NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Microscale spatiotemporal dynamics during neocortical propagation of human focal seizures

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ARTICLE INFO

Article history:
Received 8 April 2015
Accepted 6 August 2015
Available online xxxx

Keywords:
Epilepsy
Collective dynamics
Secondary generalization
Cortical waves
Neural state segmentation

ABSTRACT

Some of the most clinically consequential aspects of focal epilepsy, e.g. loss of consciousness, arise from the generalization or propagation of seizures through local and large-scale neocortical networks. Yet, the dynamics of such neocortical propagation remain poorly understood. Here, we studied the microdynamics of focal seizure propagation in neocortical patches (4 × 4 mm) recorded via high-density microelectrode arrays (MEAs) implanted in people with pharmacologically resistant epilepsy. Our main findings are threefold: (1) a newly developed stage segmentation method, applied to local field potentials (LFPs) and multiunit activity (MUA), revealed a succession of discrete seizure stages, each lasting several seconds. These different stages showed characteristic evolutions in overall activity and spatial patterns, which were relatively consistent across seizures within each of the 5 patients studied. Interestingly, segmented seizure stages based on LFPs or MUA showed a dissociation of their spatiotemporal dynamics, likely reflecting different contributions of non-local synaptic inputs and local network activity. (2) As previously reported, some of the seizures showed a peak in MUA that happened several seconds after local seizure onset and slowly propagated across the MEA. However, other seizures had a more complex structure characterized by, for example, several MUA peaks, more consistent with the succession of discrete stages than the slow propagation of a simple wavefront of increased MUA. In both cases, nevertheless, seizures characterized by spike-wave discharges (SWDs, ~2–3 Hz) eventually evolved into patterns of phase-locked MUA and LFPs. (3) Individual SWDs or gamma oscillation cycles (25–60 Hz), characteristic of two different types of recorded seizures, tended to propagate with varying degrees of directionality, directions of propagation and speeds, depending on the identified seizure stage. However, no clear relationship was observed between the MUA peak onset time (in seizures where such peak onset occurred) and changes in MUA or LFP propagation patterns. Overall, our findings indicate that the recruitment of neocortical territories into ictal activity undergoes complex spatiotemporal dynamics evolving in slow discrete states, which are consistent across seizures within each patient. Furthermore, ictal states at finer spatiotemporal scales (individual SWDs or gamma oscillations) are organized by slower time scale network dynamics evolving through these discrete stages.

Introduction

Epilepsy is one of the major neurological disorders affecting about 65 million people worldwide (Thurman et al., 2011). In the specific case of focal epileptic seizures, seizures appear to initiate in a localized region

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http://dx.doi.org/10.1016/j.neuroimage.2015.08.019
1053-8119/

(seizure focus) and then spread or propagate to other brain areas via local and large-scale network interactions. In particular, large spread throughout neocortical areas, clinically referred to as secondary generalization to distinguish it from primarily generalized seizures, can be the crucial event leading to loss of consciousness or impairment in motor or language function. Despite its importance, neocortical propagation of focal seizures remains poorly understood. Advances in this front could lead to new therapies based on early seizure detection followed by guided drug delivery or electrical stimulation to prevent spread (Morrell, 2011). In addition, the problem is also relevant for the general understanding of multiscale neural dynamics in neocortical networks.

Recent advances in MEA recordings have opened a new window into seizure propagation by allowing the simultaneous recordings of ensembles of single unit activity (SUA), localized multiunit activity (MUA) and high-density spatial local field potentials (LFPs) over neocortical patches during seizures in people with intractable epilepsy (Keller et al., 2010; Truccolo et al., 2011, 2014; Schevon et al., 2008, 2012). Schevon et al. (2012) addressed seizure propagation in neocortical patches by examining how peaks in MUA rate evolved in time and space during seizures. In some of the patients, where the MEA was away from the putative seizure onset area, they observed that the peak in MUA slowly traveled across the MEA. Their main proposed hypothesis is that this slow MUA peak propagation reflects an ictal wavefront advancing over areas under a feedforward inhibitory veto ("penumbra" areas), which needs to be broken in order for a distal area to be recruited into the ictal state.

Here, we adopted an approach to segment and track the evolution of different seizure stages based on several MUA and LFP features, not only MUA peaks. The focus is on MUA, instead of single neuron spiking activity (Truccolo et al., 2011, 2014), since the former more easily relates to the bulk population activity. We examined the time evolution of all of these features and corresponding stages on 4 mm × 4 mm neocortical patches recorded via 96-channel MEAs in 5 patients. Etiologies consisted of four cases of mesial temporal sclerosis and one case of cortical dysplasia. Recorded patches included middle or superior temporal gyri. In all these cases, the MEA was implanted in an area outside the putative seizure onset zone, such that the ictal activity examined here required propagation.

Our results indicate that seizures spread through a succession of discrete stages characterized by specific and reproducible spatiotemporal dynamics occurring at the time scale of seconds. These dynamics involved, in some of the seizures, the propagation of what appeared to be a slow wavefront as observed previously by others (e.g. Schevon et al. 2012). However, in several other seizures this phenomenon was not observed, even though the related neural dynamics showed clear features of ictal states (e.g. MUA-LFP phase-locking during 2–3 Hz spike-wave discharges). Finally, depending on the seizure type, these stages influenced the propagation patterns of individual spike-wave discharges (SWDs) or gamma oscillations, which occurred at a finer time resolution.

Materials and methods

Patients and clinical/research MEA recordings

Research was approved by local Institutional Review Boards at Massachusetts General Hospital/Brigham and Women's Hospitals (Partners Human Research Committee) and at Rhode Island Hospital. Five patients with pharmacologically intractable focal epilepsy freely consented to the study. These patients underwent neuromonitoring for seizure localization and functional assessment of neocortical areas via standard clinical recordings based on subdural electrocorticograms (ECoGs), strip electrodes, and depth electrodes placed in subcortical structures, as decided by a clinical team completely independent from this research. Following the clinical team's decision, patients were contacted by the research team. The five patients in this study (P1–P5) were implanted for a period of 5–14 days with an additional 10 × 10 (4 mm × 4 mm) NeuroPort MEA (Blackrock Microsystems, Utah; Hochberg et al., 2006; Schevon et al., 2008; Truccolo et al., 2008; Waziri et al., 2009; Truccolo et al., 2011) in a neocortical area expected to be resected with high probability, in either the middle (P1, P3, P4, P5) or superior (P2) temporal gyrus. This research probe consisted of 96 recording platinum-tipped silicon probes, with a length of either 1-mm (P4, P5) or 1.5-mm (P1, P2, P3), corresponding to neocortical layer III as confirmed by histology after resection. Seizures were identified by experienced encephalographers (S.S.C. and A.S.B.) via inspection of ECoGs and clinical manifestations recorded in video. Seizure onsets were detected ~2 cm (P1, P4, P5) or ~3 cm (P2 and P3) away from the research MEA, based on the clinical ECoG electrodes. These recordings were therefore outside the seizure onset zone. Details of the clinical cases and seizures are given below. These data have been previously used in another study (Truccolo et al., 2014). Participants 1 to 5 in that earlier study correspond here to patients P5, P3, P2, P4 and P1 respectively.

Patient P1 (mesial temporal sclerosis)

Patient P1 was a 45-year-old right-handed man at the time of his surgery, with a history of medically refractory focal seizures which included impairment of consciousness and observable motor components. Specifically, his seizures lasted 1–2 min, started with arousal and bilateral arm/leg extension, followed by leftward head deviation, left arm flexion, and generalized tonic–clonic activity. He underwent placement of grids, strips and depths over the right hemisphere. During secondary generalization, the seizures spread to the location of the NeuroPort MEA in the middle temporal gyrus and beyond. The MEA site was in the irritative zone, but not in the epileptogenic lesion. It was not clear whether the site was in the symptomatogenic zone. The patient underwent a right temporal lobectomy and has remained seizure-free for 4 years while on medications (ILAE surgical outcome scale 1, last update 28 months post-surgery).

Patient P2 (mesial temporal sclerosis)

Patient P2 was a left-handed, 32-year-old man at the time of his surgery, with a history of pharmacologically intractable focal seizures which included impairment of consciousness, autonomic and motoric components. Seizures began when he was 10 years old. His seizures were characterized by sudden onset of nonsensical speech followed by staring and unresponsiveness with head turning to the right, automatisms, and posturing involving the right more than left arm and hand. These spells lasted ~1–2 min. MRI suggested left (dominant) temporal polymicrogyria. He underwent placement of grids and strips to delineate the seizure focus with respect to this area of abnormal sulcation. Seizures were found to emanate from the mesial temporal structures (including the MEA implant site) and beyond. The MEA site was not in the epileptogenic lesion or in the irritative zone. It was not clear whether the site was in the symptomatogenic zone. The patient underwent a left temporal lobectomy. Histology showed extensive sclerosis in the hippocampus and mild gliosis with no evidence of cortical dysplasia in the microelectrode implant site. He has been seizure-free for 3.5 years (ILAE surgical outcome scale 1, last update 40 months post-surgery).

Patient P3 (cortical dysplasia)

Patient P3 was a 25-year-old, left-handed woman at the time of her 7-day phase II video-EEG study. Her seizures began at age 14 and were medically intractable focal seizures which included some impairment of awareness and autonomic components. Her events began with an aura of nausea and/or a "tunneling" sensation, then a flattening of affect,

Please cite this article as: Wagner, F.B., et al., Microscale spatiotemporal dynamics during neocortical propagation of human focal seizures, NeuroImage (2015), http://dx.doi.org/10.1016/j.neuroimage.2015.08.019