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Emergent network topology at seizure onset in humans

Mark A. Kramer [a,*], **Eric D. Kolaczyk** [b], **Heidi E. Kirsch** [c]

[a] *Center for BioDynamics, 111 Cummington Street, Boston University, Boston, MA 02215, USA*
[b] *Department of Mathematics and Statistics, Boston University, Boston, MA 02215, USA*
[c] *Department of Neurology, University of California, San Francisco, CA 94143-0138, USA*

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Summary Epilepsy — the world's most common serious brain disorder — is defined by recurrent unprovoked seizures that result from complex interactions between distributed neural populations. We explore some macroscopic characteristics of emergent ictal networks by considering intracranial recordings from human subjects with intractable epilepsy. For each seizure, we compute a simple measure of linear coupling between all electrode pairs (more than 2400) to define networks of interdependent electrodes during preictal and ictal time intervals. We analyze these networks by applying traditional measures from network analysis and identify statistically significant global and local changes in network topology. We find at seizure onset a diffuse breakdown in global coupling, and local changes indicative of increased throughput of specific cortical and subcortical regions. We conclude that network analysis yields measures to summarize the complicated coupling topology emergent at seizure onset. Using these measures, we can identify spatially localized brain regions that may facilitate seizures and may be potential targets for focal therapies.

Introduction

An important, perhaps fundamental, characteristic of seizures is the emergence of macroscopic order as observed in electrical activity recorded at the scalp and cortical surface. This order appears as, for example, ripples (Grenier et al., 2003) and beta frequency oscillations (Schiller et al., 1998) at seizure initiation, continues with increased synchronization during the middle phase of seizures (Schiff et al., 2005), and concludes as an abrupt cessation of activity (Schindler et al., 2007) at seizure termination. For focal epilepsies these macroscopic changes begin in spatially localized regions (i.e., the epileptogenic zone) and spread outward to affect other parts of the brain (Braizer, 1973). When focal epilepsy does not respond to seizure medications, the epileptogenic zone may be identified and surgically removed (Engel, 1996). Improved imaging and analysis techniques have refined but not substantially altered this procedure since the middle of the 20th century; a better understanding of how macroscopic order emerges

* Corresponding author. Tel.: +1 617 353 1493.
E-mail addresses: mak@bu.edu (M.A. Kramer), kolaczyk@math.bu.edu (E.D. Kolaczyk), Heidi.Kirsch@ucsf.edu (H.E. Kirsch).

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from the epileptogenic zone would help to refine surgical techniques and perhaps produce alternative therapies.

To characterize the spatiotemporal dynamics of ictal activity researchers have applied linear and nonlinear measures to recordings from individual electrodes (e.g., the power spectrum and correlation dimension) and from electrode pairs (e.g., coherence and phase synchronization). For a small number of electrodes, the latter results are easily displayed and interpreted. For example, one may compute the cross-correlation or coherence to infer properties of seizure propagation between a few electrode pairs (Braizer, 1973; Bertashius, 1991; Kramer et al., 2007). But, as the number of electrodes increases, interpreting the coupling results becomes much more complicated: the zero lag cross-correlation between all electrode pairs from an 8-by-8 subdural electrode grid produces $(64 \times 63)/2 = 2016$ values. How does one analyze the topological organization of these results and deduce the brain regions important for seizure facilitation or propagation? Similar challenges now face many neuroscientists as improved imaging and acquisition techniques yield ever-expanding quantities of multivariate, coupled data.

Network analysis provides many techniques to interpret such complicated coupling topologies. It has been used to characterize, for example, the network of electric power grids in the western United States (Watts and Strogatz, 1998) and the network of hyperlinks between different Internet web pages (Broder et al., 2000). In both cases, the network of interactions — among hundreds or millions of entities — is quite complex, yet has a topology whose structure is amenable to natural forms of summary and characterization. Recent studies suggest that networks derived from brain activity possess a ''small-world'' topology in which most connections are local and few are distant (Bassett and Bullmore, 2006; Ponten et al., 2007). Bispectral analysis of human intracranial EEG recordings has shown that the small-world characteristics of macroscopic neural activity increase at seizure onset (Wu et al., 2006), and simulation studies suggest that small-world networks better support phase synchronization and seizure-like activity (Percha et al., 2005; Netoff et al., 2004). Yet the role of small-world topology in seizures remains unclear; an *in vitro* model of stroke-induced epilepsy suggests that seizure-like discharges occur more frequency in random (not small-world) networks (Srinivas et al., 2007). In this manuscript, we attempt to further characterize the topological properties of the seizing human cortex. To do so, we apply a variety of network analysis measures to high-dimensional, multivariate electrocorticographic (ECoG) data recorded simultaneously from more than 70 electrodes in each of four human subjects with epilepsy. We show how — in this small group of subjects — the emergent coupling between electrodes changes at seizure onset and warrants further study. We also propose potential targets for therapeutic intervention identifiable only in the context of the entire network of coupled activity.

Methods

In this section we describe the human subject data and define the coupling measure and six measures of network analysis. For the primary subject, we show an example of the coupling between electrodes preceding and immediately following seizure onset, and note the qualitative differences. We apply the network analysis measures to quantify the changes in coupling that occur at seizure onset in the primary subject and in the aggregate group of four subjects in Results.

Recording equipment

Intracranial EEG were collected using the Viasys Nicolet BMSI 6000 NT Long Term Monitoring System (Viasys, Madison, WI, USA). Data were recorded from up to 128 channels at a fixed sampling rate of 400 Hz and bandpass filtered at a frequency range of 0.5—50 Hz (Butterworth filter) for later processing. A board-certified neurophysiologist (HEK) reviewed each dataset and verified the integrity of the recording. No artifacts (e.g., due to faulty electrode or recording cable performance) were identified.

Human subject data

Data were collected from four subjects with intractable epilepsy who had undergone electrode implantation as part of clinical care at the University of California, San Francisco (UCSF) Epilepsy Center. The implanted electrodes consisted of: a single 8-by-8 subdural electrode grid supplemented by subdural electrode strips and/or depth electrodes. All strip and grid electrodes were 4 mm diameter platinum—iridium discs embedded in 1.5 mm thick silastic sheet with 2.3 mm diameter exposed surfaces and 10 mm spacing between the discs. Depth electrodes were 1 mm in diameter and had four or six platinum contacts spaced 10 mm apart. To observe multiple seizures, physicians recorded ECoG data continuously for several days. For each subject, ictal data were extracted from the clinical record and analyzed for research purposes in accordance with UCSF and Boston University human subjects guidelines.

We begin with a description of the primary human subject (a 39-year-old right handed woman with medically refractory complex partial seizures) whose ECoG data we analyze in detail. Scalp video-EEG telemetry captured nine seizures that all arose from the left frontotemporal region (this was her dominant hemisphere for language) with some semiological features atypical for mesial temporal onset. Because of the relatively diffuse scalp localization and the origin in the language dominant hemisphere, it was decided to implant subdural electrodes to better determine focal ictal onset and to map functional brain regions. We show the craniotomy for this subject in Fig. 1a. In this figure, the left hemisphere of the brain is exposed. Approximately 44 of the 64 grid electrodes over the left frontotemporal region are visible; the remaining 20 electrodes are hidden below the edge of the craniotomy. The tails for the electrode strip (over the left suborbital frontal lobe) and of two, six-contact, left hippocampal depth electrodes are visible at the middle left and lower right portions of the figure, respectively; we indicate the location of these electrodes in the X-ray image shown in Fig. 1b. In Fig. 1c we show a three-dimensional reconstruction of the subject's cortex with the 8-by-8 electrode grid superimposed. For simplicity the strip and depth electrodes are not shown in this figure.

Physicians recorded ECoG data continuously from the primary subject for 5 days and detected nine seizures. Each seizure began near the distal end of both depth electrodes in the hippocampus and, approximately 15 s later, was observed on the (cortical) electrode grid. ECoG epochs containing eight of the patient's seizures and recorded simultaneously at 76 electrodes were extracted from the clinical record and saved for further analysis. (We note that one archived seizure data file was corrupted and no longer available for extraction, and that we omitted from analysis one set of six-contact depth electrodes that was saturated throughout the recording.)

For the primary subject, we analyze the eight recorded seizures in detail. We also apply three summary measures to three additional human subjects described below. The first was a 31-year-old