Cortical chimera states predict epileptic seizures

Cite as: Chaos **29**, 121106 (2019); doi: 10.1063/1.5139654
Submitted: 21 November 2019 · Accepted: 9 December 2019 ·
Published Online: 30 December 2019

Claudia Lainscsek,[1,2,a] Nuttida Rungratsameetaweemana,[1,3,4,a] Sydney S. Cash,[5] and Terrence J. Sejnowski[1,2,3,6]

AFFILIATIONS

[1]Computational Neurobiology Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, USA
[2]Institute for Neural Computation, University of California San Diego, La Jolla, California 92093, USA
[3]Department of Neurosciences, University of California San Diego, La Jolla, California 92093, USA
[4]US Combat Capabilities Development Command Army Research Laboratory, Aberdeen Proving Ground, Maryland 21005, USA
[5]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA
[6]Division of Biological Sciences, University of California San Diego, La Jolla, California 92093, USA

[a]**Contributions:** C. Lainscsek and N. Rungratsameetaweemana contributed equally to this work.

ABSTRACT

A chimera state is a spatiotemporal pattern of broken symmetry, where synchrony (coherent state) and asynchrony (incoherent state) coexist. Here, we report chimera states in electrocorticography recordings preceding, by several hours, each of seven seizures in one patient with epilepsy. Before the seizures, the onset channels are not synchronized, while the remaining channels are synchronized. During the seizures, this pattern of behavior flips and the nononset channels show a more asynchronous behavior. At a seizure offset, synchrony can be observed that might facilitate termination.

Worldwide, more than 50 million people live with epilepsy, a common neurological disorder characterized by aberrant neuronal firing. While these periods are brief, they are unpredictable and can be devastating for the patient and family. Substantial research has focused on trying to predict seizures using machine learning techniques, advanced signal processing, and other computational tools. To date, however, there is no clearly successful method. Consequently, it is imperative that we understand the dynamics of neuronal activity that leads to seizures. One way to further our understanding of epilepsy is through examining the transition from desynchronized to highly synchronized cortical states. We found that this transition can occur through an extended hybrid or chimera state, where synchronization coexists with desynchronization. In one patient, each seizure was reliably preceded by chimera states that lasted up to 2 hours, suggesting a new feature that can be used for long-term seizure forecasting in some patients.

I. INTRODUCTION

Chimera states exhibit a hybrid structure of coexisting synchronous (coherent) and asynchronous (incoherent) behavior. This phenomenon was first described by Kuramoto and Battogtokh in 2002[1] and named "chimera states" by Abrams and Strogatz in 2004.[2] Panaggio and Abrams[3] published a systematic review of the field and collected several references to "bump states," as they were called before the invention of chimera states. In fact, in 1967, Winfree[4] discussed synchronization and mixed states. Experimental chimeras were reported by Tinsley *et al.*,[5] Hagerstrom *et al.*,[6] Nkomo *et al.*,[7] Abrams and Strogratz,[2] and Dudkowski *et al.*,[8] among others. Outside laboratories, many real world chimeras have been reported. These include unihemispheric sleep, ventricular fibrilation, power grids, social systems, neural networks, and the brain (see Refs. 3 and 9 for references). Tognoli and Kelso[10] report the coexistence of metastable and stable states in electroencephalography (EEG) data for cognitive tasks. Chimera states have also been reported by Showalter and his group and a special issue in *Chaos* was dedicated to him in 2019.[11]

The connection between human epilepsy and chimeras has been of recent interest, and networks of model neurons have been studied.[12–17] The present study investigated this question and hypothesized that the asynchrony-synchrony transition that leads to epileptic seizures can be explained by the induction and dynamics of chimera states. We analyzed electrocorticography (ECoG) data from patients with intractable focal epilepsy, and found that in one patient,

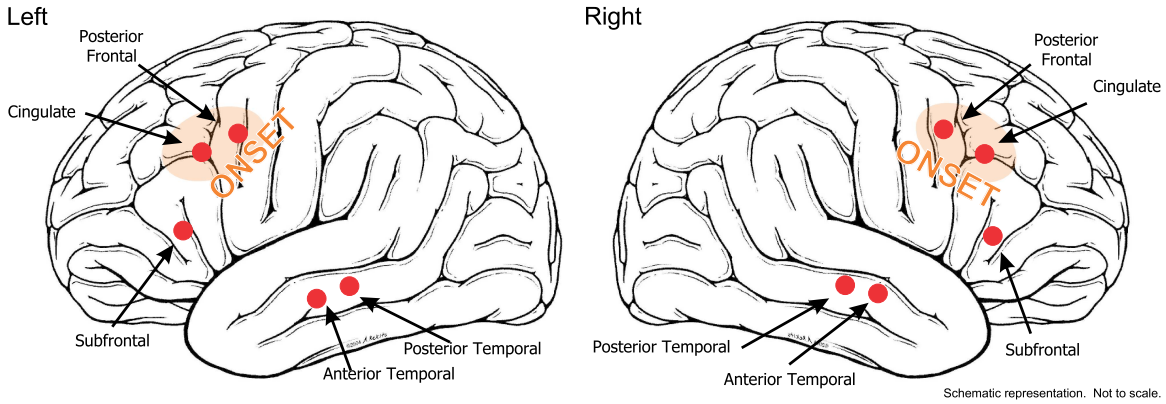

FIG. 1. Locations of the implanted ECoG electrodes. The locations of the onset channels were determined by a neurologist and are highlighted in orange here. Channel numbers 1–8, 9–16, 17–24, and 25–32 refer to electrodes in the right posterior frontal, left cingulate, right posterior frontal, and right cingulate region, respectively.

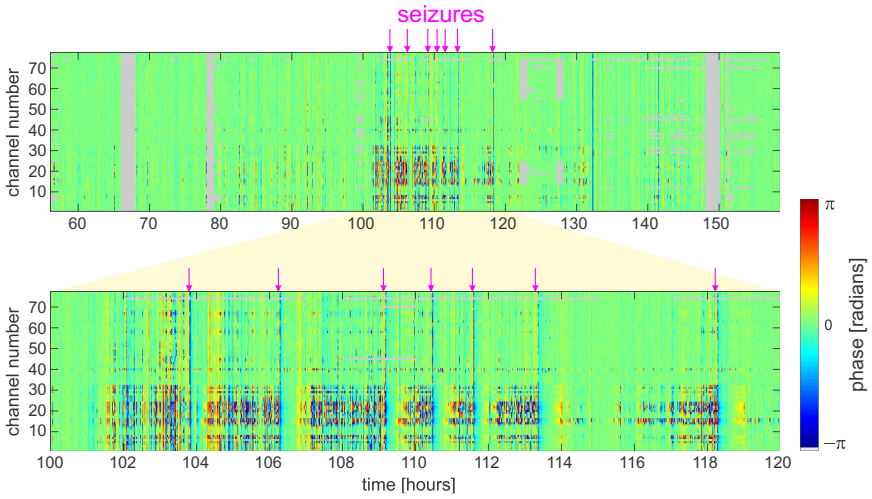

FIG. 2. DDA feature a_1 corresponding to each of the 77 recording channels over time. The top panel shows a_1 over 100 hours of recording. The bottom panel zooms in on the hour 100 to hour 120 of recording, during which all seven seizures occurred. The recording channels are sorted such that the onset channels, as determined by the neurologist, are shown here as channel numbers 1–32 and the nononset channels are shown here as channel numbers 33–77. The onset of each of the seven seizures is indicated by an arrow.

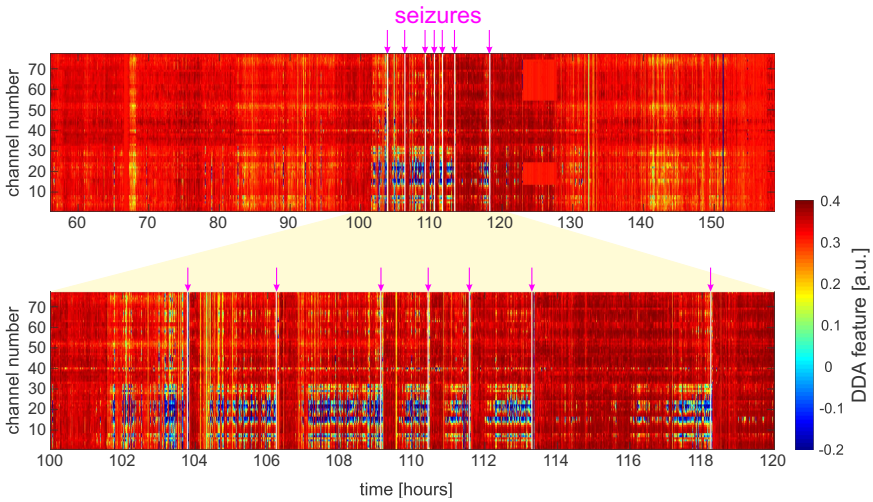

FIG. 3. Phases of the DDA feature a_1 corresponding to each of the 77 recording channels over time. The top panel shows the phase of a_1 over 100 hours of recording. The bottom panel zooms in on the hours between 100 and 120 of recording, during which all seven seizures occurred. The recording channels are sorted such that the onset channels, as determined by the neurologist, are shown here as channel numbers 1–32 and the nononset channels are shown here as channel numbers 33–77. The onset of each of the seven seizures is indicated by an arrow. Missing data are marked in gray.

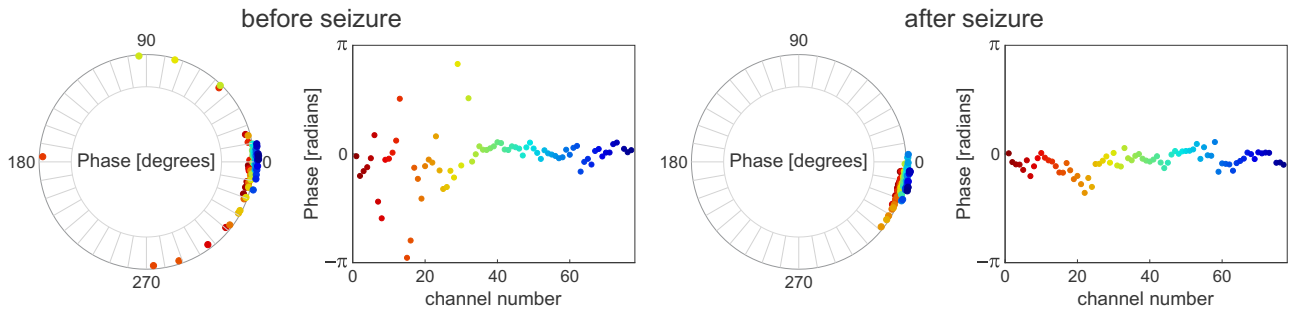

FIG. 4. Phases for two time points, 10 min before and 10 min after the fourth seizure: the onset channels (the first 32 channels) show desynchronization before the seizure onset with coexisting synchronized nononset channels. After the seizure, all channels are well synchronized. The colors of the dots in the circular phase plots are identical to those in the phase by channel number plots.

each seizure was consistently preceded by a chimera state. Therefore, in this patient, chimera states were 100% predictive of seizures before their onsets. Additionally, our analyses revealed that the brain stayed in these chimera states for up to 2 hours prior to a seizure. This is, to the best of our knowledge, the first direct evidence of chimera states in the human epileptic brain.

II. DELAY DIFFERENTIAL ANALYSIS

Delay differential analysis (DDA) is a nonlinear computational method that combines differential embeddings with linear and nonlinear nonuniform functional delay embeddings[18–20] to relate the current derivatives of a system to the current and past values of the system variables.[21,22] Inspired by Max Planck's "natural units",[23] the DDA model maps experimental data onto a set of natural embedding coordinates.

The general nonlinear DDA model is

$$\dot{x} = \sum_{i=1}^{I} a_i \prod_{n=1}^{N} x_{\tau_n}^{m_{n,i}} \tag{1}$$

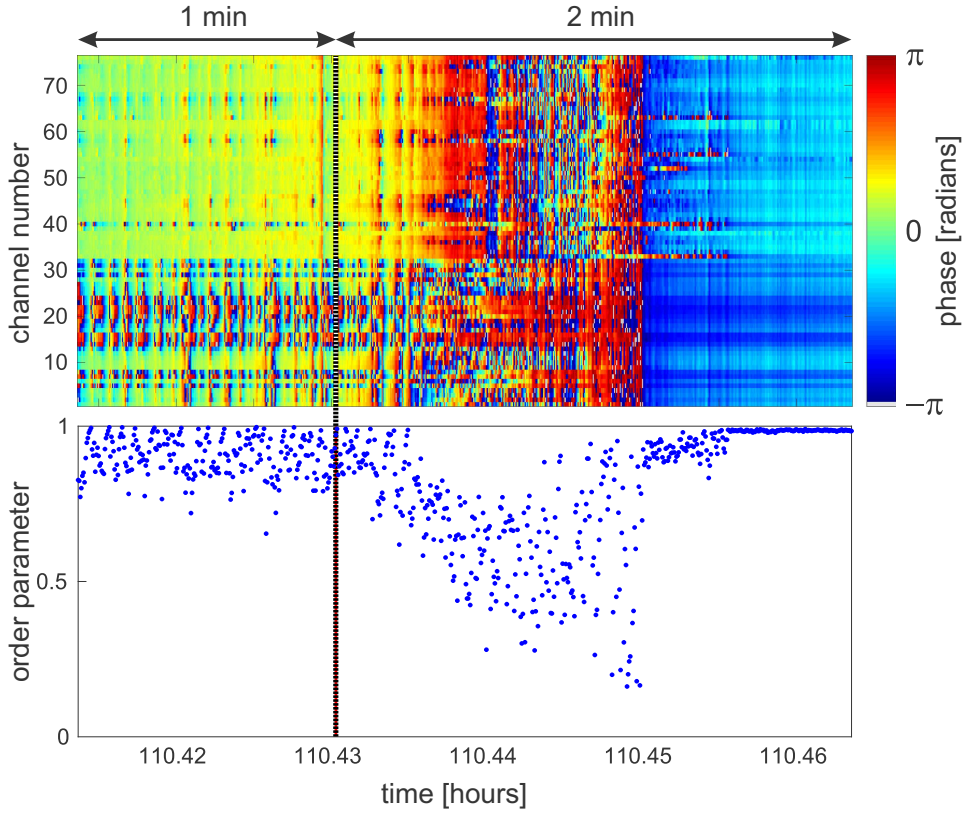

FIG. 5. Seizure 4: Phases (upper panel) for 77 channels and Kuramoto order parameter (lower panel) from 1 min before seizure onset (dashed line) to 2 min after the seizure onset.

for $\tau_n, m_{n,i} \in \mathbb{N}_0$, where N is the number of delays (usually 2), I is the number of terms (typically around 3), and $x_{\tau_n} = x(t - \tau_n)$, relating the signal derivative $\dot{x}$ to the signal nonuniformly shifted in time. We then used the coefficients a_i and the least square error ρ as features. To restrict the complexity of the DDA model, most of the terms in Eq. (1) were set to zero. We, therefore, considered here DDA models with two delays τ_n, three terms, and one degree $\sum_i m_{n,i} \leq 4$ of nonlinearity.

DDA is a computational framework that (1) uses unprocessed data so as not to disturb the nonlinear properties of the data, (2) uses sparse models that match the macroscopic architecture of the underlying dynamical system, (3) disregards amplitude information

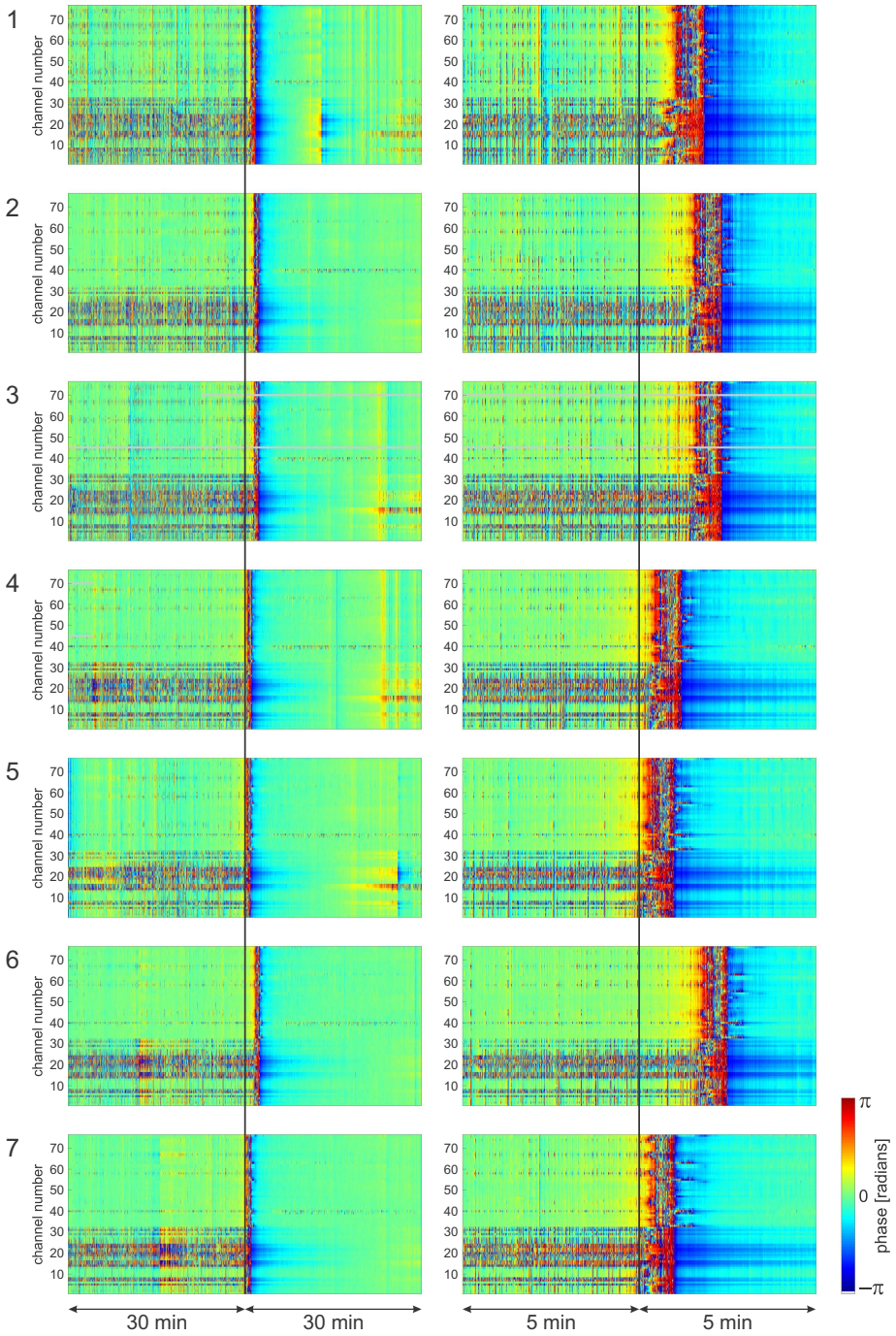

FIG. 6. Phases of all seven seizures centered around the seizure onsets (one hour of data). The channels are sorted by onset channels (numbers 1–32) and nononset channels (33–77) as determined by the neurologist.

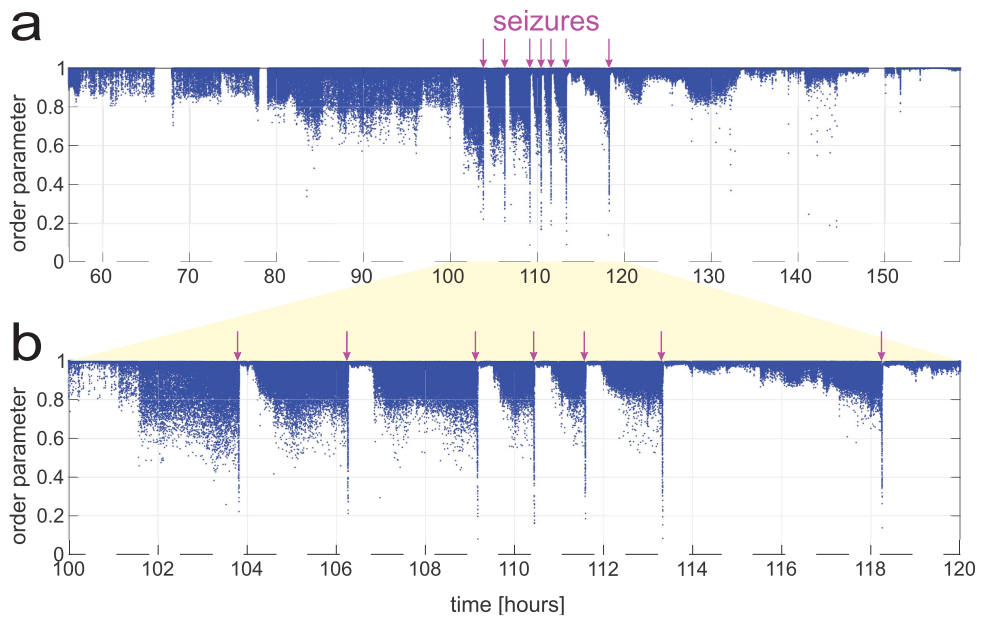

FIG. 7. Kuramoto order parameter $\mathcal{O}(t)$. (a) 100 hours of data from 77 channels and (b) zoomed in version for 20 hours around the seven seizures.

to focus on the dynamical aspects of the data, and (4) can be extended for the detection of dynamical causality in the data to understand information flow in the system. Previous applications to brain data have demonstrated that DDA efficiently captured essential properties of brain dynamics and classified brain states with a high level of performance.[24–26]

III. EPILEPTIC SEIZURES

The patient demographics and characteristics are described in Ref. 25.

A DDA model with minimum error was chosen using a genetic algorithm (GA) to maximally discriminate between preictal and postictal recordings. Around one million one second data segments were used from one hour periods centered around the seizure onset times.[25]

The selected DDA model is

$$\dot{x} = a_1 x_1 + a_2 x_2 + a_3 x_1^4, \tag{2}$$

with $x_i = x(t - \tau_i)$ and $\boldsymbol{\tau} = (7, 10)\ \delta t$, where $\delta t = \frac{1}{f_s}$ with the sampling rate $f_s = 500$ Hz. This model (2) bifurcates at the seizure onset, as shown in Ref. 25: It has a low error after seizure onset, but not before. The delays were chosen in the same way: $\tau_2 = 10$ is a good delay (low error) before seizures and $\tau_1 = 7$ is a good delay after seizures. The combination $\boldsymbol{\tau} = (7, 10)\delta t$ then proved to be a good choice and we, therefore, used this model for seizure characterization. As shown in Refs. 25 and 27, the parameter a_1 by itself is sufficient for seizure analysis.

All of the analyses in this article were performed on 100 h of recording from one patient (electrode locations are shown in Fig. 1) with a sampling rate of 500 Hz and 77 implanted electrodes (one bad electrode was excluded from the analysis). The sliding data windows were half a second long and the window shift was a quarter second. The data were not preprocessed, except for normalizing each data window to zero mean and unit variance. Figure 2 shows the DDA feature a_1, and Fig. 3 shows the phases of the DDA feature a_1 as a function of time for all 77 implanted electrodes. The channel numbers were rearranged such that the first 32 channels are the onset channels as determined by the neurologist and the remaining 45 channels are the nononset channels. Each of the seven seizures has a preceding time segment of chimera states. These states last for around 2 hours (2.1951, 2.0418, 2.2509, 0.7108, 0.5645, 1.2334, and 2.6969 hours) before the seizure onsets.

Figure 4 shows the phases of a_1 at two time points: 10 min before and 10 min after the fourth seizure. Before the seizure onset, the onset channels (the first 32 channels) were desynchronized, while the nononset channels were synchronized. In contrast, all channels became synchronized after the seizure offset.

An expanded version of seizure 4 is shown in Fig. 5 (upper panel). Microevents of seizurelike behavior can be observed before the seizure onset. Interestingly, after seizure onset the mixed synchrony/asynchrony behavior switches during the seizure. At seizure termination most of the channels are immediately synchronized, but a few need more time to synchronize with the rest. A movie for this seizure from 5 min before to 5 min after the seizure onset is shown in the supplementary material (S4.mp4). This behavior is consistent across all seven seizures as can be seen in Fig. 6 where the phases of all seven seizures are plotted and centered around the seizure onsets (one hour of data) as marked by the neurologist.

We calculated the order parameter as introduced by Kuramoto,[1]

$$\mathcal{O}(t) = \frac{1}{N}\sum_{k=1}^{N} e^{i\phi_k(t)} \tag{3}$$

from $a_1(t)$ for all 77 implanted electrodes, where k is the rearranged channel number. In Fig. 5 (lower panel), we show this order parameter for a three minute window around seizure 4. Figure 7(a) shows the order parameter for the entire recording period, and Fig. 7(b) shows the zoomed time frame around the seizures. The seizures have the lowest order parameters followed by the time segments before the seizures during which chimera states are observed, consistent with Refs. 28 and 29.

In addition to the order parameter, which was computed from phases, we introduced a new DDA order parameter that can be calculated directly from DDA feature a_1 (see Fig. 8): all pairwise L2 differences in a_1 between channels were computed in a sliding window 5 s in duration (20 a_1 values) and a shift of 250 ms. A smaller pairwise difference indicates higher degree of similarity and synchronization between channels. The channels in the lower 30% of the L2 distances were displayed as a function of time (see Fig. 8). In a chimera state, the synchronized channels have values that are between 0.5 and 1 [dark to light brown colors in Figs. 8(c) and 8(d)] and in the desynchronized state, the channels have values that are between 0 and 0.5 [light to dark gray colors in Figs. 8(c) and 8(d)]. In a nonchimera state, where all channels are either synchronized or desynchronized the value for all channels should be one or zero [light

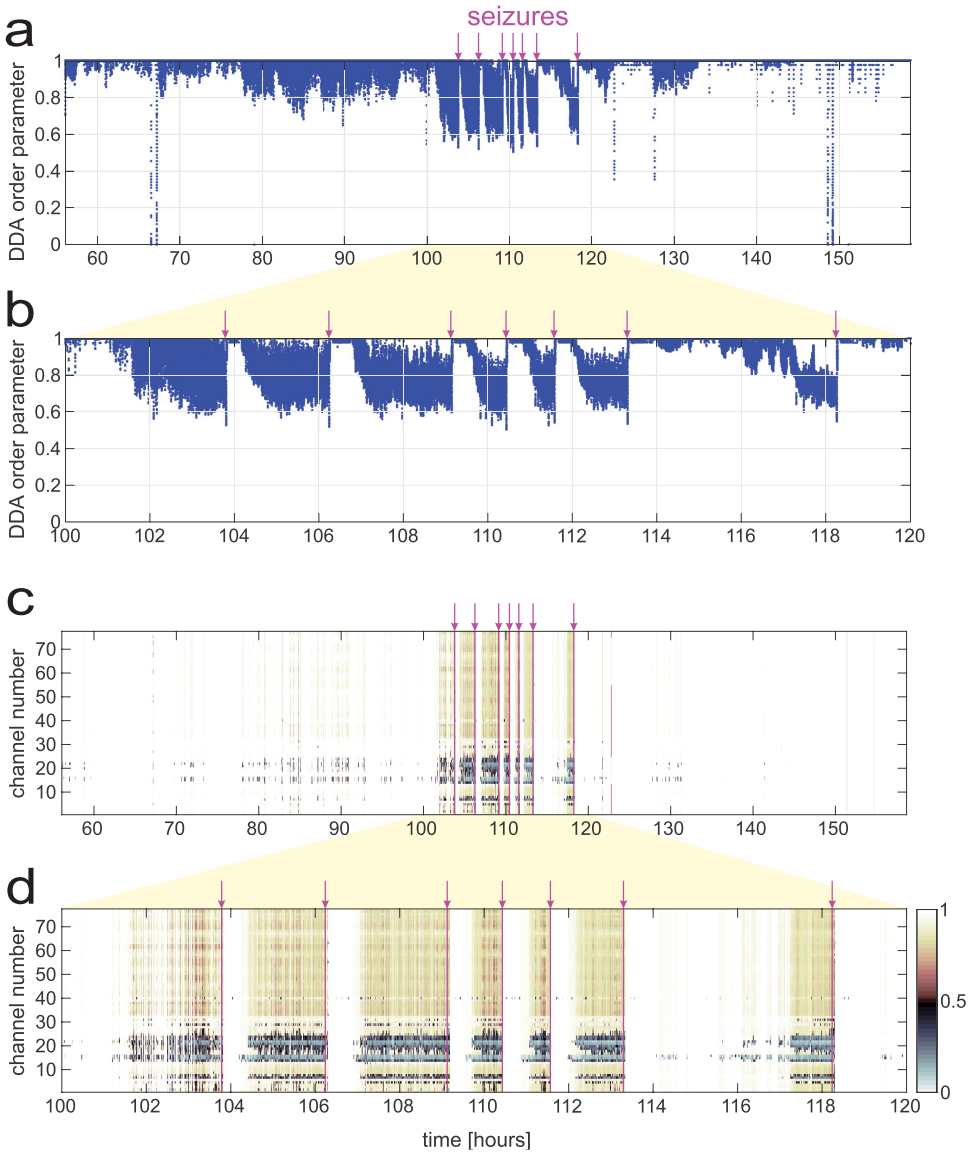

FIG. 8. DDA order parameter. (a) 100 hours of data from 77 channels, (b) zoomed in version of 20 hours around the seven seizures, (c) and (d) DDA order values for the individual channels.

colors in Figs. 8(c) and 8(d)]. The DDA order parameter is then the sum of these values for each time window divided by N, where N is the number of channels.

IV. CONCLUSIONS

We found chimera states in human ECoG data for one patient that reliably preceded each of this patient's seven seizures. These chimeras can be seen in the DDA feature a_1 and in the phases of a_1. We have so far analyzed 15 patients and only found chimeras in one patient. This might be because we used the same delays for all patients. We restricted our analysis to this one delay pair because of the amount of data to be analyzed. We, therefore, developed a DDA order parameter that detects chimera states in a completely automatic manner. With such an automatic procedure, we hope to find more chimera states in other patients by looking at more delay pairs.

Up to now, chimera states were reported in neuronal and epilepsy models. The findings in this paper are the first evidence of chimeras in the human brain.

SUPPLEMENTARY MATERIAL

See the supplementary material for a movie of the phases of seizure 4 from 5 min before to 5 min after the seizure onset.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Health (NIH)/NIBIB (Grant No. R01EB026899-01), NIH/NINDS (Grant No. R01NS104368), Office of Naval Research (ONR) (Grant No. N0014-15-1-2328), NIH/NINDS (Grant Nos. NS062092 and NS088568), and mission funding from the U.S. Army Research Laboratory. The authors would like to thank Robert Kim and Christopher Gonzalez for valuable discussions.

REFERENCES

[1]Y. Kuramoto and D. Battogtokh, "Coexistence of coherence and incoherence in nonlocally coupled phase oscillators," Nonlinear Phenom. Complex Syst. **5**(4), 380–385 (2002).
[2]D. M. Abrams and S. H. Strogatz, "Chimera states for coupled oscillators," Phys. Rev. Lett. **93**, 174102 (2004).
[3]M. J. Panaggio and D. M. Abrams, "Chimera states: Coexistence of coherence and incoherence in networks of coupled oscillators," Nonlinearity **28**(3), R67–R87 (2015).
[4]A. T. Winfree, "Biological rhythms and the behavior of populations of coupled oscillators," J. Theor. Biol. **16**(1), 15–42 (1967).
[5]M. R. Tinsley, S. Nkomo, and K. Showalter, "Chimera and phase-cluster states in populations of coupled chemical oscillators," Nat. Phys. **8**, 662–665 (2012).
[6]A. M. Hagerstrom, T. E. Murphy, R. Roy, P. Hövel, I. Omelchenko, and E. Schöll, "Experimental observation of chimeras in coupled-map lattices," Nat. Phys. **8**, 658–661 (2012).
[7]S. Nkomo, M. R. Tinsley, and K. Showalter, "Chimera states in populations of nonlocally coupled chemical oscillators," Phys. Rev. Lett. **110**, 244102 (2013).
[8]D. Dudkowski, K. Czołczyński, and T. Kapitaniak, "Traveling chimera states for coupled pendula," Nonlinear Dyn. **95**(3), 1859–1866 (2019).
[9]S. Majhi, B. K. Bera, D. Ghosh, and M. Perc, "Chimera states in neuronal networks: A review," Phys. Life Rev. **28**, 100–121 (2019).
[10]E. Tognoli and J. A. Scott Kelso, "The metastable brain," Neuron **81**(1), 35–48 (2014).
[11]O. Steinbock, R. Wackerbauer, and D. Horváth, "Nonlinear chemical dynamics and its interdisciplinary impact: Dedicated to Ken Showalter on the occasion of his 70th birthday," Chaos **29**(8), 080401 (2019).
[12]P. Jiruska, M. de Curtis, J. G. R. Jefferys, C. A. Schevon, S. J. Schiff, and K. Schindler, "Synchronization and desynchronization in epilepsy: Controversies and hypotheses," J. Physiol. (Lond.) **591**(4), 787–797 (2013).
[13]V. K. Jirsa, W. C. Stacey, P. P. Quilichini, A. I. Ivanov, and C. Bernard, "On the nature of seizure dynamics," Brain **137**(8), 2210–2230 (2014).
[14]E. Schöll, "Synchronization patterns and chimera states in complex networks: Interplay of topology and dynamics," Eur. Phys. J. Spec. Top. **225**(6), 891–919 (2016).
[15]T. Chouzouris, I. Omelchenko, A. Zakharova, J. Hlinka, P. Jiruska, and E. Schöll, "Chimera states in brain networks: Empirical neural vs. modular fractal connectivity," Chaos **28**(4), 045112 (2018).
[16]R. Kozma and W. J. Freeman, "Intermittent spatio-temporal desynchronization and sequenced synchrony in ECoG signals," Chaos **18**(3), 037131 (2008).
[17]I. Omelchenko and A. Zakharova, "Intriguing coexistence of synchrony and asynchrony in the brain: Comment on chimera states in neuronal networks: A review by Soumen Majhi, Bidesh K. Bera, Dibakar Ghosh, Matjaž Perc," Phys. Life Rev. **28**, 134–136 (2019).
[18]F. Takens, "Detecting strange attractors in turbulence," in *Dynamical Systems and Turbulence, Warwick 1980*, edited by D. A. Rand and L.-S. Young, Lecture Notes in Mathematics (Springer, Berlin/Heidelberg, 1981), Vol. 898, pp. 366–381.
[19]N. H. Packard, J. P. Crutchfield, J. D. Farmer, and R. S. Shaw, "Geometry from a time series," Phys. Rev. Lett. **45**, 712 (1980).
[20]T. Sauer, J. A. Yorke, and M. Casdagli, "Embedology," J. Stat. Phys. **65**, 579 (1991).
[21]M. Kremliovsky and J. Kadtke, "Using delay differential equations as dynamical classifiers," AIP Conf. Proc. **411**, 57 (1997).
[22]C. Lainscsek, J. Weyhenmeyer, M. E. Hernandez, H. Poizner, and T. J. Sejnowski, "Non-linear dynamical classification of short time series of the Rössler system in high noise regimes," Front. Neurol. **4**, 182 (2013).
[23]M. Planck, "Über irreversible Strahlungsvorgänge," Ann. Phys. **306**(1), 69–122 (1900).
[24]C. Lainscsek and T. J. Sejnowski, "Electrocardiogram classification using delay differential equations," Chaos **23**(2), 023132 (2013).
[25]C. Lainscsek, J. Weyhenmeyer, S. S. Cash, and T. J. Sejnowski, "Delay differential analysis of seizures in multichannel electrocorticography data," Neural Comput. **29**(12), 3181–3218 (2017).
[26]C. Lainscsek, A. L. Sampson, R. Kim, M. L. Thomas, K. Man, The COGS Investigators, X. Lainscsek, N. R. Swerdlow, D. L. Braff, T. J. Sejnowski, and G. A. Light, "Nonlinear dynamics underlying sensory processing dysfunction in schizophrenia," Proc. Natl. Acad. Sci. U.S.A. **116**(9), 3847–3852 (2019).
[27]C. Lainscsek, C. E. Gonzalez, A. L. Sampson, S. S. Cash, and T. J. Sejnowski, "Causality detection in cortical seizure dynamics using cross-dynamical delay differential analysis," Chaos **29**(10), 101103 (2019).
[28]A. Rothkegel and K. Lehnertz, "Irregular macroscopic dynamics due to chimera states in small-world networks of pulse-coupled oscillators," New J. Phys. **16**(5), 055006 (2014).
[29]R. G. Andrzejak, C. Rummel, F. Mormann, and K. Schindler, "All together now: Analogies between chimera state collapses and epileptic seizures," Sci. Rep. **6**, 1–10 (2016).