2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

*ALESSANDRA CAMASSA, Maurizio Mattia, and Maria V. Sanchez-Vives

ENERGY-BASED HIERARCHICAL CLUSTERING OF CORTICAL SLOW WAVES IN MULTI-ELECTRODE RECORDINGS

Abstract— **The recent development of novel multi-electrode recording technologies has revealed the existence of traveling patterns of cortical activity in many species and under different states of awareness. Among these, slow activation waves occurring under sleep and anesthesia have been widely investigated as they provide unique insights into network features such as excitability, connectivity, structure, and dynamics of the cerebral cortex. Such characterization is usually based on clustering methods which are constrained by *a priori* assumptions as to the number of clusters to be used or rely on wave-by-wave pattern reconstruction. Here, we introduce a new computational tool based on modal analysis of fluid flows which is robustly applied to multivariate electrophysiological data from cortical networks, namely the Energy-based Hierarchical Waves Clustering method (EHWC). EHWC is composed of three main steps: (1) detecting the occurrence of global waves; (2) reducing the data dimensionality via singular value decomposition; (3) clustering hierarchically the singled-out waves. The analysis does not require the single-channel contribution to the waves, which is a typical bottleneck in this kind of analysis due to the unavoidable intrinsic variability of locally recorded activity. For testing and validation, here we used *in vivo* extracellular recordings from mice cortex under three different levels of anesthesia. As a result, we found slow waves with an increasing number of propagation modes as the anesthesia level decreases, giving an estimate of the increasing complexity of network dynamics. This and other wave's features replicate and extend the findings from previous literature, paving the way to extend the same approach to non-invasive electrophysiological recordings like EEG and fMRI used clinically for the characterization of brain dynamics and clinical stratification in brain lesions.**

Clinical Relevance— **The properties of cortical waves are highly informative about brain states. The quantification and classification of brain states are clinically relevant to the diagnosis of consciousness disorders. Further, abnormal waves have also been described in perilesional tissue. A new method is introduced to cluster similar cortical spatiotemporal patterns like slow waves in electrophysiological and simulated multichannel data under different brain states. This is a novel method that requires no channel-by-channel detection or *a priori* assumptions on the number of clusters to be used. The method has the potential to be exploited in non-invasive recordings like EEG and fMRI.**

I. INTRODUCTION

The spatiotemporal patterns of brain activity spontaneously generated by the cerebral cortex represent an important hallmark of neural computation and information transfer. The use of multichannel recording technologies has recently revealed traveling patterns of neuronal activity; that is, cortical waves, occurring across many species [1]–[3], and under different states of awareness [4]–[6]. Also, traveling waves are strongly shaped by the brain state and by neural activity; in turn, while propagating across the cortical networks, they transiently modulate neural excitability and responsiveness over a wide range of spatial and temporal scales [7]. Across single areas or distant regions, the cortical oscillations travel as synchronous events characterized by non-zero phase offsets changing from time to time. Phase latencies identify spatiotemporal patterns like planar, radial, and spiral waves, or even more complex motifs generated by the interaction and combination of multiple traveling waves [7]. Previous works have shown that the study of the spatiotemporal patterns of activity of the cerebral cortex may provide important information about the underlying networks in terms of excitability, connectivity, structure, and dynamics [4], [8], [9]. Many methods exist to classify cortical spatiotemporal patterns of activity based on clustering methods [10], [11]. Here, we aim to provide a new computational tool based on modal analysis of fluid flows for the grouping of similar spatiotemporal patterns in electrophysiological cortical data, what we call the Energy-based Hierarchical Waves Clustering method (EHWC). Here, we applied this method to global brain states dominated by slow wave activity (SWA) in cortex, where slow oscillations (SO) between active (Up) and silent (Down) periods occur at approximately 1 Hz. SO spontaneously emerge in cortical networks both when they are anatomically disconnected (i.e. *in vitro*) [2], [12], as well as when they are functionally disconnected (i.e. *in vivo*) under physiological or pharmacological unconscious states [11], [13], [14] or in pathological conditions [6], [15], [16]. It has been demonstrated that the SOs are traveling waves that periodically sweep the cerebral cortex and originate from specific cortical areas [4], providing an ideal test bed for our method. So, in this work we apply the EHWC method

* IDIBAPS is funded by the CERCA program (Generalitat de Catalunya). This project/research has received funding from the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3).

A. Camassa is with the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. (Tel: +343 932275707 e-mail: ale.camassa22@gmail.com)

M. Mattia is with the Natl. Center for Radioprotection and Computational Physics, Istituto Superiore di Sanità (ISS), Rome, Italy.

M.V. Sanchez-Vives is with the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, and ICREA, Barcelona, Spain.

for the clustering of cortical traveling waves *in vivo* under three different levels of anesthesia [17].Our results strongly agree with previous studies performed on the same data set [11], validating our method and providing a novel analytical tool for clustering similar cortical spatiotemporal patterns, and overcoming some of the limitations of former works in the field.

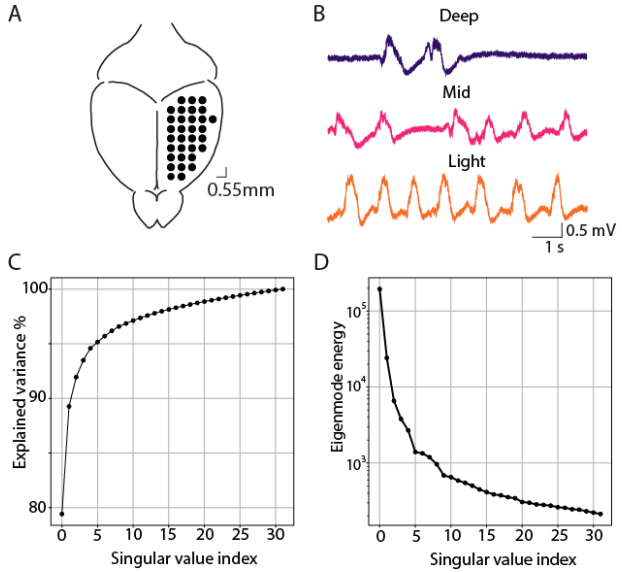

Fig. 1 Experimental setup and dimensionality reduction. A, schematic representation of the *in vivo* recording with a 32ch-MEA (multi-electrode array) placed on top of the cortical surface of one hemisphere in mice. **B**, Traces representing the local field potential (LFP) recorded from one electrode *in vivo* at Deep, Medium and Light (blue, pink and orange trace, respectively) anesthesia level (adapted from Dasilva et al. 2021). **C**, percentage of total data variance explained by each singular value in one example case under Medium anesthesia. **D**, energy related to each singular value in the same example case shown in **C**.

II. METHODS

A. Experimental methods

For the purpose of this study, we recorded extracellular local field potential (LFP) from one hemisphere of anesthetized mice (N = 8) via a 32-channel multi-electrode array [18] placed on the cortical surface (Fig. 1A). Anesthesia was induced by intraperitoneal injection of ketamine and medetomidine and maintained by the inhalation of isoflurane in pure oxygen (details in [11]. Each animal went through a modulation of anesthesia obtained by varying isoflurane concentrations resulting in three different levels: Deep = 1.16 ± 0.08 % (mean ± s.e.m.), Medium = 0.34 ± 0.06 % and Light = 0.1 ± 0%. Each anesthesia level was maintained for 20–30 minutes and recordings consistently showed a stable slow oscillatory regime (Fig. 1B). All procedures were approved by the Ethics Committee at the Hospital Clinic of Barcelona and were carried out to the standards laid down in Spanish regulatory laws (BOE 34/11370-421, 2013) and in the European Union directive 2010/63/EU.

B. Signal processing

We extracted the multiunit activity (MUA) from the recorded LFP as in [19], [20]. Briefly, the MUA was estimated, independently for each channel, as the relative change of the power in the [0.2, 1.5] kHz frequency band of the raw signal, and down-sampled at 200Hz. The lower bound at 0.2 kHz in the recorded unfiltered field potential is sufficient to exclude all the possible contribution from high-frequency LFP fast oscillations observed in cortex. MUA were eventually low-pass filtered by averaging on a moving window of 80 ms.

C. Dimensionality reduction

We performed a standard singular value decomposition (SVD) [21] on the multivariate MUA time series F:

$$F = U\Sigma V^T \quad (1)$$

where F is a $m \times n$ matrix composed of the m MUA samples measured from the $n = 32$ recording electrodes. U is the $m \times m$ matrix of columnar orthogonal temporal bases (u_i), V is the $n \times n$ matrix of columnar orthogonal spatial bases (v_i), while Σ is the diagonal matrix of singular values (σ_i), and V^T indicates the transpose of V. In the analyzed data the first three components explained on average 92% of the variance (Fig. 1C-D). We then reduced the dimensionality of our problem taking into account only the projections on the temporal eigenmodes u_i associated to the first three σ_i ($i \in \{1,2,3\}$).

D. Wave activations as low-dimensional trajectories

According to [22], each σ_i^2 is proportional to the energy ΔE_{ji} of the spatial eigenmode v_i at time j

$$\Delta E_{ji} = (F^T v_i)_j^2 = \sigma_i^2 u_{ji}^2 \quad (2)$$

with $i = 1, \dots, n$, such that the energy fraction incorporated by the first m modes at the time step j is

$$E_{jm} = \frac{\sum_{i=1}^{m} \sigma_i^2 u_{ji}^2}{\sum_{i=1}^{n} \sigma_i^2 u_{ji}^2} \; m < n \quad (3)$$

An example of this instantaneous energy from an example recording for each m is shown in Fig. 2A, top panel. Setting a suited threshold on the MUA averaged across channels (i.e., the multi-electrode activity MUA, MEAMUA), we detected the onset time of traveling activation waves resulting from the coordinated Down-to-Up transitions in single channels (Fig. 2A, bottom panel). The time windows of 0.25 s centered around these onset times constitute snapshots of the spatiotemporal patterns associated with each single wave which is a chunk of F. From these chunks we singled out the points $(\Delta E_{j1}, \Delta E_{j2}, \Delta E_{j3})$ in the three-dimensional space defined by the first three spatial eigenmodes. These points developed in time as low-dimensional trajectories (Fig. 3A). Example trajectories from the chunks associated with different wave activations (i.e., Down-to-Up transitions) are depicted in Fig. 3C. As a result, each wave is represented by a vector with $3k$ elements

corresponding to the three coordinates for each of the k points of the chunk (where here $k = 0.25 * 200 = 50$).
In general, the number of spatial eigenmodes (NEig) on which we project the MEA activity corresponding to a wave may vary across experiments and is determined as follows:

$$NEig = \langle min\{m | E(t_{up})_m \geq 0.9\} \rangle \quad (4)$$

That is the number of spatial eigenmodes required to account for 90% of the energy of the data over time, averaged in the time periods corresponding to the Up states (t_{up}; Fig. 2A, middle panel) [22].

E. Hierarchical clustering analysis

From the set of vectors/trajectories we eventually computed the pairwise Euclidean distance determining a square Distance Matrix (DM). For each experiment and anesthesia level, we performed a Hierarchical Clustering Analysis (HCA) [23] on the DM using the Ward variance minimization algorithm [24], and applied a suited distance cut-off to obtain the number of clusters in our data. Here, we applied the same cut-off distance equal to 25 [a.u.] to all the data. To visualize the DM in form of a tree, we used truncated dendrograms (Fig. 3A–C), and then sorted the DM according to the leaves of the dendrogram, obtaining what we call the Ordered Distance Matrix (ODM, Fig. 3D–F).

F. Dynamical richness estimation

In order to obtain an estimation of the dynamical richness of cortical activity under each different anesthesia level, we performed a measure of complexity based on the Shannon entropy [11] here computed on the distribution of the Euclidean distance between the vectors/trajectories associated to the detected waves contained in each DM. As a result, a value of complexity/entropy is obtained for each subject and each brain state ($n = 8 \times 3 = 24$).

III. RESULTS

We presented here the EHWC analysis as a new unsupervised method allowing for (1) clustering of spatiotemporal patterns (slow waves) in electrophysiological multi-channel cortical data and (2) estimation of cortical complexity under different brain states. As shown in Fig. 3, here we were able to reduce the dimensionality of our problem and map the electrophysiological activity of the cerebral cortex into a low-dimensional embedding space. In particular, the first three singular values extracted by SVD (given in (1)) explained on average a percentage of the variance of the data equal to 90.8 ± 2.8% under Deep anesthesia, 92.5 ± 1.8% under Medium anesthesia, and 93.6 ± 2.1% under Light anesthesia. The detected waves were consistent with those singled out in [11] relying on a different method. We extracted matrices of pairwise distance between waves, i.e. the distance matrix (DM), and used them to calculate both the number of clusters and to estimate under each condition the complexity/richness of the propagation modes of the spontaneous and quasi-periodic cortical activation. Using the EHWC, we found that the number of clustered modes of propagation increases as the anesthesia level decreases. In Fig. 4 we show, for one example subject, the dendrograms obtained under Deep (Fig. 4A), Medium (Fig. 4B) and Light (Fig. 4C) anesthesia. The dendrograms (Fig. 4A–C), and the corresponding ordered distance matrix (ODM, Fig. 4D–F) revealed the presence of two homogeneous clusters under Deep anesthesia, with a relatively small distance among waves within each cluster, that become larger and highly variable when we move towards lighter anesthesia states. These results were confirmed at the population level, where the average number of clusters under the three different levels of anesthesia was: Deep = 2.87 ± 0.83 (SD), Medium = 4.5 ± 1.2 and Light = 9.12 ± 1.5, as shown in Fig. 4G. These results and their statistics did not change by taking different lengths of time

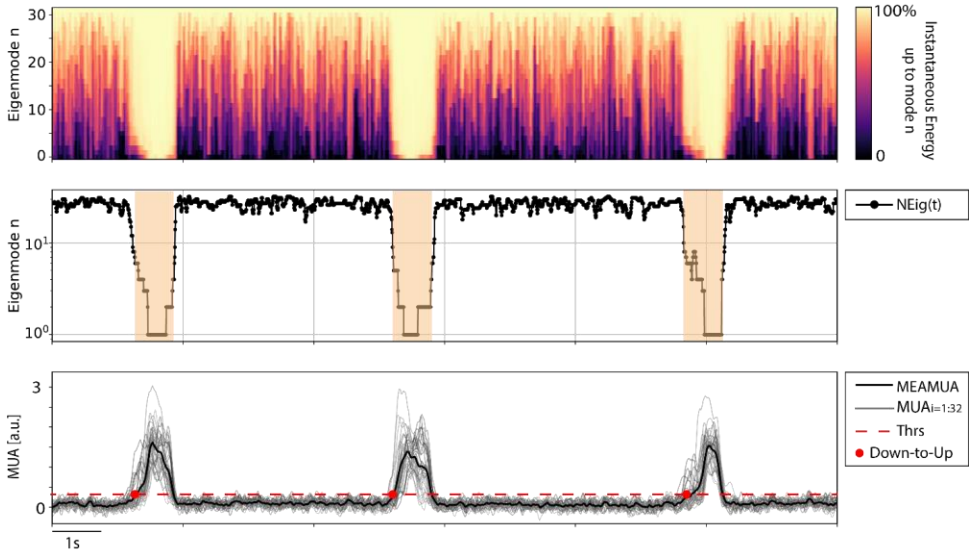

Figure 2 Instantaneous energy of the cortical activity from the MEA and wave detection. Bottom panel shows the time course of the multiunit activity (MUA) extracted from each channel (gray traces) in one example recording, and the corresponding average, the MEAMUA (black trace, see methods section **D**). Red dashed line, threshold used to detect the cortical events, i.e. the Down-to-Up transitions (red dots). Middle panel, the number of eigenmodes required to account for the 90% of the energy of the data over time (**NEig(t)**). Highlighted intervals correspond to the Up states area in which we averaged the values to obtain the final **NEig** (see Methods section **D**). Top panel, sorted percentage of instantaneous energy for each eigenmode.

windows and different cut-off distances (not shown). Moreover, the Shannon entropy computed on the DM allowed us to quantify the complexity of the propagation modes of cortical waves spontaneously expressed under each anesthesia level, leading to find a significant increase of the entropy as anesthesia fades out (Fig. 4H). The presented results are highly consistent with those reported with methodologies requiring the reconstruction of individual waveforms [11], validating the current approach, while it allows unsupervised clustering of waves and estimation of their complexity.

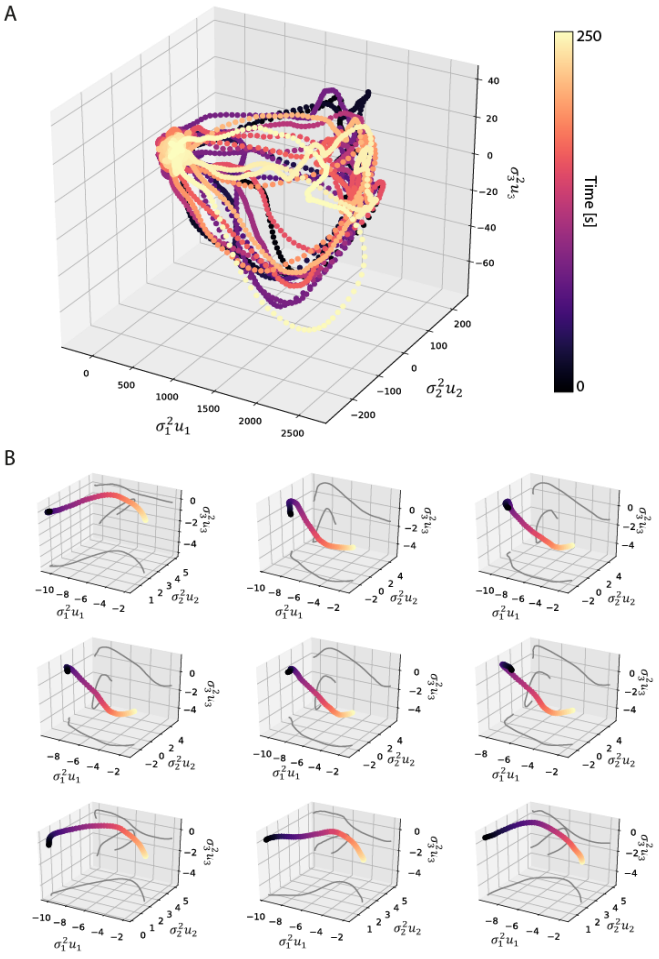

Figure 3 System trajectories in the energy space. A, energy trajectory of 250s of cortical activity in the three-dimensional space defined by the first three principal components from an example experiment. **B**, Trajectories in the three-dimensional energy space associated to six waves randomly sampled from the same example experiment.

IV. DISCUSSION

The precise determination of the brain state is a relevant problem in basic as well as in clinical neuroscience, where it is tightly linked to the stratification of levels of consciousness. Previous studies have shown the importance of understanding the dynamics of the cerebral cortex through the study of spatiotemporal patterns of activity that bring relevant information about the network state and its properties [4], [8], [9]. However, the existing methods still present limitations with regard to *a priori* assumptions on the number of clusters to be used and the need for wave-by-wave pattern reconstruction. Departing from the idea that the brain may be seen as a non-linear system outside of equilibrium [22], here we developed a novel analytical tool for the grouping of similar cortical spatiotemporal patterns based on the application of an empirical eigenfunction approach for dimensionality reduction. This allowed us to reconstruct the energy trajectories of cortical events such as planar, spiral, and complex waves, and classify them using a hierarchical clustering analysis (HCA). In addition to the estimation of a finite number of clusters of cortical motifs, the analysis performed here also provides insights into the dynamics of the network generating the activity. Indeed, the method revealed that in the transition from deep anesthesia towards wakefulness, a form of transition across brain states, the fade-out of anesthesia leads to an increasing variability of the spatiotemporal patterns generated by the cortex and in general to an increase in cortical complexity, as shown by the entropy results. This represents the rich repertoire of spatiotemporal configurations that the cortical networks express when approaching wakefulness. Coherently with previous studies, our results support the idea that anesthesia fade-out translates into a complex re-organization of the coupling between distant brain regions, leading to increasingly richer and more diverse long-range connectivity and activity patterns [25]–[27], representing what happens in the transition from synchronous towards asynchronous or alert states, e.g. recovery from disorders of consciousness. Regional brain areas can also present abnormal waves when in perilesional regions [28], preventing normal function. Our results strongly agree with previous literature [11] and, at the same time, present the advantage of relying on an unsupervised method, requiring no channel-by-channel detection or *a priori* assumptions regarding the number of clusters to be used. However, our method still requires the selection of the linkage strategy to be used to compute the dendrograms, and the choice of a distance threshold to be applied to them to obtain a finite number of clusters. A potential limitation of the Energy-based Hierarchical Waves Clustering method (EHWC) is that it requires the detection of the wave's onset to reconstruct the single-wave trajectories, complicating its use in asynchronous states in which event detection is not straightforward. However, we speculate that the same technique may be successfully applied to any condition in which a stimulation or perturbation is used (e.g., clustering of cortical response to a stimulation), as is the case in the clinical use of transcranial magnetic stimulation for the diagnosis of disorders of consciousness [29]. The method presented here is also suitable to the analysis of simulated cortical data from multimodular networks of spiking neurons (not shown). We conclude that EHWC provides a robust novel method for cortical patterns clustering in electrophysiological and

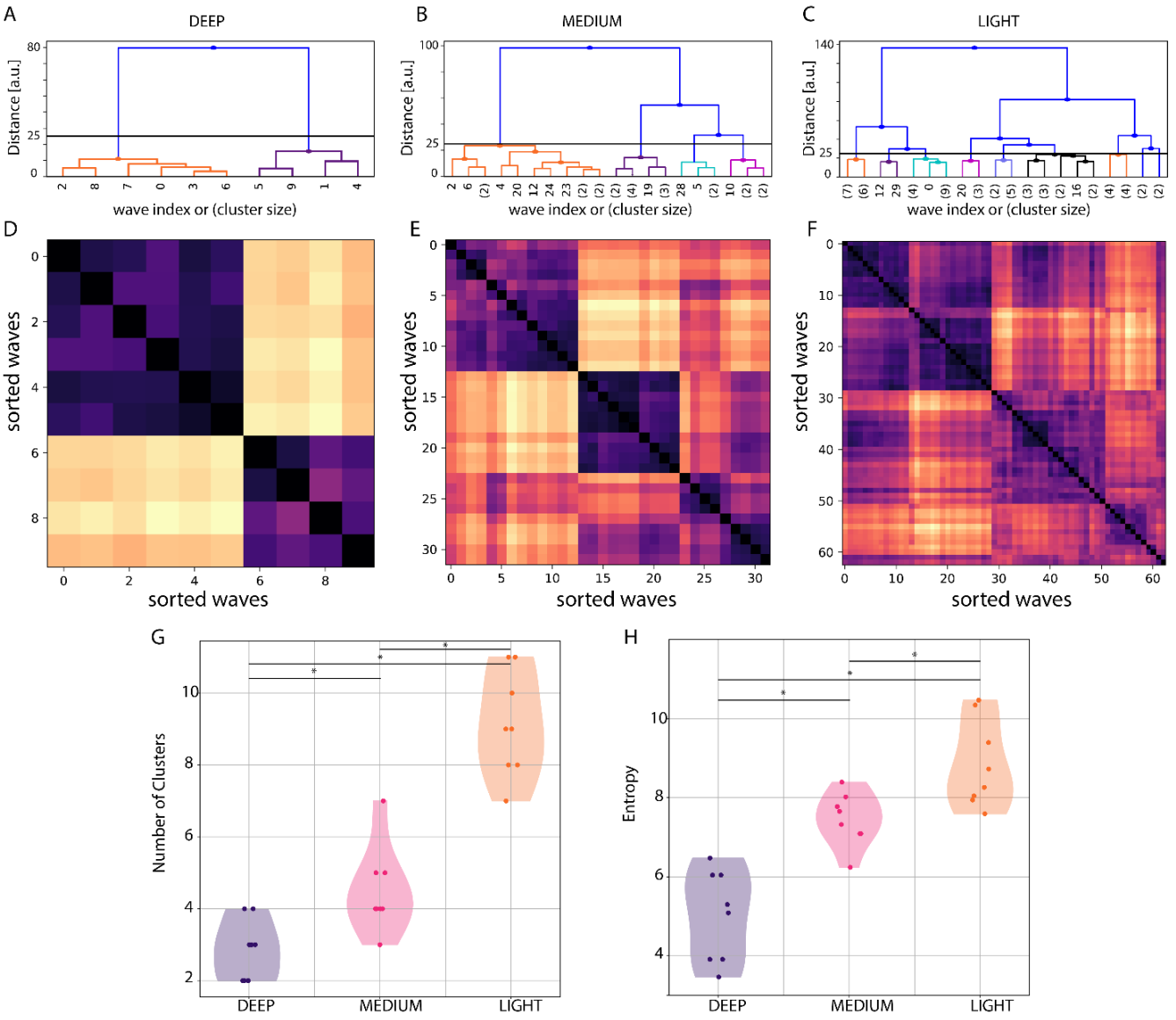

Figure 4 Hierarchical clustering analysis. Dendrograms representing the hierarchical clustering analysis (**HCA**) output, showing the clusters of waves under Deep (**A**), Medium (**B**) and Light (**C**) anesthesia levels. Ordered Distance Matrix (**ODM**) arranged according by the clustering provided by the dendrograms leaves for Deep (**D**), Medium (**E**) and Light (**F**) anesthesia level of an example animal. Colors in **D, E, F** represent the distance between the waves' trajectories, ranging from zero (black) to the maximum distance (light yellow). Distances are also reported into the y axis of the corresponding dendrogram. Violin plot showing the distribution of the number of clusters (**G**) and entropy (**H**) across different anesthesia levels. Statistical significance was assessed by Wilcoxon signed-rank test with Benjamini–Hochberg corrections: *p<0.05.

simulated data characterized by synchronous activity, with the potential to be exploited in non-invasive recordings like EEG and fMRI used in clinical realms for the characterization of brain dynamics under different brain states such as those related to disorders of consciousness or brain lesions.

References

[1] Z. W. Davis, L. Muller, J. Martinez-Trujillo, T. Sejnowski, and J. H. Reynolds, "Spontaneous travelling cortical waves gate perception in behaving primates," *Nature*, vol. 587, no. 7834, pp. 432–436, 2020, doi: 10.1038/s41586-020-2802-y.

[2] I. Timofeev, F. Grenier, M. Bazhenov, T. J. Sejnowski, and M. Steriade, "Origin of slow cortical oscillations in deafferented cortical slabs.," *Cereb. Cortex*, vol. 10, no. 12, pp. 1185–99, Dec. 2000.

[3] M. Sheroziya and I. Timofeev, "Global intracellular slow-wave dynamics of the thalamocortical system.," *J. Neurosci.*, vol. 34, no. 26, pp. 8875–93, Jun. 2014, doi: 10.1523/JNEUROSCI.4460-13.2014.

[4] M. Massimini, R. Huber, F. Ferrarelli, S. Hill, and G. Tononi, "The Sleep Slow Oscillation as a Traveling Wave," *J. Neurosci.*, vol. 24, no. 31, pp. 6862–6870, 2004, doi: 10.1523/JNEUROSCI.1318-04.2004.

[5] L. Muller, G. Piantoni, D. Koller, S. S. Cash, E. Halgren, and T. J. Sejnowski, "Rotating waves during human sleep spindles organize global patterns of activity that repeat precisely through the night," *Elife*, vol. 5, no. NOVEMBER2016, pp. 1–25, 2016, doi: 10.7554/eLife.17267.001.

[6] P. Gloor, G. Ball, and N. Schaul, "Brain lesions that produce delta waves in the EEG," *Neurology*, vol. 27, no.

4, pp. 326–333, 1977, doi: 10.1212/wnl.27.4.326.
[7] L. Muller, F. Chavane, J. Reynolds, and T. J. Sejnowski, "Cortical travelling waves: mechanisms and computational principles.," *Nat. Rev. Neurosci.*, vol. 19, no. 5, pp. 255–268, Apr. 2018, doi: 10.1038/nrn.2018.20.
[8] C. Capone *et al.*, "Slow Waves in Cortical Slices: How Spontaneous Activity is Shaped by Laminar Structure," *Cereb. Cortex*, vol. 29, no. 1, pp. 319–335, Nov. 2019, doi: 10.1093/cercor/bhx326.
[9] G. B. Ermentrout and D. Kleinfeld, "Traveling electrical waves in cortex: Insights from phase dynamics and speculation on a computational role," *Neuron*, vol. 29, no. 1, pp. 33–44, 2001, doi: 10.1016/S0896-6273(01)00178-7.
[10] L. Grossberger, F. P. Battaglia, and M. Vinck, *Unsupervised clustering of temporal patterns in high-dimensional neuronal ensembles using a novel dissimilarity measure*, vol. 14, no. 7. 2018.
[11] M. Dasilva *et al.*, "Modulation of cortical slow oscillations and complexity across anesthesia levels," *Neuroimage*, vol. 224, Jan. 2021, doi: 10.1016/j.neuroimage.2020.117415.
[12] M. V. Sanchez-Vives and D. A. McCormick, "Cellular and network mechanisms of rhythmic recurrent activity in neocortex.," *Nat. Neurosci.*, vol. 3, no. 10, pp. 1027–1034, Oct. 2000, doi: 10.1038/79848.
[13] C. Cirelli and G. Tononi, "Is sleep essential?," *PLoS Biol.*, vol. 6, no. 8, pp. 1605–1611, 2008, doi: 10.1371/journal.pbio.0060216.
[14] M. T. Alkire, A. G. Hudetz, and G. Tononi, "Consciusness and Anesthesia," *Science (80-.).*, vol. 7, no. 322, pp. 876–880, 2008, doi: 10.1126/science.1149213.Consciousness.
[15] M. Butz *et al.*, "Perilesional pathological oscillatory activity in the magnetoencephalogram of patients with cortical brain lesions," *Neurosci. Lett.*, vol. 355, no. 1–2, pp. 93–96, Jan. 2004, doi: 10.1016/j.neulet.2003.10.065.
[16] M. Rosanova *et al.*, "Sleep-like cortical OFF-periods disrupt causality and complexity in the brain of unresponsive wakefulness syndrome patients," *Nat. Commun.*, no. 1, p. 4427, Dec. 2018, doi: 10.1038/s41467-018-06871-1.
[17] M. V. Sanchez-Vives, "Propagation modes of slow waves in mouse cortex [Data set]." Human Brain Project Neuroinformatics Platform., 2020, doi: 10.25493/WKA8-Q4T.
[18] L. Pazzini *et al.*, "An ultra-compact integrated system for brain activity recording and stimulation validated over cortical slow oscillations in vivo and in vitro.," *Sci. Rep.*, vol. 8, no. 1, p. 16717, Nov. 2018, doi: 10.1038/s41598-018-34560-y.
[19] M. Mattia, S. Ferraina, and P. Del Giudice, "Dissociated multi-unit activity and local field potentials: A theory inspired analysis of a motor decision task," *Neuroimage*, vol. 52, no. 3, pp. 812–823, Sep. 2010, doi: 10.1016/j.neuroimage.2010.01.063.
[20] M. Ruiz-Mejias, L. Ciria-Suarez, M. Mattia, and M. V. Sanchez-Vives, "Slow and fast rhythms generated in the cerebral cortex of the anesthetized mouse.," *J. Neurophysiol.*, vol. 106, no. 6, pp. 2910–2921, Dec. 2011, doi: 10.1152/jn.00440.2011.
[21] D. E. Stewart, "PRODUCT ALGORITHMS FOR EIGENSYSTEMS," pp. 1–18, 1994.
[22] S. J. Schiff, X. Huang, and J. Y. Wu, "Dynamical evolution of spatiotemporal patterns in mammalian middle cortex," *Phys. Rev. Lett.*, vol. 98, no. 17, pp. 1–4, 2007, doi: 10.1103/PhysRevLett.98.178102.
[23] S. C. Johnson, "Hierarchical clustering schemes," *Psychometrika*, vol. 32, no. 3, pp. 241–254, 1967, doi: 10.1007/BF02289588.
[24] JH Ward, "Hierarchical Grouping to Optimize an Objective Function," *J. Am. Stat. Assoc.*, vol. 9, no. 1, pp. 76–99, 1963.
[25] R. G. Bettinardi, N. N. Tort-Colet, M. Ruiz-Mejias, M. V. Sanchez-Vives, and G. Deco, "Gradual emergence of spontaneous correlated brain activity during fading of general anesthesia in rats: Evidences from fMRI and local field potentials.," *Neuroimage*, vol. 114, pp. 185–198, Jul. 2015, doi: 10.1016/j.neuroimage.2015.03.037.
[26] A. Demertzi, E. Tagliazucchi, S. Dehaene, G. Deco, and P. Barttfeld, "Human consciousness is supported by dynamic complex patterns of brain signal coordination," no. February, pp. 1–12, 2019.
[27] A. López-González *et al.*, "Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics," *bioRxiv*, 2020, doi: 10.1101/2020.11.20.391482.
[28] S. Sarasso *et al.*, "Local sleep-like cortical reactivity in the awake brain after focal injury," *bioRxiv*, p. 2019.12.19.882290, Feb. 2019, doi: 10.1101/2019.12.19.882290.
[29] S. Casarotto *et al.*, "Stratification of unresponsive patients by an independently validated index of brain complexity," *Ann. Neurol.*, vol. 80, no. 5, pp. 718–729, 2016, doi: 10.1002/ana.24779.