ONLINE METHODS

Participants, clinical electrodes and recordings. Four patients (A, B, C and D, ages 21–52 years (mean 29.7), three women) with medically intractable focal epilepsy underwent clinically indicated intracranial cortical recordings using grid electrodes for epilepsy monitoring[38,39]. Clinical electrode implantation, positioning, duration of recordings and medication schedules were based purely on clinical need as judged by an independent team of clinicians. Patients were implanted with intracranial subdural grids, strips and/or depth electrodes (Adtech Medical Instrument Corporation) for 5–10 d in a specialized hospital setting until data sufficiently identified the seizure focus for appropriate resection. Continuous intracranial EEG was recorded with standard recording systems (XLTEK) and captured many seizures. Seizure onset times were determined by an experienced encephalographer (S.S.C.) through inspection of ECoG recordings, referral to the clinical report of the ECoG and clinical manifestations recorded on video. The number of seizures varied across the participants. Owing to operational issues, not all of these seizures were recorded or provided data with a high signal-to-noise ratio. Among data sets with clearly separable single units, we selected eight different seizures among the four participants. All steps of the analysis of intracranial EEG data were performed using Neuroscan Edit software (Compumedics) and custom designed Matlab (MathWorks) software.

Participant A. Participant A was a right-handed woman 52 years old at the time of the continuous 8-d video and invasive EEG monitoring study. She had a history of complex partial seizures with occasional secondary generalization beginning at the age of 4 and typically suffered from 10–15 events per day. Her seizures usually presented with sudden speech arrest associated with confusion and repetition of the activity she was doing just before the onset of the seizure. Magnetic resonance imaging (MRI) showed a large lesion in the left hemisphere extending from the occipital region to the temporal region, which was consistent with encephalomalacia. Moreover, a positron-emission tomography (PET) scan showed hypometabolism in the left occipital, temporal and parietal regions. On the basis of these findings, the patient was implanted with a combination of a subdural grid and strip electrodes and depth electrodes over the left hemisphere. The NeuroPort microelectrode array was placed in the middle temporal gyrus in a region of cortex nearly certain to be resected. The distance to the nearest ECoG electrode where seizure onsets were detected was ~2 cm.

There were several seizures throughout the recordings; all lasted about 1 min or less and had a similar electrographic pattern. They typically began with low-amplitude, fast activity—up to 300 μV, ~30 Hz—in an anterior temporal strip, sometimes with an associated burst of polyspike activity in an occipital strip, or began at an occipital site (**Fig. 1**). Simultaneously, there was a generalized suppression of the grid activity beginning in the posterior inferior quadrant and then spreading to encompass the entire grid. After the onset, there was a buildup of high frequencies and higher amplitudes (up to 500 μV) in the posterior inferior quadrant and occipital region. Sometimes, rhythmic ECoG spikes occurred in the anterior temporal strip and posterior temporal depths.

At the conclusion of the study the patient underwent resection of the left anterior temporal lobe. Pathology showed hippocampal sclerosis with secondary cortical gliosis. The patient remained seizure free for 1 year after the resection, but seizures returned after this period.

Participant B. Participant B was a right-handed man 21 years old at the time of the continuous 8-d video and invasive EEG monitoring study. He had suffered from seizures since at least age 15. Most of his events were characterized by a blank stare and oral automatisms accompanied by stiffening and posturing of the right hand. He was implanted with a series of strip electrodes covering the left frontal and temporal regions. The NeuroPort array was placed in the middle temporal gyrus about 1–2 cm posterior to the temporal tip. The distance to the nearest ECoG electrode where seizure onsets were detected was ~2 cm. Sharp waves were observed interictally in the posterior temporal regions. Four seizures, all with similar clinical and electrographic features, were recorded. Seizures were characterized by a left gaze preference and tonic and then clonic movements of the right arm. Electrographically, the seizures began with a generalized burst of sharp waves followed by sharp wave complexes that were maximal in mesial temporal leads. The patient subsequently underwent a left temporal lobectomy. Pathological examination of the tissue revealed mild dysplastic changes in the lateral temporal neocortex and gliosis and moderate neuronal loss in regions CA4 and CA3 of the hippocampus. Thirteen months after his surgery, he remains seizure free.

Participant C. Participant C was a right-handed woman 22 years old at the time of the continuous 8-d video and invasive EEG monitoring. She had a history of partial seizures with rapid generalization beginning around 14 years of age and typically suffered four to seven attacks per day. Several different clinical manifestations of her seizures had been observed, including events that would occur out of sleep and consist of screaming and whole body shaking. She also had spells of staring, unresponsiveness and oral automatisms. These occasionally progressed to generalized tonic-clonic activity or atonia. Imaging studies including MRI and PET showed diffuse atrophy and questionable abnormalities in the right frontal lobe. Previous EEG monitoring suggested a right-sided region of epileptogenesis, emanating from the either the right frontal or temporal lobe, so she was implanted with extensive subdural coverage of the right hemisphere. The NeuroPort array was implanted in the middle frontal gyrus within a broad onset region.

There were a total of 30 definite seizures throughout the recording session. Each clinical seizure was characterized by a subtle head turn and drop to the right or left that lasted 10–15 s. Electrographically, the seizures fell into four different groups depending on the presence of generalized EEG spikes as well as the seizure onset evolution. The seizures incorporated into our analysis are described in detail below:

Seizure 1 began with an onset of generalized epileptiform spiking activity, followed by 1–2 s of generalized attenuation and then prominent spike and wave activity. Clinically, the subtle head turn corresponded to the generalized EEG spike discharges. The electrographic seizure lasted approximately 11 s.

Seizure 2 started with a generalized EEG spike followed by 1–2 s of attenuation and then the onset of a generalized, high-frequency buzz lasting 4 s. This was followed by EEG spike and wave discharges in the frontopolar strip, the subfrontal strip and segments of the grid of electrodes, lasting 5 s. The seizure corresponded clinically to subtle head movements after the onset of the seizure. The electrographic seizure lasted approximately 11 s.

At the conclusion of the study the patient underwent resection of the left temporal lobe. Pathology confirmed the lesion to be a cortical dysplasia. Six months after surgery the patient had experienced a reduction in the overall number of seizures but continued to have episodes of behavioral arrest.

Participant D. Participant D was a right-handed woman 24 years old at the time of the continuous 4-d video and invasive EEG monitoring study. She had a history of complex partial seizures beginning at the age of fourteen. Her seizures tended to present with staring spells, gulping sounds, a general feeling of heat and hand automatisms. She often had no awareness of the events. Previous EEG monitoring suggested that these seizures originated from the left anterior temporal region. MRI showed a large lesion in the left temporal lobe, believed to be a glioma. In accordance with the above findings, the patient was implanted with a combination of subdural and depth electrodes focused on the left temporal region. The NeuroPort research electrode was placed in the middle temporal gyrus about 2 cm posterior to the temporal tip. The distance to the nearest ECoG electrode where seizure onsets were detected was ~4 cm.

There were five electrographic seizures captured over the course of the 4-d recording session: three typical clinical seizures lasting 20–40 s and two subclinical seizures of shorter duration. The three clinical seizures manifested with staring spells and the participant's report of a general sensation of heat. The EEG revealed the electrographic onset for each of these seizures in the anterior temporal region with a typical subsequent spread across the superior and middle anterior strip electrodes, as well as to the depth electrodes.

At the conclusion of the study, the patient underwent a left anterior temporal lobectomy, a left amygdalohippocampectomy and a lesionectomy of the posterior temporal lobe. Pathology determined the lesion to be a low-grade glioneuronal tumor. At last evaluation, 6 months after surgery, the patient was seizure free.

Microelectrode array location, recordings and analysis. Approval for these studies was granted by local Institutional Review Boards (Partners Human Research Committee) and participants were enrolled after informed consent was obtained. The implanted NeuroPort array (Blackrock Microsystems), which has been used in several previous studies[26–31], is a 4 mm × 4 mm microelectrode array composed of 100 platinum-tipped silicon probes. Arrays with 1.0-mm

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electrode lengths were implanted in the middle frontal gyrus (participant C) and middle temporal gyrus (participants A, B and D). The array's distance to the nearest ECoG electrode containing seizure onsets, calculated using MRI and post-operative computed tomography registration, was calculated as ~2 cm in participants A and B, ~4 cm in participant D, and within a broad seizure onset zone for participant C. Histology after resection confirmed that the tips of the electrodes were in the lower portion of layer III in two of the three cases (A and B). In these two cases, the histology around the array appeared normal. In a third participant (D), the histology of the cortex also appeared normal but the exact path of the electrode could not be reconstructed. In the fourth participant (C), the array was placed in an area of cortex that was the suspected focus and looked abnormal on visual inspection during the time of the initial craniotomy. Ultimately, however, this area was not resected. For detection and extraction of extracellularly recorded action potentials, the analog signal (0.3 Hz–7.5 kHz) from each of the 96 active electrodes was sampled at 30 kHz, online digitally high-pass filtered (250 Hz–7.5 kHz, fourth-order Butterworth filter) and automatically amplitude thresholded (Cerebus system, Blackrock Microsystems). The extracted waveforms were sorted using standard methods[40] and Offline Sorter (Plexon) and were tracked to ensure that spike rate changes were not obvious artifacts due to waveform changes. Spike sorting was performed on projections of waveforms into feature spaces given by principal components and a nonlinear energy measure. (This nonlinear energy measure is akin to the product of the raw amplitude times the derivative of the signal; Offline Sorter User Guide, version 3, Plexon). In the case of consecutive seizures occurring within ~1 h, we were able to track the neuronal spike waveforms and ensure that the same unit was being isolated. Single-neuron bursting rates were computed as previously described[41]. Classification of neurons into putative interneurons or principal cells[42] was based on neuronal spike waveforms extracted after offline high-pass filtering (forward-backward Kaiser filter, 250 Hz high-pass cutoff) of the original data. Local field potentials were low-pass filtered at 250 Hz. The probability that Pearson correlation coefficients were statistically different from 0 was computed using the Matlab function corrcoef.m (MathWorks).

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