible areas to seizure induction, i.e. most vulnerable to disruption of normal neuronal homeostasis by epileptiform spikes or some other pro-epileptic influence in a separate area of the brain.

To use a metaphor in this two-part hypothetical model, different mechanisms are at play in creating a spark and catching fire. If spikes—or some other pro-epileptic influence, are seen as the spark, then the seizure onset zone may be seen as the dry-leaves or kindling (fuel) that burns when exposed to a spark. Dry leaves do not burn in the absence of a spark, and sparks falling upon inadequate kindling do not cause fires.

A spark-on-kindling type model for epileptogenesis would suggest that the earliest areas involved in a seizure represent those areas that are most likely to burn when showered with sparks—or to seize when showered with spikes or whatever the pro-epileptic influence may be. Conversely, deep nuclei, cerebellum, or cortical areas that tend to avoid ictal activity are the damp undergrowth that whose homeostatic milieu withstands pro-ictogenic influence and may not easily burn when exposed to sparks. Epilepsy patients will often continue to have epileptiform spikes on EEG even if their seizures have been cured by surgery[46, 47]. It may be that surgery in these patients has removed or isolated areas most susceptible to seizures, from the areas of brain generating pro-seizure influence—i.e., removed the kindling from the sparks, or reduced the amount of kindling such that anti-epileptic drugs are sufficient to dampen the remaining ictogenic cortex. Recent studies have shown resection of cortical-stimulation sites that elicit a patient's habitual seizures improves rates of seizure freedom[48].

Data-driven models of the epileptic network present an opportunity to link theory regarding seizure start and spread with empirical evidence. The hypothetical model of a spark-on-

kindling mechanism of ictogenesis may be supported by properties of the epileptic network organization during the interictal state. Specifically, stereotypic patterns of connectivity during the early phases of a seizure may be recapitulated during the interictal state, in the absence of epileptiform activity, and may represent communities of nodes that are more vulnerable and prone to seize when exposed to spikes[49, 50]. A dynamical network model that tracks how network communities are progressively recruited during seizures may help objectively define critical state-dependent targets for intervention[51, 52]. Recent findings from *in silico*, simulation-based models of resective surgery suggest that specific state-dependent network features that are expressed prior to seizure onset predict whether a seizure will spread and generalize, and that the key nodes involved in this prediction were located beyond the clinically-defined seizure-onset zone[53]. Validation of this approach could hold promise in identifying key nodes involved in seizure spreading mechanisms.

Conclusion

The goal of epilepsy surgery planning is to strictly define the margins of the epileptogenic zone[2, 6]. A strict definition of margins will allow for accurate surgery and accurate interpretation of the efficacy of the margins that are drawn. The literature summarized here points to the first 3 – 10 seconds of ictus as candidate thresholds for rapid spread. Sparing cortex involved before this timepoint in epilepsy surgery may be more likely to lead to recurrence of seizures postoperatively. It should be noted that the timeline suggested here is couched in the limitations inherent in a systematic review. This study by necessity pieces together data from other studies whose primary goals are not unanimously aligned with the stated goal of delineating timeframes for seizure spread, and thus further focused studies on the relevance and validity of these timeframes are paramount. The critical question of the exact timeframe of early seizure spread, remains to be definitively determined. The heterogeneity of definitions critical for surgical decision-making, suggests that clinical equipoise remains and such quantitative approaches may eventually lend important refinements to surgical margin estimates in epilepsy surgery planning. In the face of such ambiguity, controlled prospective cohort studies or trials are needed to evaluate these timeframes.

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Summary

- This study summarizes the literature linking seizure spread to postoperative seizure outcome.
- 15 studies from 1990–2019 had ≥10 subjects, measured seizure spread on intracranial EEG and linked it to ≥1-year postoperative outcomes.
- 7/15 studies supported the primary hypothesis: Areas of early seizure spread represent cortex with seizure-generating potential.
- Targeting cortex involved during the initial 3–10s of ictus may provide meaningful impact on seizure freedom.

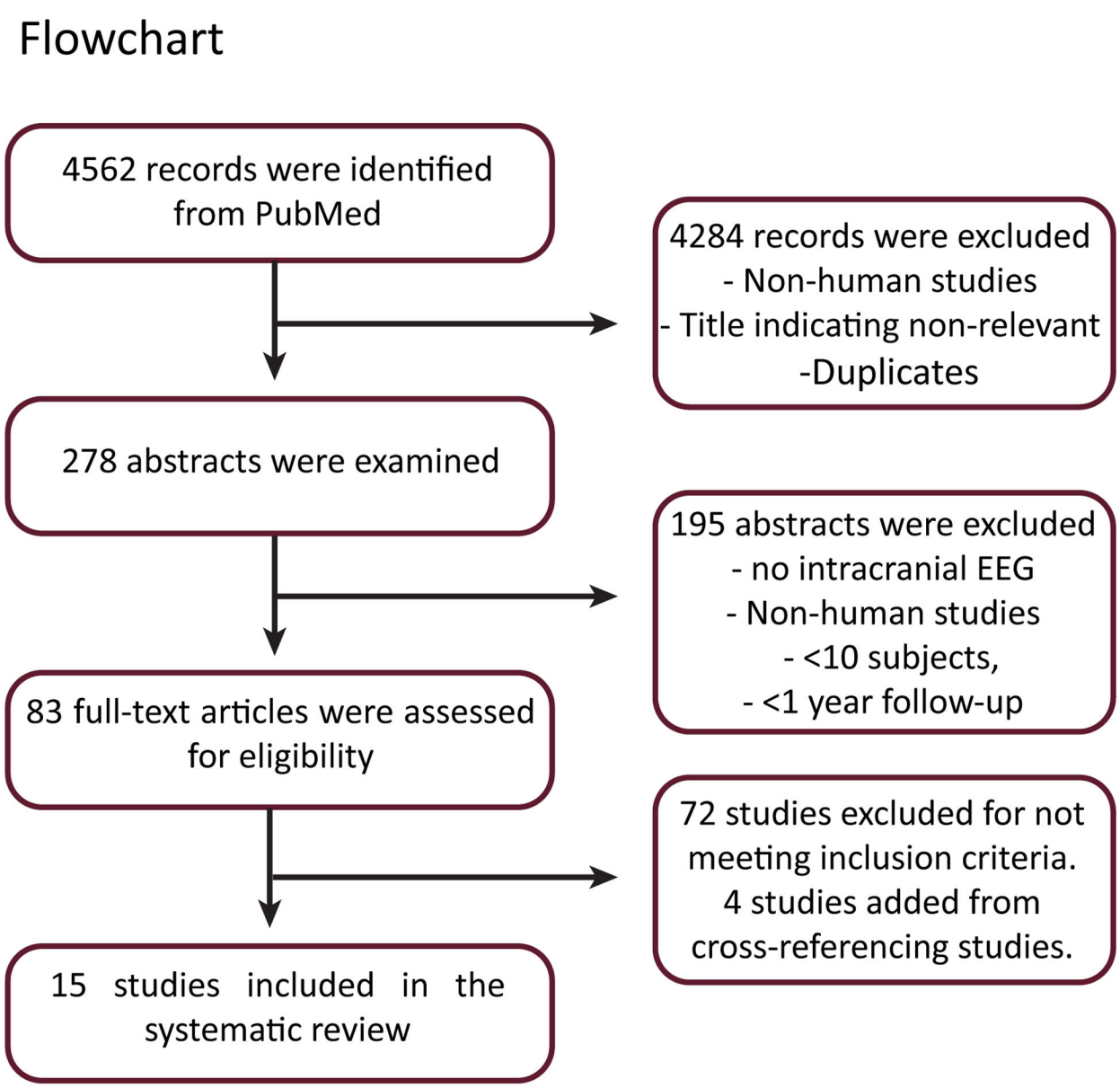

Figure 1: Systematic review flow chart
General overview of the method of searching for, eliminating and including studies.

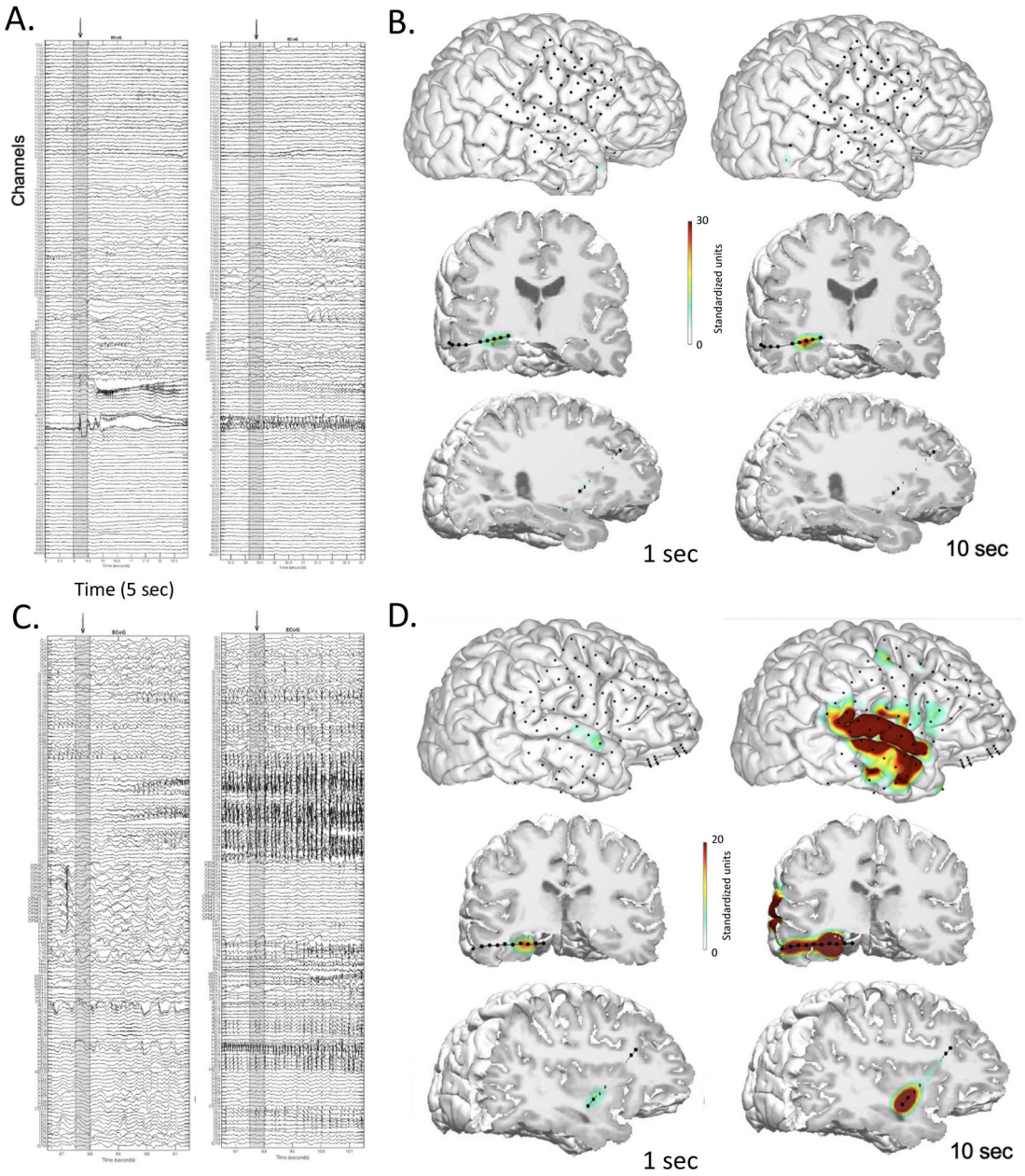

Figure 2. Seizure spread

Slow-spreading mesial temporal seizure. A. ECoG recordings (5 sec window shown) of a slow-spreading mesial temporal seizure at 1 sec and 10 sec after seizure onset (left and right panels respectively). B. Heatmap of epileptiform activity depicted in grey window in A over lateral surface of brain (top), on hippocampal depth (middle, roughly coronal plane), and insula depth (bottom, roughly sagittal plane) at 1 sec and 10 sec after seizure onset (left and right columns respectively). Ictal activity remains limited to the mesial temporal region. C. ECoG recordings (5 sec window shown) of a fast-spreading mesial temporal seizure (different patient with similar electrode coverage) ECoG recordings (similar to A). D. Heatmap of epileptiform activity depicted in grey window in C (similar to B). By the 10 sec,

epileptiform activity has spread not only to lateral temporal cortex but also extratemporally (suprasylvian, insula).

Table 1.

TLE = temporal lobe epilepsy. Neo = neocortical epilepsy. n.l. ET = non lesional extratemporal. Ped = pediatric. Mix = heterogenous epilepsy type and/or etiology. FLE = frontal lobe epilepsy. cont = continuous. SDE = subdural electrodes, grids and strips +/− depths.

Author	N	Epilepsy	iEEG Types	Measure of Spread	Time course	Metrics of Spatial spread	Correlation	Follow-up (years)	Class of evidence	Support of hypothesis
Lieb et al. 1991[12]	24	TLE	depth	time to lobe involvement	cont	lobe sequence	Sequence does not correlate with outcome	≥ 1	Class III	No support
Kutsy et al. 1999[13]	26	Neo	SDE	time to maximal cortical spread	< 1 s	neocortex	rapid spread ∝ poor outcomes	≥ 2	Class II	Supports
Kim et al. 2010[14]	177	Neo	SDE	Ictal involvement, visually assessed	≤ 3 s	2 cm	Resecting cortex involved in first 3 s ictus ∝ seizure freedom	≥ 2	Class II	Supports
Zakaria et al. 2012[15]	41	n.l. ET	SDE	diffuse onset > 5 electrodes	N/A	5 electrodes	Onset zone ≤ 5 contiguous electrodes ∝ favorable outcome	≥ 1	Class II	Indeterminate
Holtkamp et al. 2012[16]	25	FLE	SDE	Latency to spread	6.5 s	2 cm†	rapid spread ∝ poor outcomes	≥ 1	Class II	Supports
Fujiwara et al. 2012[17]	48	Ped	SDE	Ictal HFOs	≤ 10 s	5 electrodes	Resection of early ictal HFO ∝ good outcomes	1.17‡	Class II	Indeterminate
Weiss et al. 2015[18]	45	mix	SDE	Phase locked high gamma (PLHG)	14 ± 2 s	4 electrodes	Resection of early PLHG ∝ good outcome	2.4‡	Class II	Supports
Memarian et al. 2015[19]	31	TLE	SEEG	Hypersynchronous (HYP) and low voltage fast activity	N/A	N/A	Resection of HYP activity ∝ good outcomes	3.67‡	Class II	Indeterminate
Martinet et al. 2015[20]	16	mix	SDE	Ictal recruitment	N/A	N/A	organized spread patterns ∝ good outcome	4.92‡	Class III	Indeterminate
Memarian et al. 2015[21]	20	TLE	SDE	Latency to initial spread	cont	N/A	Latency to initial spread improves outcome prediction model	4.5‡	Class III	Indeterminate
Ochoa et al. 2016[22]	15	mix	SDE	Spread of HFOs	N/A	N/A	Ictal HFO and initial propagation	1–2	Class III	Indeterminate

Author	N	Epilepsy	iEEG Types	Measure of Spread	Time course	Metrics of Spatial spread	Correlation	Follow-up (years)	Class of evidence	Support of hypothesis
							resection ∝ seizure freedom			
Yang et al. 2016[23]	47	FLE	SDE	Spread of ictal onset	1.4±2.9 s	2 cm†	Shorter latency to spread ∝ poor outcomes	≥ 2	Class II	Supports
Wang et al. 2017[24]	43	TLE	SEEG	early ictal propagation	≤ 3 s	N/A	Ictal propagation outside temporal lobe in ≤ 3s ∝ poor outcome	≥ 1	Class II	Supports
Müller et al. 2018[25]	20	mix	SDE	electrode involvement during 10% of ictus	10% of seizure	N/A	seizure spread to have no relation with surgical outcome	≥ 1	Class III	No Support
Andrews et al. 2019[11]	118	TLE	SDE	Beta power and visual analysis	< 10 s	2 cm†	Rapid spread and spread outside resection ∝ poor outcomes	6.5‡	Class II	Supports

† Spread defined as ictal pattern at electrodes at least 2 cm from site of seizure onset.

‡ mean years