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Review

Multiscale recordings reveal the dynamic spatial structure of human seizures

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ABSTRACT

The cellular activity underlying human focal seizures, and its relationship to key signatures in the EEG recordings used for therapeutic purposes, has not been well characterized despite many years of investigation both in laboratory and clinical settings. The increasing use of microelectrodes in epilepsy surgery patients has made it possible to apply principles derived from laboratory research to the problem of mapping the spatiotemporal structure of human focal seizures, and characterizing the corresponding EEG signatures. In this review, we describe results from human microelectrode studies, discuss some data interpretation pitfalls, and explain the current understanding of the key mechanisms of ictogenesis and seizure spread.

1. Introduction

The long-standing question of the nature of electrophysiological activity that drives and characterizes the transition to seizure, despite its obvious importance to the field of epilepsy, remains unresolved. Its importance cannot be overstated, as it impacts both diagnostic studies in epilepsy patients carried out for the purpose of guiding treatment decisions, and laboratory investigations of ictogenesis and seizure propagation.

Although EEG is the most direct technique for accessing neurophysiological function at a fine temporal scale, it provides only a limited view of brain activity, being dominated by the summated postsynaptic currents in the superficial neocortical layers (Trevelyan and Schevon, 2014). Such currents can spread rapidly over long distances, and can have variable amplitudes due to constructive interference or to variations in dipole orientation relative to the recording electrode (Einevoll et al., 2013). As a result, the view of seizures provided by EEG recordings is often confusing. For example, there is frequent inter-reader disagreement regarding the location and timing of seizure onset (Wilson et al., 2003). The apparent rapid, broad spread of ictal activity contributed to the emergence of the notion that large-area networks, rather than small foci, are responsible for generating seizures (Spencer, 2002). This has led to an active debate regarding the extent to which seizures involve large-area networks, or whether they truly begin at a single, spatially restricted focus. In short, despite over 50 years of basic science and clinical research, the processes by which seizures begin, spread, and terminate are still the subject of considerable controversy.

The availability of continuous microelectrode recordings from patients undergoing invasive seizure monitoring as part of surgical treatment for pharmacoresistant focal epilepsy has provided an unprecedented window into the cellular basis of the epileptiform EEG, and permits investigators to draw parallels with laboratory studies in animal models. This has led to the definition of key spatial and temporal properties of seizure activity in humans at both the microscale and macroscale. In this review, we discuss the spatial structure of human seizures and how it can provide a useful framework for addressing open questions in ictogenesis, while also providing a clinically useful model for identifying seizure foci for therapeutic purposes.

2. Recording single and multiunit activity in humans

Cerebral signals that are recorded in EEG are composed of superimposed oscillations in a range of frequencies. In the sub-gamma frequency bands (< 25–30 Hz), oscillations demonstrate a complex relationship with neuronal firing (Buzsaki et al., 2012; Lakatos et al., 2005), and oscillatory phase can carry independent information

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(O'Keefe, 1993). In the gamma bands, especially in the high gamma (> 80 Hz) range, field potentials become highly correlated with population firing (Ray and Maunsell, 2011). These observations, however, were made under normal physiological conditions. In the epileptic brain, the relationship between oscillations and cellular activity can be disrupted (Menendez de la Prida and Trevelyan, 2011; Smith et al., 2016; Valero et al., 2015).

To record unit activity directly, microelectrodes and a specialized acquisition system must be employed. Ethical considerations limit both the number of patients eligible for microelectrode studies and the locations sampled. Currently, there are two types of microelectrodes approved for use in humans and that have been used for long-term recordings in epilepsy surgery patients. The Utah array has 96 microelectrodes arranged in a 10 × 10 grid spanning a 4 mm by 4 mm square area, and is designed to be implanted in accessible lateral neocortex and record from cortical layers 3–5 (House et al., 2006; Schevon et al., 2012; Waziri et al., 2009). Behnke-Fried microwire depth arrays are composed of a two-layer shaft with clinical cylindrical depth electrodes in the outer layer, and up to 9 microwires in the inner layer that protrude several mm beyond the tip of the shaft (Fried et al., 1999; Misra et al., 2014). These are capable of recording from deep structures, such as the hippocampus, amygdala, and cingulate gyrus. New devices are currently being developed and used on an investigational basis. An example is the Neurogrid, a biocompatible, conformable dense sensor grid designed to record from the pial surface, that has been shown to detect action potentials (Khodagholy et al., 2015).

In order to capture clinical seizures, continuous recording over multiple days is necessary. This procedure also permits tracking of unit waveshapes over time (Niediek et al., 2016). Such an endeavor in a clinical environment presents several technical and organizational challenges. Frequent, regular monitoring is required to ensure consistent recording quality, for both the research and clinical recordings (Schevon et al. 2008, 2012; Truccolo et al., 2011), and also for patient safety reasons. Precise temporal synchronization with the clinical video EEG system can be challenging (Keller et al., 2010; Schevon et al., 2008, 2012). Archiving and analysis of the resulting large data sets can be resource-intensive and time-consuming (Stead et al., 2010). For these reasons, relatively few groups have acquired and analyzed microelectrode recordings of seizures, and the total number of patients thus recorded is limited. Due to the heterogeneity of surgical epilepsy syndromes and seizure characteristics, the small patient sample represents an important limitation of human microelectrode studies. The steady growth of data collection and sharing in the epilepsy community, however, will facilitate comparison between these precious recordings, thereby increasing the prospect of identifying general features of epileptic pathophysiology.

3. What is a seizure?

In interpreting studies of ictal neuronal activity and their contribution to our understanding of the pathophysiology of seizures, it is important to consider that the ictal transition can be viewed quite differently depending on the methods used to define its location and timing. The International League Against Epilepsy defines a seizure as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain", emphasizing a clinical change as well as a temporally related change in neural activity (Fisher et al., 2005). Identification of the first prominent clinical change during a seizure is the first step in defining seizure type, and is strongly considered in localization and lateralization of an epileptogenic focus (Luders and Rosenow, 2001). It is well known that ictal semiologies may precede the first EEG evidence of a seizure (Spencer et al., 1982; Spencer and Spencer, 1994; Gavaret et al., 2014). However, in animal recordings and often in human microelectrode or quantitative EEG studies, the analysis of the interictal-ictal transition is typically based solely on the recorded electrographic patterns (Bower et al., 2012; Elahian et al., 2018; Jirsch et al., 2006; Liou et al., 2018; Misra et al., 2018; Schevon et al., 2012; Schindler et al., 2007; Truccolo et al., 2011; Wendling et al., 2003).

These considerations suggest that the seizure onset, as identified from electrophysiology recordings, may in fact represent seizure spread rather than true seizure initiation. One possible reason for this dissociation is that EEG signals are very impoverished representations of the underlying neuronal activity, being relatively insensitive to the unit activity that can help distinguish local from remote onset (Schiller et al., 1998; Trevelyan and Schevon, 2013, 2014). The cryptic nature of these EEG signals as typically visualized during clinical review make them prone to significant inter-reader variability (Iwasaki et al., 2005; Wilson et al., 2003). Both localization and timing may be further limited by sparse spatial sampling, which applies not only to human but also to many animal model recordings. This can result in some uncertainty regarding when the seizure starts, resulting in incorrect classification of preictal versus early and late ictal time periods, and onset versus spread locations. For example, in the surgical evaluation of temporal lobe epilepsy cases, mesial temporal structures are often densely sampled in comparison to neocortical brain regions, which may lead to a bias toward classification of these structures as seizure onset sites. Such issues are even more acute in human studies employing microelectrodes, as these are subject to undersampling to a greater degree than is the case with clinical electrodes. These considerations can help to place microelectrode findings, such as variations in seizure-associated neural firing patterns, in their proper context.

The use of automated methods to detect seizure events recorded by microelectrodes and other quantitative measures to characterize seizures allows for the identification of potentially pathological signals that extend far beyond clinical seizures alone (Esteller et al., 2005; Gardner et al., 2007). For example, in patients undergoing continuous intracranial EEG recording with macroelectrodes, quantitative EEG measures such as accumulated energy can be used to predict impending seizures (Litt and Echauz, 2002). Microelectrodes used to measure unit activity may also capture events such as "microseizures" that are not necessarily pathological (Schevon et al., 2008). In a study including a control group without epilepsy implanted with microelectrodes, ictal-like events were detected with fields limited to single microelectrodes in both epilepsy and control groups, although less frequently in the controls. Instances of microepileptiform activity evolving spatially and becoming detectable in the macroelectrodes were present in epilepsy patients, but not in controls (Stead et al., 2010). These examples underscore the need to consider all available clinical data when interpreting recordings of neuronal firing activity and making implications regarding pathophysiologic mechanisms.

4. Spatial structure of seizures in microelectrode recordings

A number of studies have characterized the single- or multi-unit activity signature during clinical seizures in humans (Babb and Crandall, 1976; Bower et al., 2012; Isokawa-Akesson et al., 1987; Schevon et al., 2012; Truccolo et al., 2011, 2014; Wyler et al., 1982). A striking result shared across these studies is that most of the cases reported demonstrated an absence of intense or synchronized neuronal activity during seizures. Increased firing rates at seizure onset has been reported in as few as 7% of recorded units in spontaneous human seizures (Babb and Crandall, 1976; Bower et al., 2012). Modest firing rate increases of up to 5-fold with a heterogeneous firing pattern across microelectrode sites have been reported even in recordings taken from within the seizure onset zone (Schevon et al., 2012; Truccolo et al., 2011). This runs counter to the expected finding, reported across a wide range of animal model studies (Dichter and Ayala, 1987), of synchronized paroxysmal depolarizations with reduced amplitude action potentials, and a tonic-clonic transition. Paroxysmal depolarizing shifts (PDS), indicative of pathologically strong excitation and characterized by intense firing bursts followed by prolonged afterhyperpolarization,

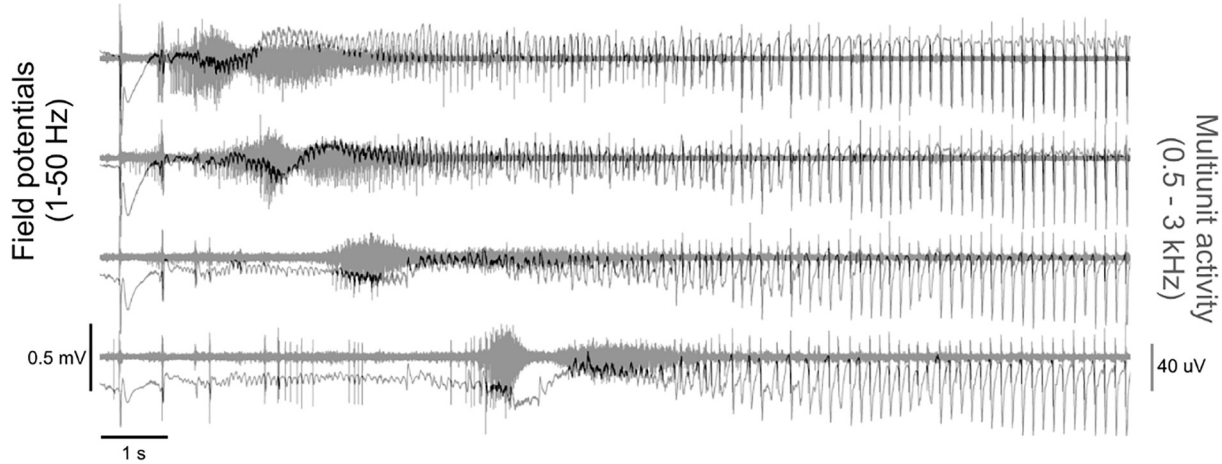

Fig. 1. Ictal wavefront and tonic-clonic transition in a human seizure recorded with microelectrodes. This recording from a Utah microelectrode array implanted in the seizure onset zone of a patient with focal neocortical temporal lobe epilepsy demonstrates the progression of seizure invasion following global seizure onset, indicated by the initial pair of discharges. Data from four channels spaced ~800 μm apart are shown, filtered into low frequencies (1–50 Hz, black) and multiunit activity (0.5–3 kHz) with traces superimposed. The wavefront is clearly visible in MUA, but leaves little trace in the low frequencies and was entirely invisible to adjacent clinical electrodes. A slow expansion of the invaded territory can be seen. The tonic firing converts after 2–3 s to clonic bursting that synchronizes across the invaded territory.

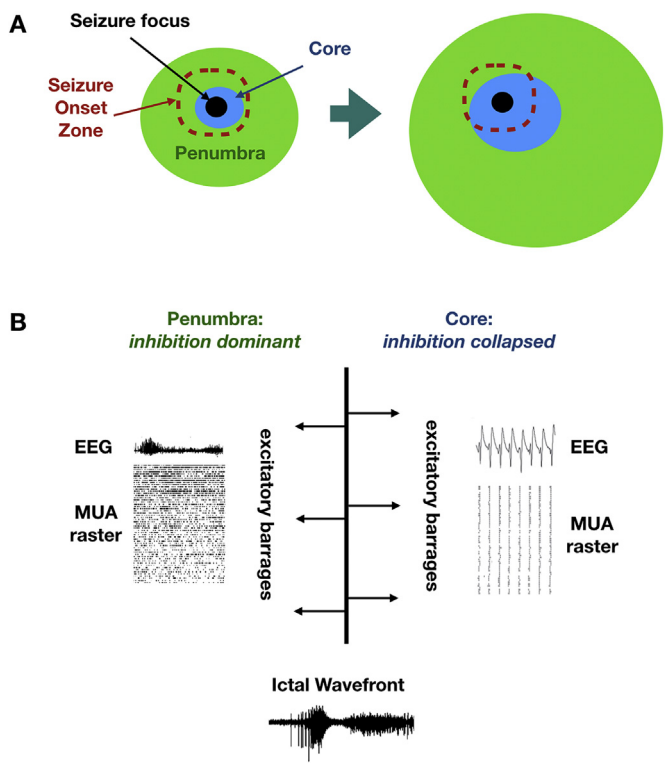

Fig. 2. Schematic descriptions of the dual-territory hypothesis. (A) Relationship between the ictal core (blue) and penumbra (green). The seizure focus is indicated by a black disc within the core. On standard visual EEG review, all activities would appear as a single monolithic event. The seizure onset zone (red dashed line), determined typically from visualized EEG, may include both core and penumbra territories. As the seizure evolves, the penumbra expands faster than the core, and covers a much greater area. (B) The transition between core and penumbra is the ictal wavefront, a brief period of intense, tonic firing with little, if any, manifestation in EEG. Excitatory barrages emanating from the wavefront into both core and penumbra territories result in dramatically different neuronal firing characteristics, depending on the status of inhibition. EEG, however, will show seizure-specific abnormalities in both territories, making it difficult to distinguish them clinically. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

are considered the primary electrographic hallmark of seizures (Goldensohn and Purpura, 1963; Matsumoto and Marsan, 1964).

A small number of cases, reported by one of the groups utilizing Utah arrays implanted into epileptic neocortex (Schevon et al., 2012) and by another group studying microwire recordings in mesial temporal structures (Misra et al., 2018), demonstrated the expected tonic-clonic neural firing pattern in the microelectrode recordings, time-locked to EEG recorded from adjacent electrodes. These involved multiunit firing rate increases up to 30-fold, with a classic tonic to clonic firing pattern (Schevon et al., 2012) and loss of action potential waveshape definition (Merricks et al., 2015). An example of this pattern is shown in Fig. 1. The microelectrode recordings revealed that at varying times in each individual channel, there was an abrupt onset of intense, continuous firing lasting a few seconds (Fig. 1). This band of tonic firing formed an "ictal wavefront" that measurably progressed through the microelectrode recording area at a pace of < 1 mm/s, which is consistent with propagation speeds measured in brain slice models (Trevelyan et al., 2006; Trevelyan et al., 2007a, b). In the wake of the ictal wavefront, the classic pattern of clonic multiunit firing bursts was seen (Fig. 1). These multiunit activity bursts were highly coherent across microelectrode recording sites within the same region, and correlated with ictal discharges recorded from adjacent macroelectrodes. The area demonstrating this hypersynchronized bursting was termed the ictal core. The propagation speed of the ictal wavefront is consistent with the pace of evolution of seizure semiologies such as the well-known Jacksonian march (Penfield and Jasper, 1954). In a classic Jacksonian march, the progressive sequence of clonic activation of primary motor function (e.g. face, then arm, then leg) implies a slowly expanding region of intense, hypersynchronized clonic burst firing advancing through the motor homunculus map in primary motor cortex.

The slow propagation of the ictal wavefront results in variable delays in the ictal transition across channels (Fig. 1). Thus, most channels showed a latency of several seconds from the overall start of the seizure before the ictal wavefront actually arrived at that channel. During this pre-wavefront period, a low-level, heterogenous firing pattern was seen across channels. The activity in this territory at this time is referred to as the "penumbra". Such activity can also be identified in microelectrode recordings that never actually progress into a full ictal event, characterized by the spreading ictal wavefront (Misra et al., 2018; Schevon et al., 2012). Thus, the classification of a given site as penumbral can only ever be done if a seizure is ongoing elsewhere in the brain, and is thus a function of both time and location. This

hypothesized dual structure of the ictal core and penumbra (Fig. 2), delineated by the slow-moving ictal wavefront, provides a cogent view that is capable of reconciling the disparate and apparently contradictory observations of seizure activity sampled in humans and studied in animal models.

It is important to recognize that seizures are dynamic events, with the cortical territory invaded by the seizure evolving with time, as the ictal wavefront slowly expands. In the penumbra, while local neuronal firing rates are variable with at most modest increases in overall rate, the local field (i.e. EEG) amplitude can be very large, on account of the large synaptic currents (typically, both glutamatergic and GABAergic). This large penumbral signal is often misinterpreted as indicative of seizure activity. Thus, even when there is widespread alteration in the EEG signal, the ictal core might be rather small. Based on this reasoning, we contend that the majority of reported ictal microelectrode recordings from epilepsy patients were located outside the seizing brain region (i.e., the ictal core). In these cases, the microelectrode recordings show the variable and heterogenous neural firing patterns indicative of the penumbra.

5. Spatial structure of seizures in macroelectrode recordings

Obtaining a large-area view of the spatial structure of seizures requires utilizing data from subdural or depth macroelectrodes, which cannot directly detect multiunit activity. However, high gamma activity, specifically high frequency oscillations (HFOs) can serve as a useful index of synchronized population firing (Eissa et al., 2016; Ray and Maunsell, 2011), and indeed high amplitude discharges in the ictal core are tightly coupled to bursts of high frequency activity and to corresponding bursts of population firing (Weiss et al., 2013). Thus, ictal HFOs can be used to infer the spatial location and spread of seizures, overcoming the blurring effects of EEG as it is typically visualized. This is of immediate clinical utility, and may be a useful adjunct to the interpretation of intracranial EEG recordings. A measure based on a combination of ictal high gamma signal and phase locking value (phase-locked high gamma, or PLHG) was developed to detect the ictal core and distinguish it from the adjacent penumbra using clinical intracranial EEG recordings (Weiss et al., 2013). In recordings simultaneously obtained from subdural and microelectrodes, the putative ictal core included the region sampled by microelectrodes in cases where the ictal wavefront and tonic-clonic transition were detected, and the direction of ictal core expansion determined from the timelocked intracranial EEG recording matched that of the ictal wavefront detected with microelectrodes. In cases where the tonic-clonic pattern was not present in microelectrode recordings, the putative ictal core (predicted by the PLHG measure) skirted around the microelectrode implant site. Remarkably, the ictal core was detected as close as 1 cm away from the microelectrode site, underscoring how sharp the spatial boundary of the ictal core can be. This study provided validation for ictal HFOs as identified using the PLHG measure as a method of detecting the ictal core, and suggests that an ictal core is present elsewhere in cases where microelectrode recordings show only heterogeneous firing (Weiss et al., 2013). Relating the spatial structure of seizures to interictal HFOs, which have been extensively assessed as independent predictors of surgical outcome (for review, see Frauscher et al., 2017), remains an open area of investigation. There is evidence that ictal and interictal HFOs may be co-located (Zijlmans et al., 2011).

The use of ictal HFOs as a proxy for synchronized neuronal bursting made it possible to assess the extent of the ictal core. Consistent with the small proportion of human microelectrode recordings in which direct seizure invasion can be confirmed, the ictal core as viewed in intracranial EEG recordings was much smaller than the region spanned by visual-range ictal EEG activity (approximately 1–30 Hz). Further, resection of early-appearing ictal core sites was a positive predictor of postoperative seizure control (Weiss et al., 2015). In contrast, resection of sites demonstrating early high gamma activity without the phase-locking property was not a significant surgical outcome predictor. The small and sharply defined extent of the ictal core is promising for epilepsy surgery procedures, in which success relies on the hypothesis that seizures are triggered and sustained from the activity of small, discrete brain regions. The imperative now is to improve our skill in localizing ictal core regions in patient recordings.

6. Identifying single units across the ictal transition

Thus far, we have discussed unit firing at seizure onset in terms of multi-unit activity, rather than single units. Spike sorting and clustering, the process of identifying single units from extracellular microelectrode recordings, and classifying by cell type, permits assessment of separate classes of neurons (Gold et al., 2006; Quiroga et al., 2004). Briefly, action potentials from neurons of the same cell type show similar features to one another, but the exact geometry between the neuron and the recording electrode results in varying extracellular action potential waveforms ("spikes"), due to the flow of ions (Gold et al., 2006). Since neurons must be in different locations, these alterations to the spike shape allow for classification into clusters of spikes that putatively arise from specific neurons. As such, this procedure is heavily dependent on stability of both the single unit waveforms and the technical aspects of the recording itself. Unfortunately, both of these are disrupted by seizures for several reasons (Fig. 3). Mechanisms not intrinsic to neuronal function include movement artifacts from both the patient and attending hospital staff impacting the multi-unit band, and intense population firing causing unit waveforms to collide temporally, making it difficult to separate out action potential spikes from individual neurons (Merricks et al., 2015).

A consequence of intense neuronal firing is an increase in the extracellular K^+ concentration (Somjen and Giacchino, 1985). This affects the repolarization phase of the action potential. Because the repolarization is less extreme, it further reduces the de-inactivation of Na^+ channels, resulting in reduced amplitude of subsequent action potentials, or even depolarization block (Kandel and Spencer, 1961). Such reduced amplitude action potentials occur on the crest of paroxysmal depolarizing shifts (Traub and Wong, 1982). Taken together, these effects result in a wider, shorter waveform originating from the same neuron. Any of these distortions can be sufficient to confound waveshape identification during spike sorting, which may give the impression that a new unit has appeared or a previously active unit has ceased firing (Fig. 3). Indeed, the ability to identify and sort units through seizure onset using standard spike-sorting techniques (e.g. Bower et al., 2012; Truccolo et al., 2011) is a strong indication that the recording site has not directly been invaded by a seizure (Merricks et al., 2015). In contrast, identifying individual spike waveforms during full ictal events can be challenging, affecting the apparent spike rate and ability to assign waveforms to specific neurons (Merricks et al., 2015; Miri et al., 2018). It is important to recognize that the clinically defined seizure onset zone can include territories that remain penumbral throughout the seizure; that is to say, microelectrode location within the seizure onset zone does not guarantee seizure invasion at that site (Merricks et al., 2015; Schevon et al., 2012; Weiss et al., 2013). Thus, the location of recorded cells with respect to the ictal territory as well as the robustness of the spike-sorting methodology need to be considered in the interpretation of ictal single unit recordings.

7. Role of feedforward inhibition in seizure propagation

The cellular mechanisms responsible for the abrupt, dramatic transition in neural activity at the ictal wavefront remain a topic of debate, although much of the confusion almost certainly arises from conflating different types of epileptic discharge. During recruitment of new territories to an existing ictal event, it is reasonable to assume that the driving force is provided by the glutamatergic output of the seizing, "core" territories. Both parvalbumin and somatostatin interneurons

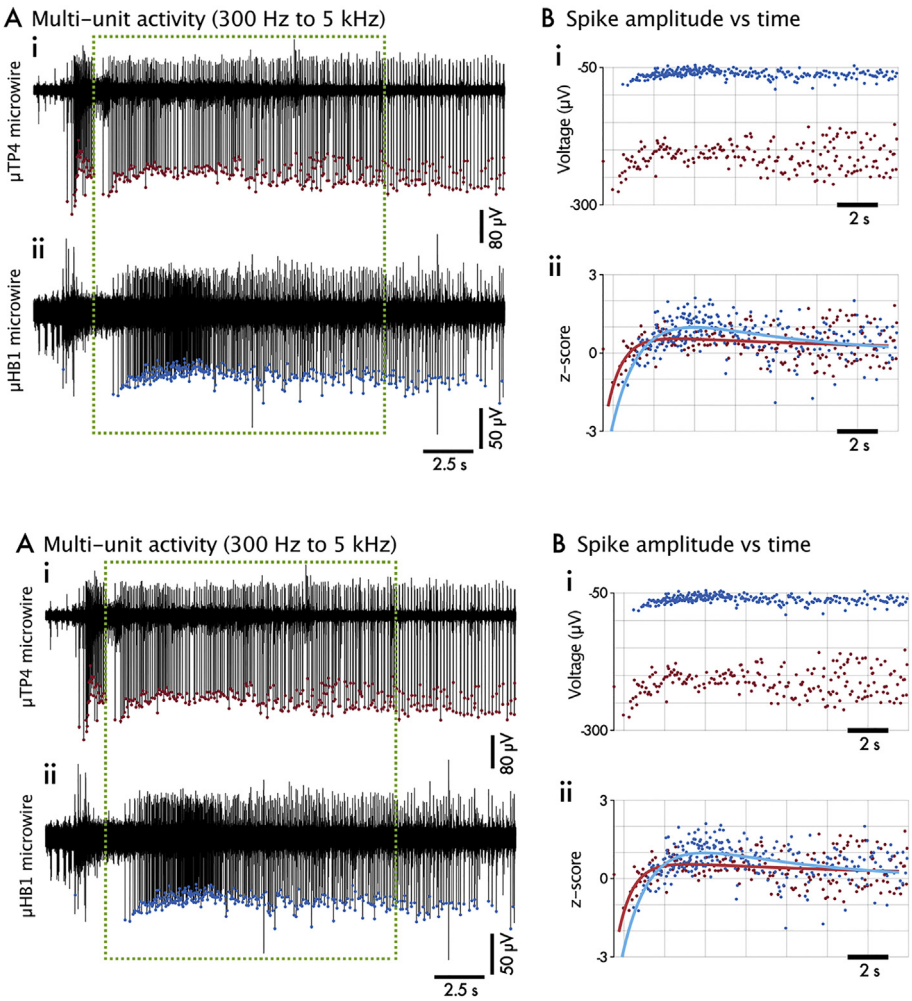

Fig. 3. Action potential waveshape changes at seizure onset in a human hippocampal seizure. Microwire recordings from two Behnke-Fried depth arrays about 1 cm apart captured the ictal transition, each demonstrating a highly visible unit. (A) Onset of tonic firing at different times, after which gradual reduction in amplitude of each unit is evident. (B) Raw and z-scored voltage plots demonstrate a lag in the timing of amplitude reduction between the blue and red units, indicating that this is likely related to ictal activity rather than extracerebral factors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

contribute to the feedforward inhibitory response, and both can sustain extremely high firing rates (bursts of 5–15 action potentials, sometimes exceeding 300 Hz) (Parrish et al., 2019). Although both theoretical and experimental models point to a prominent role for parvalbumin expressing basket cells (Cammarota et al., 2013; Li et al., 2012; Miri et al., 2018; Pouille et al., 2013; Rossignol et al., 2013; Sloviter, 1987; Tan et al., 2011), evidence suggests an equally important role for suppression of dendritic plateau potentials, mediated by NMDA receptors and voltage-gated Ca^{2+} channels, thus explaining the importance also of the somatostatin-expressing interneurons (Lovett-Barron et al., 2012; Parrish et al., 2019).

Pathophysiologic cortical surround inhibition was recognized very early on in the history of in vivo cortical studies (Powell and Mountcastle, 1959; Prince and Wilder, 1967). In surround inhibition, increased excitatory activity triggers a reactive increase in nearby inhibitory firing via feedforward connections, restraining pyramidal firing in adjacent territories (Cammarota et al., 2013; Liou et al., 2018; Wenzel et al., 2017). In a series of experiments using simultaneous calcium imaging and voltage clamp recordings of a mouse in vitro 0 Mg^{2+} model, Trevelyan and colleagues demonstrated that the ictal wavefront phenomenon coincides with a collapse of inhibition (Trevelyan et al., 2006; Trevelyan et al., 2007; Schevon et al., 2012), with a shift from predominately inhibitory to predominately excitatory currents (Ellender et al., 2014; Fujiwara-Tsukamoto et al., 2003). Ahead of this event, there were strong inhibitory current surges that were temporally matched to excitatory discharges behind the wavefront, effectively blocking pyramidal firing (Trevelyan et al., 2006; Trevelyan, 2009). This “inhibitory veto” is a key mechanism that operates in the penumbra and limits the ictal wavefront's advance, and amounts to a built-in defense against seizures (Trevelyan, 2016; Trevelyan and Schevon, 2013). This phenomenon explains findings of increased firing of putative fast-spiking interneurons just after the onset of seizures, identified from extracellular microelectrode recordings. This finding has been reported during hippocampal low voltage fast activity seizure onset types in humans (Elahian et al., 2018), in a range of human seizure types recorded from a neocortically implanted microelectrode array (Ahmed et al., 2014), and in electrographic seizure-like events in ex vivo human peritumoral tissue from patients with gliomas (Pallud et al., 2014). In the human in vivo studies, the recordings were almost certainly taken from the ictal penumbra, as evidenced by the successful use of spike-sorting and clustering in each instance.

This sequence of events gives rise to a characteristic, interneuronal, followed by pyramidal, sequence of activation. A similar sequence of interneuronal first, pyramidal later, activation is also seen in tissue bathed in 4-aminopyridine (4AP) (Gnatkovsky et al., 2008; Uva et al., 2015). See also companion articles in this special issue (de Curtis et al., 2019; Lévesque and Avoli, 2019; Weiss et al., 2019). 4AP blocks A-type potassium channels, which are expressed, at very high levels, in certain types of fast-spiking interneurons. The action of this drug appears to destabilize the resting state of these interneurons, such that they are prone to spontaneous intense bursts of firing, even in the absence of any glutatamatergic drive (Michelson & Wong, 1994; Avoli et al., 2002; Bohannon & Hablitz, 2018). These bursts of activity quickly drive chloride into the postsynaptic cells, and because of repeated bursts of activity this progressively leads to a more chronic, chloride-loaded

state. After each sharp burst of interneuronal firing, most of the chloride entry (if not quite all) is subsequently extruded mainly via the KCC2 co-transporter, and consequently, this transiently increases the extracellular K^+ level, $[K^+]_o$ (Viitanen et al., 2010). This is supplemented by K^+ efflux due to the interneuronal firing, although because interneuron population is quite small, the dominant extracellular K^+ rise is thought to be via KCC2 mediated movement out of pyramidal cells. Both the rises in intracellular Cl^- and in extracellular K^+ are positive feedback mechanisms, the first because it undermines GABAergic inhibition, and the latter because it shifts E_K in a positive direction, and thus depolarizes the resting membrane potential. This secondary $[K^+]_o$ rise is likely to underlie the late pyramidal rebound bursting, perhaps also supplemented by the action of I_h, that can follow the burst of interneuronal activity. The same mechanism was also demonstrated, following optogenetic stimulation of a cross-population of interneurons (ChR expression under the VGAT promoter) in the late-stage of the $0\,Mg^{2+}$ model (Chang et al., 2018). Unlike the early $0\,Mg^{2+}$ activity, which was not examined in this study, the late-stage $0\,Mg^{2+}$ model also appears to be a chloride-loaded state. Under such conditions, paradoxical excitatory effects of inhibitory (chloride) currents have been reported (Burman et al., 2018; Dzhala et al., 2010, and see discussion below).

Despite the similar order of interneuron-pyramidal recruitment, there is an important difference between these 4AP-induced events, and the pattern of recruitment in the slowly propagating events early in the $0\,Mg^{2+}$ model. In the latter, there is additionally a very large glutamatergic drive, arising from already recruited territories. The key experiment is shown in fig. 5 of (Trevelyan et al., 2006) where a careful, voltage-clamp dissection of the synaptic bombardment shows that the glutamatergic drive is orders of magnitude larger than what would normally drive the cell to firing, and yet there is a protracted period lasting several seconds, when there is little pyramidal firing. Notably, the $0\,Mg^{2+}$ model closely parallels human recordings of recruited seizures (Schevon et al., 2012) while there are important differences between human seizures and pure 4AP model events (Liou et al., 2018).

The mechanisms of the inhibitory collapse that presages seizure invasion of cortical tissue have yet to be investigated in detail. These are likely to be multifactorial, and also may vary across epilepsy models and syndromes. One hypothesis relates to weakening of the GABAergic potential due to intracellular accumulation of chloride, which occurs when intense neuronal firing outpaces the ability of the cell membrane to pump chloride ions out. Perturbation of chloride homeostasis has been linked to epileptic activity in ex vivo human tumor tissue studies (Huberfeld et al., 2007; Pallud et al., 2014) and in a mouse hippocampal slice model (Lillis et al., 2012). Immaturity of chloride transporters such as NKCC1 and KCC2 has been proposed to facilitate perinatal seizures, and may explain their poor response to GABAergic anticonvulsants such as phenobarbital and benzodiazepines (Dzhala et al., 2005; Magloire et al., 2018). Chloride dysregulation, modulated by bidirectional optogenetic control of chloride transport in mouse neuronal cultures, has been shown to trigger epileptic activity in vitro, although only in the presence of low levels of chemoconvulsant (Alfonsa et al., 2015). This suggests that chloride dysregulation may be an adjunct for other epileptic mechanisms, but by itself may not be sufficient for ictogenesis.

Another mechanism contributing to inhibitory failure is interneuronal depolarization block. In this scenario, interneurons receiving strong excitatory input abruptly stop or reduce their firing, thus impairing their inhibitory effect. Analysis of human recordings taken from sites not directly invaded by focal seizures have demonstrated cessation of firing of putative fast-spiking interneurons during the seizure (Ahmed et al., 2014). A reduction in interneuronal firing rate has been reported just prior to ictal invasion in mesial temporal structures (Misra et al., 2018). Similar interneuronal firing rate reductions have been observed during seizure-like events in a pharmacological model (Ziburkus, 2006), and in a mouse glioma model associated with disrupted perineuronal nets (Tewari et al., 2018). The role of paradoxical interneuronal firing rate reduction in ictogenesis was explored using a computational model employing a Gaussian activation function that reduces neuronal firing at pathologically high excitation levels, validated against human microelectrode recordings capturing full seizure invasion (Meijer et al., 2015). A possible mechanism for depolarization block is the extreme membrane potential depolarization resulting in deactivation of voltage-gated sodium ion channels (Bikson et al., 2003). However, the reasons and conditions that precipitate this effect, and its precise role in ictogenesis, remain poorly understood.

8. Network effects of the ictal wavefront

Long clinical experience with EEG recordings of human seizures as appearing to spread rapidly through large brain areas has led to the hypothesis that seizures are generated from large-scale pathological networks (Spencer, 2002). Network analyses of ictal and interictal EEG have demonstrated increased connectivity between seizure-generating areas and related structures (Kramer et al., 2010; Schevon et al., 2007), and computational modeling based on long-range interictal connectivity alone has been shown to predict surgical outcome following resection (Jirsa et al., 2017; Khambhati et al., 2016; Sinha et al., 2017). These observations, at first glance, are difficult to reconcile with the notion that seizures are driven from a limited, sharply delineated brain area.

A key reason for the difficulty in mapping seizing brain territories in the clinical setting is the fact that the ictal wavefront, i.e. the electrophysiological event defining the interictal-ictal transition at a given location, leaves remarkably little trace in the "Berger band" range of 1–30 Hz. Thus, the wavefront cannot generally be detected using standard visual EEG interpretation techniques (Meijer et al., 2015; Schevon et al., 2012; Smith et al., 2016). This explains why ictal HFOs as defined by the PLHG metric are delayed relative to the time of seizure onset, as it takes time for the ictal wavefront to pass through a macroelectrode's listening sphere, and for the tonic firing to transition to the hypersynchronized clonic bursting that gives rise to the high gamma signature (Meijer et al., 2015; Weiss et al., 2013). There are several possible explanations for the lack of macroscopic signature of the ictal wavefront. Tonic firing cannot be sustained for more than a few seconds due to intrinsic neuronal mechanisms such as spike rate adaptation (Beverlin et al., 2012; Lytton and Omurtag, 2007; Marcuccilli et al., 2010; Meijer et al., 2015). For this reason, the spatial extent of the ictal wavefront is limited to ~1 mm (Schevon et al., 2012) which may result in its obscuration by spatial averaging due to the listening sphere of clinical electrodes being substantially larger than 1 mm. Another possible explanation is that the lack of temporal organization during tonic firing does not easily permit propagation across spatial scales via volume conduction, which is a basic requirement for producing oscillations detectable in EEG (Eissa et al., 2016; Nunez and Srinivasan, 2006).

Direct detection of the ictal wavefront in clinical intracranial EEG recordings, while generally impossible using standard visual EEG review, can be done using novel biomarkers derived from the EEG signal. DC shifts, or power fluctuations in the infradelta band that may be detectable in clinical EEG recordings, may serve as a useful indicator of ictal wavefront passage (Fig. 1). As large increases in extracellular potassium have been associated with DC shifts (Aiba and Noebels, 2015), it is therefore conceivable that intense population firing, even if too asynchronous to generate an EEG oscillation, can lead to a DC potential fluctuation. Another potential biomarker makes use of the high amplitude discharges that are prominent in the ictal EEG, as evidenced by both human and animal recordings (Liou et al., 2018; Martinet et al., 2017; Smith et al., 2016; Trevelyan et al., 2007). While these EEG oscillations may give the illusion of synchronized activity (Jiruska et al., 2013; van Drongelen et al., 2003; Zaveri et al., 1999), EEG discharges are in fact composed of rapidly moving, traveling waves with speeds

ranging from 20 to 100 cm/s (Alarcon et al., 1997; Emerson et al., 1995; Gonzalez-Ramirez et al., 2015; Smith et al., 2016; Trevelyan et al., 2007) and that traverse long distances (Eissa et al., 2017; Liou et al., 2017, 2018; Martinet et al., 2017; Sabolek et al., 2012). Moreover, the direction of discharge travel is dependent on the location of the wavefront relative to the recording site (Smith et al., 2016; Trevelyan et al., 2007). Specifically, ictal discharges radiate away perpendicular to the wavefront, i.e. outward through the penumbra and inward into the core (Smith et al., 2016). A comparison of traveling wave speed in the two seizure territories shows slower speeds in the penumbra, where inhibition is presumably intact, compared to speeds in the core, where inhibition has failed (Sabolek et al., 2012; Smith et al., 2016). This spatial organization of fast and slow moving waves, i.e. fast-moving traveling waves of excitatory bursts and the slow moving ictal wavefront, may be described using an analogy. Imagine an invisible slow-moving train, representing the ictal wavefront, near a stationary observer (i.e. an electrode). The stationary observer cannot see the train, but can hear its whistle. The sound of the whistle travels much faster than the train and can be detected quickly at far distances. As the train passes the observer, the observer experiences a change in direction of the train's whistle. In much in the same way, there is a shift in traveling wave direction as the ictal wavefront passes through the recording site (Smith et al., 2016; Trevelyan et al., 2007).

The mechanisms by which the ictal wavefront generates EEG discharges can be attributed to a dual, scale-dependent role of feedforward inhibition. In the unrecruited region just outside the wavefront, the intense excitatory firing is met by enhanced feed-forward inhibition. Initially, this restrains the wavefront, but eventually inhibition collapses and the wavefront slowly propagates outward (Trevelyan et al., 2007; Trevelyan et al., 2006; Trevelyan, 2009). In contrast, more distal territories show engaged and intact feed-forward inhibition that produces EEG oscillations (Eissa et al., 2017, 2018). The close temporal alignment of EEG oscillations produced in the ictal core and in the penumbra, together with the rapid pace of synaptic distribution, results in the appearance of a large, monolithic, synchronized event. Rapid synaptic distribution to distant regions with impaired inhibitory function can also result in seeding independent seizure foci, which can further enhance the total brain area impacted by prominent EEG activity (Liou et al., 2018). These hypothesized mechanisms can explain apparent wide-area cortical activation from a small initial seizure generator.

Seizure termination, an inherently wide-area event, can also be explained through the dual-spatial hypothesis (Eissa et al., 2017; González-Ramírez and Kramer, 2018; Smith et al., 2016). In simple terms, seizure termination occurs after the ictal wavefront weakens to the point where the excitatory bursting it is generating can no longer overcome the effects of the prolonged afterhyperpolarization that follows paroxysmal depolarization. In this scenario, the ictal wavefront is annihilated, and the fast-moving traveling waves abruptly cease (Smith et al., 2016).

9. Conclusion

By considering the electrophysiological signatures of seizures across scales from single unit activity to local field potential, a spatiotemporal structure emerges in which seizures are generated from small discrete foci and constrained by a much larger surrounding area of feedforward inhibition. These small foci nevertheless can have large-area network effects. The existence of human microelectrode recordings of seizures, even with all the attendant limitations of such data, are critical for accurately identifying the driving events and mechanisms of focal seizures.

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Competing interests

The authors have no competing interests to declare

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