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# 1 Disordered information processing dynamics in experimental epilepsy

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# 7 Abstract

8 Neurological disorders share common high-level alterations, such as cognitive deficits, anxiety,

9 and depression. This raises the possibility of fundamental alterations in the way information

10 conveyed by neural firing is maintained and dispatched in the diseased brain. Using

11 experimental epilepsy as a model of neurological disorder we tested the hypothesis of altered

12 information processing, analyzing how neurons in the hippocampus and the entorhinal cortex

13 store and exchange information during slow and theta oscillations. We equate the storage and

14 sharing of information to low level, or primitive, information processing at the algorithmic level,

15 the theoretical intermediate level between structure and function. We find that these low-level

16 processes are organized into substates during brain states marked by theta and slow

17 oscillations. Their internal composition and organization through time are disrupted in epilepsy,

18 loosing brain state-specificity, and shifting towards a regime of disorder in a brain region

19 dependent manner. We propose that the alteration of information processing at an algorithmic

20 level may be a mechanism behind the emergent and widespread co-morbidities associated with

21 epilepsy, and perhaps other disorders.

# 22 Introduction

23 Most, if not all, neurological pathologies, including Alzheimer's disease, epilepsies, and 24 Parkinson's disease, aside from their specificities, display commonalities in terms of cognitive 25 (e.g., memory) and mental (e.g., anxiety and depression) disorders (Hesdorffer, 2016). 26 Historically, attempts have been made to correlate higher-level changes to the underlying 27 structural alterations. However, structural alterations may be very different from one pathology 28 to the next, even within a given brain disorder. The origin of shared and generic deficits must 29 therefore be sought for at a level higher than the structural one. We hypothesize that diverse 30 pathological mechanisms can lead to similar modifications of information processing, emerging 31 from, and existing between, structural and functional levels. Whether information processing is 32 modified in a pathological context is not known. Furthermore, a formal framework for the 33 quantification of these processes is missing.

34

35 As a model of neurological disorder, we consider Temporal Lobe Epilepsy (TLE), the most 36 common form of epilepsy in adults (Tatum, 2012). TLE is itself highly heterogenous in terms of 37 differences of histopathology (Blumcke et al., 2013), semiology (Barba et al., 2007; Bartolomei et 38 al., 2008) and cognition and mental state (de Barros Lourenco et al., 2020; Holmes, 2015; 39 Krishnan, 2020). Such heterogeneity is also found in experimental models of TLE (Rusina et al., 40 2021). Structural alterations may change several features that are relevant for information 41 processing, such as rate coding, temporal coding, synaptic plasticity, and network oscillations 42 (Lenck-Santini & Scott, 2015). In keeping with this proposal, hippocampal place cells are unstable, 43 firing becomes randomized during ripples, synaptic plasticity, and oscillations are altered, and

these changes are correlated with deficits in hippocampus-dependent spatial memory in experimental epilepsy (Chauvière et al., 2009; Inostroza et al., 2013; Lenck-Santini & Holmes, 2008; Lopez-Pigozzi et al., 2016; Suarez et al., 2012; Valero et al., 2017). Given this diversity of deficits, it is reasonable to presume that in TLE local information processing is altered at a more fundamental level, with widespread impacts on multiple functions.

49

50 It is difficult to link specific alterations at the structural level to high order cognitive deficits as we 51 do not know where information processing is localized, what is being processed, nor how it is 52 integrated into function. In other words, with reference to the notion of the *algorithmic* level 53 introduced by Marr and Poggio (1977), we do not know what are the "algorithms" that bridge 54 structure and function. The common axiomatic view is that neural information processing stems 55 from the spatiotemporal organization of the firing of neurons. Information theory was designed 56 to be agnostic to the content of information and thus provides useful metrics to track primitive, 57 or fundamental, information processing operations (Shannon, 1948). Neuronal firing intrinsically 58 carries information due to its statistical properties. Auto-correlations in firing actively maintain 59 this information through time - active information storage (Lizier et al., 2012; Wibral et al., 2014), 60 and cross-correlated firing between different neurons allows the sharing of this information 61 between themselves (Kirst et al., 2016). Focusing on such basic operations allows investigation 62 of how patterns of coordinated neural firing may translate into primitive low-level information processing (Clawson et al., 2019), akin to the algorithmic level. Here, we hypothesize that the key 63 64 differences between control and epileptic networks are not only present at the structural level, 65 but also at a more general and core algorithmic level of quantifiable primitive operations.

66

67	To test this hypothesis, a multilevel experimental approach is required (Scott et al., 2018). Multi-
68	channel electrode recordings of neural populations provide such a dataset which spans two levels
69	of analysis: the action potential at the neuronal level and oscillations at the population level. As
70	neural computation is brain state dependent (Quilichini & Bernard, 2012), we consider the global
71	brain states of theta (THE) and slow oscillations (SO), which can be recorded during anesthesia.
72	Previous work in control animals demonstrate that neuronal activity patterns in the hippocampus
73	and entorhinal cortex switch between different information processing substates (IPSs) (Clawson
74	et al., 2019). An IPS corresponds to an epoch in which primitive operations of information storage
75	and sharing in a local microcircuit remain temporally consistent. IPSs continuously switch from
76	one IPS to another, similarly to what has been described at higher level of organization, such as
77	the dynamics of resting state networks and EEG microstates (Calhoun et al., 2014; Van de Ville et
78	al., 2010). In the control hippocampus and entorhinal cortex, the sequences of IPSs are complex,
79	i.e. standing between order and disorder (Clawson et al., 2019).
80	
81	Using an unbiased quantification of IPSs, we compare their properties and organization between
82	control and experimental epilepsy conditions. We focus on the hippocampus and the entorhinal
83	cortex, two major structures commonly affected in TLE (Curia et al., 2008). We find that IPS'
84	internal organization and switching dynamics, although not suppressed, shift toward a less

85 structured and more random spatiotemporal organization in experimental epilepsy than in 86 control. Such disruption of information processing at the algorithmic level itself could underly the

87 general performance impairments in TLE.

#### 88 Results

# 89 Design

90 We analyze the local field potentials (LFPs) and action potentials from individual neurons 91 measured in the hippocampus (CA1) and medial entorhinal cortex (mEC) from control (n = 5) and 92 experimental epilepsy (n = 6) rats under anesthesia (Figure 1A-B, see Methods for details). 93 Unsupervised clustering of the spectral content of LFPs reveals that field activity continuously 94 switches between two states: slow oscillations (SO, 0.5-3 Hz) and theta oscillations (THE, 3-6 Hz) 95 (Figure 1B, S1). As previously reported in freely moving animals (Chauvière et al., 2009), THE 96 power and peak frequency are decreased in CA1 in experimental epilepsy (Figure S1). Although, 97 the peak frequencies of THE and SO are not modified in the mEC in epilepsy, their power is 98 decreased (Figure S1). However, both frequency and power ratios between SO and THE are 99 similar in control and epilepsy.

100

101 We extract three features from the spike trains using a sliding widow procedure (Figure 1B-C): 102 (1) firing, the number of times a neuron fired within a window, (2) storage, the information 103 theoretical measure of active information storage (Lizier et al., 2012; Wibral et al., 2014), which 104 captures temporal patterns of spiking for a single neuron within a window – notably in our case, 105 how regular or repetitive these patterns are - and (3) sharing, an information theoretical 106 measure of information sharing (Kirst et al., 2016), which captures spatiotemporal patterns of 107 coordinated spiking across neurons within a window. First, we examine whether these features 108 are dependent upon the brain state (THE versus SO), the region (CA1 versus mEC) and the 109 condition (control versus epilepsy).

# 110 Epilepsy reduces firing, storage and sharing differences between THE and SO states

111 In control animals, we find that in both regions, average firing and storage of all neurons is larger 112 during THE than SO, while average sharing is lower (Figure 1D, see also S2), in keeping with the 113 idea that neuronal computation is brain state-dependent (Quilichini & Bernard, 2012). In 114 epilepsy, we find that average firing and storage are decreased during THE, but not during SO, as 115 compared to control in both mEC and HPC. As a consequence, the brain state-dependency of 116 firing and storage, which is consistent across controls, is reduced in both regions in epilepsy 117 (Figure 1D). There is thus, in epilepsy, a large deviation from the operating mode found in control 118 conditions.

119

We have previously shown that THE and SO states are in fact characterized by a complex dynamic organization in terms of firing, storage or sharing features (Clawson et al., 2019). A feature value (e.g., storage) can remain stable during a given time period (i.e., during successive windows), before switching to a different feature value with its own period of stability. We called these periods of stability *substates* of firing, storage or sharing. We begin by assessing the properties of substates in control and in epilepsy, as substate switching constitutes an important qualitative aspect of coordinated firing dynamics.



130 Figure 1: Experimental and analytical design - (A) Cartoon representing the approximate recording 131 locations in mEC (orange) and CA1 (blue) in control and experimental epilepsy. (B) Example of LFP (top) 132 and firing (bottom, each line represents one neuron, a dot represents an action potential) data recorded 133 in control CA1 and mEC during SO and THE. Overlayed is a representation of our analytic method that 134 uses 10 s long sliding windows shifted by 1 s at each step. (C) Cartoon examples of the four acquired 135 data features. (D) Average values and difference of differences graphs for data features taken from 136 spiking data during epochs of THE and SO in mEC (top) and CA1 (bottom) in both control and epilepsy

137 conditions. See S2 for the same graph represented as a function of region, rather than oscillatory state.

138 Circles and triangles represent the mean, and all bars represent a 99% bootstrapped confidence interval.

139 Significance is shown using the symbol (\*) with their standard corresponding meaning (\*, p<0.05; \*\*,

140 p<0.01; \*\*\*, p<0.001). The numerical values are provided in Table S1.

141

#### 142 Terminology, metrics, and methodology

143 Figure 2A illustrates an example of the procedure for a  $\sim$  25 min long recording performed in the 144 mEC in a control animal. Spectral analysis of the LFP reveals the alternation between THE and SO 145 states (upper row). Through an unsupervised substate extraction procedure based on k-means 146 clustering (see *Methods*), we identify in this example 4, 3, and 5 substates of stable patterns for 147 firing, storage and sharing, respectively. The four features together, seen as 4 rows in Fig 2A, 148 define a *switching table*. Each time point in the table corresponds to an *information processing* 149 state (IPS), i.e. a combination of global state, firing rate, storage, and sharing patterns at this time 150 point. By characterizing which neurons fire, how much, and with which correlation properties, an 151 IPS provides a robust characterization of the pattern of coordinated activity occurring within each 152 temporal window. Note that the switching transitions from one substate to the next are not 153 necessarily synchronous between the different features, a property found in all recordings. In 154 Figure 2B, we show, encoded as vertical color bars, the absolute values of firing, storage and 155 sharing features that different neurons assume in the different substates. For a given feature, 156 the values appear clearly different for a given neuron between substates. We will quantify these 157 differences in the next section.

159 The switching table of Figure 2A is constructed using an unsupervised clustering algorithm, k-160 means, guided by an a priori assumption that (1) there exist separable clusters of data and (2) 161 there are exactly k of these clusters (here 4, 3, and 5 for firing, storage and sharing, respectively). 162 Using a null model, we demonstrate that there exist separable clusters (Figure S3). However, as 163 the ground truth of how many clusters exist is unknown, statistical criteria can be used to find 164 the optimal number (as done in Clawson et al., 2019). Here, we use a more general approach 165 varying the k value for each firing, storage, and sharing feature while fixing k = 2 for the spectral 166 feature. Each quadruplet of k values will produce a specific switching table. Figure 2C illustrates 167 this concept, showing the resultant clustering of storage substates through time as k increases 168 from 3 to 10. A low value may underestimate the real number of substates, while a large number 169 may be an overestimate producing substates that rarely occur more than once (see Methods). 170 We therefore use a lower bound of k = 3, and a reasonable upper bound of k = 10, wherein the 171 clusters become too fine (Figure 2C, see Methods). We thus consider eight possible k values for 172 each feature, giving rise to  $8^3 = 512$  possible switching tables. Each switching table is 173 characterized by the total number of substates it contains:  $k_{tot} = 2 + k_{firing} + k_{storage} + k_{sharing}$  with a 174 maximum value of  $k_{max}$  = 32 (32 = 2, the number of spectral states + 3 features x 10). The 175 collection of all switching tables for a given recording defines a *library* of tables (Figure 2D). We 176 chose such a method with the intention that without an a priori approach on the underlying 177 principle, if we extract generic rules, they should be valid independently of the choice of number 178 of clusters, at least for a reasonable wide range of k values. Now, all analysis that can be done on 179 a switching table is performed for each library, which gives the added benefit of assessing the 180 robustness of the results regarding the number of clusters.

181

### 182 Substates are more contrasted in epilepsy

183 The vertical color bars in Figure 2B qualitatively show that individual neurons can take different 184 firing, storage or sharing values across substates. In order to quantify these differences, we 185 measure how "contrasted" are different substates. If we consider the firing feature of a given 186 neuron, we first calculate its global mean firing rate (over the whole duration of the recording), 187 and its mean firing rate within each substate. The relative contrast is defined as the difference 188 between the substate mean firing rate and the global mean firing rate, normalized by the global 189 mean firing rate. Evaluating contrast allows better tracking of the differing compositions of 190 substates at the single neuron level. Figure 2B shows the relative contrast plots for the 44 191 recorded neurons and the various substates in the same dataset and substate decomposition we 192 use as an example in Figure 2A. The differences between substates for each feature now clearly 193 appear as large changes in the distributions of contrast values for the recorded neurons. Now, 194 we extract the substate contrast of each substate for each feature - the average of the absolute 195 values of the heights of the bars in the relative contrast plot. This substate contrast tells us how 196 much a given substate stands out from its feature's global average. Increasing the number of k197 substates may decrease the substate contrast.

198

Figure 2E shows the distributions of the differences in contrasts between control (n=5) and epilepsy (n=6), for firing, storage, and sharing features in the mEC, for the chosen k values  $(3 \le k_{firing}, k_{storage}, k_{sharing} \le 10)$ . For all values of k, for all features, the contrast differences lie entirely below zero, demonstrating that substate contrast is generally higher in epilepsy than in 203 control. We also see no clear dependence upon k values, i.e., the number of substates. The same result is found in CA1, however higher bounds closer to the 99<sup>th</sup> percentile do cross 0 (Fig S4). 204 205 We thus identify another major alteration in epilepsy; substates are more contrasted, exhibiting 206 more marked differences with respect to the mean. This suggest that in epilepsy, substate 207 switching more strongly modulates the neural population with regards to firing, storage and 208 sharing. While this seems to stand in contrast with the previously described reduction of the 209 modulatory influence exerted by global oscillatory states, this may be explained by a disrupted 210 articulation between substate and global state, as we explain in the following section.



Figure 2 – Clustering & contrast in control and epilepsy – (A) An example state table for the mEC in a control animal with a total state count of  $k_{tot}$  = 14. The different substates are color coded. Note that switching is not synchronized across the different features. (B) Relative contrast values for the table given shown in (A). The substates shown in A are shown in B as a horizontal bar with the same color. Each graph shows the relative contrast of each of the 44 neurons, for each substate, and each feature. Below each graph is a visual indicator of a neuron's feature values

218 within the substate (vertical color bar). Here, the color scale varies from near 0, dark blue, to the 219 top 10% of all average activity within the state. Therefore, any neuron whose activity is within 220 this top 10% will be bright yellow. (C) Temporal dynamics (vertical axis) of storage substates as a 221 function of k (horizontal axis). The far-left column shows the dynamics of THE and SO spectral 222 states. (D) An example of a resulting state table library, or a collection of all possible combinations 223 of all clustering with a range of  $k_{tot} = 11 - 32$ . (E) Average contrast difference between control 224 and epilepsy is shown with respect to both feature and number of states, k. The circles represent 225 the mean difference, the thick black bars represent the 25-75% quantile and the thin black bars 226 represent the 1-99% quantile. The red dotted line is to add the null hypothesis line of no 227 significant difference between control and epilepsy.

228

# 229 Loss of global state specificity of firing, sharing and storage substates in epilepsy

230 Since firing patterns are brain state-dependent, we assess whether this type of specificity is also 231 found at the level of information processing substates. For a given state table in a library, we 232 calculate the probability that a substate occurs during THE, SO or both. We name it state 233 specificity index (SSI), a metric bounded between 0 (a substate occurs equally in THE or SO) and 234 1 (a substate is exclusive to either THE or SO) (see Methods). In control animals (Figure 3, blue 235 curves), most substates are brain state specific in both mEC and CA1, independently of k. Most 236 SSI values are above 0.8, well above the null hypothesis  $0.23 \pm 0.03$  value of lack of global state 237 specificity. Global state specificity of substates is thus a robust result in control animals with 238 respect to k.

239 The same analysis performed in epilepsy reveals a region dependent alteration in SSI (Figure 3, 240 red curves). There is a large decrease in SSI for all features in the mEC, indicating a loss of the 241 constraint exerted by global oscillatory states on the selection of possible substates, again 242 regardless to the chosen k's. In contrast, there is no such large loss of brain state specificity in 243 CA1, in particular no change for sharing. We conclude that the substate distribution becomes 244 "disordered", i.e., a large proportion of substates now occur during both THE and SO in the mEC 245 in epilepsy. In contrast, CA1 retains the brain state specificity of the distribution of substates. The 246 alteration of brain state-specificity of firing, sharing and storage substates is therefore brain 247 region dependent in epilepsy.



249

Figure 3 – Loss of brain state-dependency of substates in the mEC in epilepsy – State similarity index (SSI) is shown here vs number of *k* states for each feature in mEC and CA1. Blue represents the control data while red represents epilepsy. The bold lines represent the mean while the shaded regions represent a 99% bootstrapped confidence interval. The bootstrapped null model produced via randomizing gives an average SSI of 0.23  $\pm$  0.03 and is not shown here to increase visual clarity.

256

#### 257 Computing hubs are more numerous but less substate-specific in the mEC in epilepsy

258 Within each substate/feature we extract computing hub neurons, i.e., neurons with on average, 259 exceptionally high firing, storage or sharing values with regard to the substate (see Methods). As 260 previously discussed in Clawson et al. (2019), it is important to stress that different substates are 261 associated to different sets of hubs and that a neuron acting as firing, storage or sharing hub in a 262 given substate will not necessarily do so in another substate. So, while the fraction of neurons 263 being hub in a given substate remains small, the fraction of neurons serving as hub at least in one 264 substate is much larger, approaching ~40% on average. Figure 4A illustrates an example of the 265 distribution of hubs (same recording as in Figure 2A).

266

267 In control animals, the percentage of hubs increases with  $k_{tot}$  in both mEC and CA1 (Figure 4B), 268 which is expected due to the arbitrary over-clustering as k increases. We observe furthermore 269 that the percentage of neurons serving as hubs at least once is significantly increased in epilepsy, 270 by 5% in the mEC and 2.5% in CA1 (Figure 4B). This result is in agreement with the increase in 271 substate contrast found in epilepsy: more neurons are more contrasted and therefore are 272 detected as hubs. Note that, for both control and epilepsy, the percentage of neurons marked as 273 hubs is significantly larger as compared to randomized state tables (grey dotted lines in Figure 274 4B), confirming that the emergence of hubs is a direct fingerprint of the existence of well distinct 275 substates.

277 Figure 4A also shows that some computing hubs are shared by different substates, while others 278 are specific to one substate/one feature. In order to assess how substate-specific the computing 279 hubs are, we use a measure of *similarity* (see Methods). A null value indicates that every substate 280 has a unique hub set with no overlap between substates while a 1 value means that all substates 281 have an identical distribution. Figure 4C shows that, in control animals, a majority of hubs tend 282 to be substate-specific (similarity < 0.5). In CA1, the distribution of hubs is less substate-specific 283 than in the mEC (higher similarity). In epilepsy, the distribution of hubs does not change in CA1, 284 while hubs become significantly more substate-specific in the mEC. In other words, the status of 285 being hub is for a mEC neuron less stable in epilepsy than in control animals.

286

We conclude that, in epilepsy, the mEC and CA1 display an increase in the number of neurons labeled as hubs at least once, and that the substate-specificity of hubs is increased in the mEC. Taken together, these two findings suggest a more hectic and random-like emergence of computing hubs in epilepsy as compared to control, albeit expressed in different ways; in mEC there are more hubs that are simultaneously more specific than control and in CA1 there are more hubs while staying the same, indicating a possible 'shuffling' of hubs. We believe this also further confirms that alterations in information processing are brain-region dependent.



Figure 4 – Computing Hubs and their distributions – (A) Example of computing hubs in the control mEC extracted from a given state table. The y axis is unsorted neuron label, and the x axis shows the substates for firing (5), storage (4) and sharing (6) features. A yellow bar indicates that the given neuron is a computational hub during a substate. On the right is a summed version of the graph on the left, visually showing the fraction of neurons that are a hub at least once (40%). (B) The percentage of neurons that are hubs at least once is increased in epilepsy independently

- 301 of  $k_{tot}$ . The grey dotted line represents the mean of the shuffled, null model. (C) The similarity
- 302 index plotted as a function of  $k_{tot}$ . The hubs become less substate-specific in the mEC in epilepsy.
- 303 Blue and red are for control and epilepsy data, respectively. The bold lines are the mean, and the
- 304 shaded regions are the 99% bootstrapped confidence interval.
- 305

#### 306 Alterations in the core-periphery organization of CA1 computing hubs in epilepsy

307 The partners from whom a given neuron receives or to whom it sends information are 308 continuously changing (Clawson et al., 2019). At each time step, the instantaneous sharing 309 networks can be seen as having a dynamic core-periphery structure (Pedreschi et al., 2020), with 310 a core of tightly integrated neurons, surrounded by lightly connected periphery neurons. Two 311 key measures of the core-periphery structure are the coreness, how central or well-integrated 312 within a dense subnetwork – how "core" – a given neuron is, and the Jaccard index, a measure 313 indicating how similar (or, conversely, liquid) the connections are between the recorded neurons 314 between two time steps. We find that average coreness and the overall coreness distribution 315 shapes are not significantly changed in epilepsy for either mEC or CA1 (Fig S5). Thus, the core-316 periphery architecture of information sharing networks within every substate is preserved in 317 epilepsy. However, during the SO state, the average Jaccard values in CA1 are significantly 318 decreased in epilepsy as compared to control (Fig S5). Thus, in CA1 there is enhanced connectivity 319 variance and more volatile recruitment of neurons in the core.

320

#### 321 Assessing substate sequences

The analysis of individual features (firing, storage and sharing) revealed brain state- and brain region-dependent alterations in epilepsy. We now focus on a more integrated view of the informational patterns, in which we consider both the simultaneity of the ongoing types of patterns and their articulation in sequences along time. We perform this higher-level exploration using the notion of information processing states (IPS), driven by the idea of symbolization, as shown in Figure 2A (Porta et al., 2015). From each analysis time window, we generate a four328 letter word, with the letters representing the substate labels of the global state, firing, storage 329 and sharing features measured in this time window (see Methods). When the analysis window is 330 shifted by 1 s, another word is obtained, which is identical to the previous one if the substate 331 does not change. This procedure allows us to reduce the description of the complex simultaneous 332 variations of firing, storage and sharing patterns within the neuronal population to simple strings of symbolic words, a sort of "neuronal language" built of sequences of possible words in a 333 334 dictionary. We can then assess how the properties of these strings are modified in epilepsy at the 335 level of their dictionary and syntax.

336

337 We defined all possible state tables generated through our k-means procedure as a *library* (Fig 338 2). Now, as tables are considered as a sequence of words, we define the sequence of words 339 generated as a book. The number of letters, and therefore the number of words, depend upon 340  $k_{tot}$ . As a result, we label our differently generated books by  $k_{tot}$ . All 512 possible books per 341 recording are grouped together to form a *library*. For each library, we build two sister libraries 342 for comparison: one in which we sort every book internally to be highly ordered, and one in which 343 we randomize every book internally to be highly disordered (see Methods). Using this word/book 344 analogy, we begin to explore the organization of the language of the information processing 345 contained in the books held within the library – What words are expressed? Is there a syntax, or 346 organizational rules? And how does epilepsy change these measures?

# 348 Impoverishment of the Dictionary in the mEC in Epilepsy

349 For each  $k_{tot}$ , there is a fixed number of potential words that can be generated and possibly 350 appear within the associated book (see cartoon in Figure 5A). As in any language, only a fraction 351 of all possible words is expressed. For each book, we measure the used dictionary fraction, or 352 relative dictionary (see Methods). Figure 5A illustrates two end cases. The low relative dictionary 353 (left) uses a small number of expressed words, while the high relative dictionary (right) uses a 354 much richer vocabulary, wherein almost all of the potential dictionary is expressed. While the 355 measure of relative dictionary in and of itself is informative, it is difficult to use such a measure 356 to assess meaningful changes (i.e., before control and epilepsy) without having comparative 357 baselines. Therefore, we compute not only the relative dictionary of our libraries, but also that 358 of the ordered and random sister libraries (which correspond to the null hypotheses of order and 359 disorder in the 'language' of the book, respectively). We then apply a linear transformation to 360 the relative dictionary measure, resulting in 0 representing the relative dictionary measure of 361 ordered books, and a value of 1 representing a relative dictionary measure identical to that of 362 randomized books. Such a normalized relative dictionary measure tracks not only the richness of 363 the used dictionary but also its position between order and disorder.

364

Figure 5B shows that for both the mEC and CA1 in control and epilepsy conditions, the normalized relative dictionaries lie much closer to 0 than to 1, meaning that their relative dictionaries are much more similar to a system with organization that is ordered than disordered. In epilepsy, the relative dictionary is reduced with respect to control in the mEC (Figure 5B). Thus, the dictionary of state dynamics language seems impoverished in the mEC in epilepsy. There is also a reduction

370	in CA1, but only for books with low $k_{tot}$ values whereas it is increased for $k_{tot} > 15$ . This 'crossing'
371	of control and epileptic near $k_{tot}$ = 15 may be potentially explained by the strength of clustering for sharing
372	features (Fig S3). Contrary to all features, there exists only a small window of k for sharing in CA1 in which
373	k_means clusters the feature better than a null model. Therefore, dictionaries made with poor clustering
374	may drive the dictionary too high for low values of k. This is the first instance for which the generic
375	rule that results should be independent of the choice of k, fails. However, this characterization
376	of dictionaries further demonstrates that the alterations are brain region dependent.
377	
378	The relative dictionary provides important information about the words, but not how words are
379	organized in time. This is similar to the grammar, or syntax, of a traditional sentence. To analyze

380 this syntax (how words are organized from one window not the next), we quantify the level of

381 organization present in the state tables as a whole, i.e., the overall dynamics of a system moving

though IPSs (Figure 2A).





384 Figure 5 – Relative dictionaries within the libraries – (A) Fictional cartoons representing two 385 extremes for the measure of relative dictionary. Each row represents a feature (firing, storage, 386 sharing); for simplicity we do not take into account the brain states (THE and SO). We consider 387 three substates (light blue, dark blue, green) per feature (using the same color code for 388 simplicity), which makes a total of  $3^3 = 27$  words (the representation is similar to counting in 389 base 3 with color, increasing from left to right). Words that are not observed are shaded. A low 390 relative dictionary (left) contains a low fraction of all possible words, while a high relative 391 dictionary (right) contains a high fraction. (B) Relative dictionary values as a function of  $k_{tot}$ . As 392 expected, the fraction of words used in control decreases as the number of possible words 393 increases. The relative dictionaries are similar in mEC and CA1 in controls. There is a marked decrease in the relative dictionary in the mEC in epilepsy. In CA1, the relative dictionary in 394 395 increased or decreased as compared to control as a function of  $k_{tot}$ . Blue is representative of

- 396 control data and red is representative of epileptic data. The bold lines are the mean, and the
- 397 shaded regions are the 99% bootstrapped confidence interval.
- 398

# 399 The syntax of substate sequences is less regular in epilepsy

Compressibility is a key property of an object as it represents the degree of internal order of the 400 401 object. This is because any regularity within may be described by simply referencing its previous 402 occurrence. Again, our state tables are bordered by two extreme cases: order and randomness 403 (Figure 6A). An ordered table is dominated by a highly structured syntax, typically dominated by 404 a lower dictionary and long periods of sustained words. Therefore, an ordered table is very 405 compressible due to this internal order. A random table, on the other hand, typically contains an 406 exceedingly high number of words, which follow each other in a disorderly (random) manner. 407 This results in non-compressibility. A complex table is one that lies between those extremes. In 408 order to characterize the complexity of the state tables, we compute a tailored form of 409 description length complexity (Clawson et al., 2019; Rissanen, 1978), which is scaled to the sister 410 libraries of order and disorder. Thus, in Figure 6B, 0 represents the complexity of the ordered 411 library, something very compressible, while 1 represents the complexity of our disordered library, 412 something very uncompressible (as shown in Figure 6A). In controls, the complexity is similar in 413 mEC and CA1, close to an ordered table. In epilepsy, the complexity is significantly increased for 414 all  $k_{tot}$  values, while it is increased in the mEC at the high end of our library.

415

416 Combining the results from Figures 5 & 6, we can propose the following interpretation. In CA1, 417 the increase in complexity found in epilepsy, at least for books with sufficiently large  $k_{tot}$ , can be explained, at least in part, by an enriched dictionary, since enrichment of the relative dictionary
positively correlate with complexity (Clawson et al., 2019). In the mEC, the relative dictionary
decreases while the complexity mildly increases. Thus, mEC books have a less regular syntax
despite being constructed out of a lesser number of words.



Figure 6 – Order, disorder, and complexity – (A) Examples of state tables, similar to that of Fig 2A, from the mEC showing the two extremes of order and disorder as well as one of the possible state tables taken from the state table library. (B) Complexity values for both the mEC and CA1 as a function of  $k_{tot}$ . The complexity is similar in mEC and CA1 in controls. In epilepsy, the complexity is largely increased in CA1, and only for large  $k_{tot}$  values for mEC. Blue is representative of control data and red is representative of epileptic data. The bold lines are the mean, and the shaded regions are the 99% bootstrapped confidence interval.

## 430 Discussion

This study provides evidence that epileptic conditions alter information processing in its simplest sense, the primitive storage and sharing operations as we introduce here, in a brain-region dependent manner. As these basic processes are necessarily involved in a variety of neural computations, their alterations may indirectly impact numerous cognitive functions.

435

436 The main limitation to our study is that it is made under anesthesia, versus for example, goal-437 directed behavior to assess cognitive function. The type of analysis we performed is powerful as 438 it allows unraveling basic properties of information processing without needing to know which 439 computations are ongoing. However, it requires long-duration, stable recordings with large state 440 sampling to obtain enough data points to perform reliable statistics. We did not record during 441 natural sleep, because seizures and interictal spikes (which would act as strong confounding 442 factors) mostly occur during the light phase, while they do not occur under anesthesia. However, 443 a similar type of analysis performed in control animals led to similar results during sleep and 444 anesthesia (Clawson et al., 2019), suggesting that the anesthesia procedure we use does not 445 significantly alter core information dynamics.

446

We refer to the elementary information storage and sharing operations as primitive (or low level) information processing operations, as we consider them as fundamental building blocks within an algorithm to reach an end condition (like a function), similar to the "algorithmic level", introduced by Marr & Poggio (1977). Algorithm is used here in its most generic meaning, as we do not claim that the brain is analogous to a computer. Such primitive processing operations, as

452 we define them, represent nothing else than the emergent "informational effect" of very 453 concrete neurophysiological phenomena. Storage and sharing of information directly derive from 454 auto- and cross-correlations in firing, which widely vary in neuronal populations (Schneidman et 455 al., 2006), and can be directly measured from spiking activity of neurons. Other primitive 456 processing operations exist, such as information transfer (Palmigiano et al., 2017; Schreiber, 457 2000) or information modification (Lizier et al., 2013; Wibral et al., 2017). Our recordings and 458 choice of a time-resolved approach do not provide enough data to track these more sophisticated 459 operations. However, the processing functions of storage and sharing are especially important as 460 they represent statistical measures of information flow in time, and spacetime, respectively.

461

462 We show that primitive information processes are organized in temporal sequences of 463 information processing substates (IPSs), which are extracted via a cluster analysis. We have used 464 a non-biased approach, spanning many possible combinations of numbers of clusters. The fact 465 that most results are independent from the choice of the number of clusters provides a strong 466 argument for the genericity of our conclusions. With this approach, we demonstrate a 467 degradation of complexity due to enhanced randomness in epilepsy. This conclusion stems from 468 the convergence of complementary analyses. First, storage and sharing hubs are less robust, 469 waxing and waning in a more erratic manner across substates and the recruitment of neurons 470 into the integrated core of sharing networks is more volatile. Second, average storage and 471 sharing strength are more similar between brain states, and this "dedifferentiation" occurs 472 despite the higher contrast between substates. Third, the state specificity of IPS is reduced, i.e., 473 many IPSs are now redundant between THE or SO. Together, these results imply that a change in

brain state is no longer associated to strong specificity in information processing. Fourth, freed from the constraint of being strongly state-specific, the relative dictionary in epilepsy could, in principle, be increased. However, mEC has a decreased relative dictionary, which instead implies an ability to form unique IPSs. Yet, the description complexity of IPS sequences tends to be larger in epilepsy than control. In other words, IPS sequences have a less regular syntax despite being assembled out of less unique words.

480

481 The IPS dynamics of CA1 show, in general, less alterations than that of mEC. The fact that 482 information processing is affected in brain region-dependent manner is an important result. The 483 mEC and CA1 have distinct cytoarchitectures and different fates following an epileptogenic insult. 484 Most striking is the loss of layer 3 in the mEC, and the injury of many pyramidal cells and 485 interneurons in the CA1 region (Curia et al., 2008). It is not possible to assign a given alteration 486 in information processing to a given morpho-functional changes in the mEC or CA1. Global brains 487 states (THE and SO) and IPSs are emergent properties. Any change in any brain region can 488 potentially affect neuronal dynamics anywhere from the local to the global scale. Therefore, the 489 morpho-functional alterations in mEC or CA1 may contribute to any combination of local and 490 global changes. However, changes in terms of information processing do not necessarily have to 491 be homogenous across brain regions. In fact, brain region-specific modifications are expected as 492 each region is embedded in different functional networks. How these brain-region specific 493 changes contribute to comorbidities (such as cognitive deficit, anxiety, and depression) remain 494 to be determined.

496 Our measure of complexity is that of compressibility, accounting for the internal structure, i.e., 497 how internally ordered are IPS syntaxes. Any change in this internal organization would thus 498 imply an underlying change in algorithmic operation, resulting in different computation in control 499 and epilepsy conditions. Our measure of complexity does not allow distinguishing beween an 500 increase in processing versus an increase in noise, as complexity would grow in both cases. Other 501 measures can be used, but they would require more data (Crutchfield, 2011). However, in CA1, 502 books with large  $k_{tot}$  have an increased, rather than decreased dictionary size, which may explain 503 the strong increase in sequence complexity. It is not clear, however, that this dictionary increase 504 is a positive factor as it may reflect a more irregular IPS selection, with rare IPSs indicating 505 dysfunction in IPS sequential production. Another possibility is that boosted IPS sequence 506 complexity in CA1 and, at a lesser extent, mEC is a compensatory mechanism to generate a more 507 sophisticated syntax to compensate for other shortages, such as reduced hub stability and 508 degraded state-specificity of IPS.

509

510 In a biological context, the algorithmic level change comes as a result of altered collective, spiking 511 activity and could lead to an entirely different expression of higher-level behavior, such as 512 cognition. However, the question of whether this increase of complexity (decrease of internal 513 order) observed in epilepsy is the source of cognitive deficits or not remains ultimately open. It 514 has been theorized that "biological systems manipulate spatial and temporal structure to 515 produce order – low variance – at local scales" in an effort to adapt and survive (Flack, 2019). 516 Therefore, if networks are still functional in epilepsy conditions, are these manipulations now 517 less effective? Or is the resulting low variance order now too difficult to sustain due to a

518 combination of physiological and functional changes? These issues remain to be addressed. 519 Nevertheless, the approaches presented here introduce valuable insight into aspects of the 520 collective behavior of neural populations, and provide a quantitative framework to answer such 521 questions.

522

523 In conclusion, the framework we introduce here to compare information processing between 524 control and epilepsy, can be generalized to neurological disorders. Since most, if not all, of the 525 latter, including migraine, Alzheimer's disease, and Parkinson's disease are associated with co-526 morbidities, it will be particularly interesting to determine whether information processing at the 527 algorithmic level is also affected in these disorders. Following the principle of degeneracy (Prinz 528 et al., 2004), very different structural alterations, which characterize different neurological 529 disorders, may produce similar alterations in information processing, providing an explanation 530 for the commonalities of co-morbidities across different disorders.

531

#### 532 Methods

# 533 Ethics

All experiments were conducted in accordance with Aix-Marseille Université and Inserm Institutional Animal Care and Use Committee guidelines. The protocol was approved by the French Ministry of National Education, Superior Teaching, and Research, under the authorization number 01451-02. All surgical procedures were performed under anesthesia and every effort was made to minimize suffering and maximize the animals' wellbeing from their arrival to their death. All the animals were housed in pairs in large cages with minimal enrichment, food and

540	water at libitum, in a room with controlled environment (temperature: 22 $\pm$ 1 °C; 12 h light/dark
541	schedule with lights off at 8:00 pm; hygrometry: 55%; ventilation: 15-20 vol/h).
542	Data information.
543	We use in this work a portion of the data (5 out of 7 original experiments) initially published by

544 Clawson et al. 2019 as control data, which includes local field potentials (LFPs) and single-unit 545 recordings obtained from the dorsomedial entorhinal cortex (mEC) and the dorsal hippocampus 546 (HPC) of anesthetized rats. Six recordings are original data, which includes LFPs and single-units 547 recorded in the mEC and HPC recorded simultaneously under anesthesia in epileptic condition.

548 See Figures S1 for details on recordings, number of cells, and layers recorded.

# 549 Epilepsy model and surgery.

We induced status epilepticus (SE) on 6 male Wistar (250–400 g; Charles Rivers) by a single intraperitoneal (IP) injection of pilocarpine (320 mg/kg; Sigma-Aldrich), one week after receiving the animals from the vendor. To reduce peripheral effects, rats were pre-treated with methylscopolamine (1 mg/kg, IP; Sigma-Aldrich) 30 min before the pilocarpine injection. SE was stopped by diazepam (10 mg/kg, IP, two doses within a 15-min interval) after 60 min. Then the animals were hydrated with saline (2 ml, IP, twice within 2 h) and fed with a porridge made of soaked pellets, until they resumed normal feeding behavior.

At least 8 weeks after SE induction, we performed acute recordings. Rats were first quickly placed in isoflurane (4% in 2l/min O<sub>2</sub>) and injected IP with urethane (1.5 g/kg) and ketamine/xylazine (20 and 2 mg/kg, IM), additional doses of ketamine/xylazine (2 and 0.2 mg/kg) being supplemented during the electrophysiological recordings. At all times the body temperature was monitored and kept constant with a heating pad. Heart rate, breathing rate, pulse distension, and arterial oxygen

562 saturation were also monitored with an oximeter (MouseOX; StarrLife Sciences) during the 563 duration of the experiment to ensure the stability of the anesthesia and monitor the vital 564 constants. The head was fixed in a stereotaxic frame (Kopf) and the skull was exposed and 565 cleaned. Two miniature stainless-steel screws driven into the skull above the cerebellum served 566 as ground and reference electrodes. Two craniotomies were performed to reach the mEC and 567 the CA1 field of the HPC, respectively: from bregma: -7.0 mm AP and +4.0 mm ML; and from 568 bregma: -3.0 mm AP and +2.5 mm ML. We chose these coordinates to respect known anatomical 569 and functional connectivity in the cortico-hippocampal circuitry (Witter et al., 1988; Witter et al., 570 1989). Two 32-site silicon probes (NeuroNexus) were mounted on a stereotaxic arm each. A 571 H1x32-10mm-50-177 was lowered at 5.0-5.2 mm from the brain surface with a 20° angle to reach 572 the dorso-medial portion of the mEC, and a H4x8-5mm-50-200-177 probe was lowered at 2.5 573 mm from the brain surface with a 20° angle to reach dorsal CA1. The on-line positioning of the 574 probes was assisted by: the presence of unit activity in cell body layers and the reversal of theta 575 ([3 6] Hz in anesthesia) oscillations when passing from layer 2 to 1 for the mEC probe, and the 576 presence in *stratum pyramidale* either of unit activity and ripples (80-150 Hz) for the HPC probe. 577 At the end of the recording, the animals were injected with a lethal dose of Pentobarbital Na 578 (150mk/kg, i.p.) and perfused intracardially with 4% paraformaldehyde solution. We confirmed 579 the position of the electrodes (DilC18(3) (catalog #46804A, InterChim) was applied on the back 580 of the probe before insertion) histologically on 40 µm Nissl-stained section as reported previously 581 in detail (Ferraris et al., 2018; Quilichini et al., 2010). We used only experiments with appropriate 582 position of the probe for analysis.

583 Data collection and spike sorting.

584 Extracellular signal recorded from the silicon probes was amplified (1000x), bandpass filtered (1 585 Hz to 5 kHz) and acquired continuously at 32 kHz with a 64-channel DigitalLynx (NeuraLynx) at 586 16-bit resolution. We preprocessed the raw data using a custom-developed suite of programs 587 (Csicsvari et al., 1999). The signals were down-sampled to 1250 Hz for the local field potential 588 (LFP) analysis. Spike sorting was performed automatically, using KLUSTAKWIK 589 (http://klustakwik.sourceforge.net (Harris et al., 2000)), followed by manual adjustment of the 590 clusters, with the help of auto-correlogram, cross-correlogram and spike waveform similarity 591 matrix (KLUSTERS software package, http://klusters.source-forge.net (Hazan et al., 2006)). After 592 spike sorting, we plotted the spike features of units as a function of time, and we discarded the 593 units with signs of significant drift over the period of recording. Moreover, only units with clear 594 refractory periods and well-defined cluster were included in the analyses (Harris et al., 2000). 595 Recording sessions were divided into brain states of theta (THE) and slow oscillation (SO) periods 596 using a visual selection from the ratios of the whitened power in the HPC LFP [3 6] Hz theta band 597 and the power of the mEC LFP neighboring bands ([1 3] Hz and [7 14] Hz), and assisted by visual 598 inspection of the raw traces (Ferraris et al., 2018; Quilichini et al., 2010). We then used band-599 averaged powers over the same frequency ranges of interest as features for the automated 600 extraction of spectral states via unsupervised clustering, which confirmed our manual 601 classification. We determined the layer assignment of the neurons from the approximate location 602 of their soma relative to the recording sites (with the largest- amplitude unit corresponding to 603 the putative location of the soma), the known distances between the recording sites, and the 604 histological reconstruction of the recording electrode tracks. Animals were recorded for at least 605 two hours in order to get few alternations of THE and SO episodes.

#### 606 **Feature Computation**

607 As in our previous work, for each region recorded we computed 4 main features from the 608 electrophysiological data: global oscillatory band, neuronal firing sets, active information storage 609 and the information sharing. We also keep the same sliding window paradigm where each 610 feature is computed within a 10 second window, and then the window is then moved forward in 611 time 1 second, which gives a 9 second overlap. Therefore, when features are computed as 612 described below, they are computed in this windowed fashion. The global oscillatory band 613 features were computed by examining the LFP from both EC and CA1 and computing spectral 614 power within 8 unequally sized frequency ranges (0–1.5 Hz, 1.5–2 Hz, 2–3 Hz, 3–5 Hz, 5–7 Hz, 7–

615 10 Hz, 10–23 Hz and 23–50 Hz), averaged over all channels within each of the recorded layers.

616 Firing sets, active information storage, and the information sharing networks were all computed 617 using a binarized raster built from the temporal labeling of spike firing (see Data Collection and 618 Spike Sorting). Spiking data was binned using a 50 ms bin; if a neuron fired within a given bin the 619 output is a '1', and if not, a '0'. This, for example would mean that a 2-hour recording would be 620 transformed from a 7200 second × N neuron matrix to a 7200000 × N neuron matrix that is 621 composed solely of 0's and 1's. Firing sets were computed by computing the average firing 622 density for each neuron within a window, and after these averages were compiled into time-623 dependent vectors. This resulting matrix is the Firing Features. Active information storage was 624 computed by measuring the mutual information of a neuron's binarized spike train between a 625 given window and the window previous. What active information storage seeks to capture is the temporal ordering of individual spiking neurons, rather than capturing neurons that fire 626 627 temporally close to one another (such as in the firing features). The resulting matrix is the Storage 628 *Features*. Information sharing is computed by measuring the mutual information between a given 629 neuron's binarized spike train within a window and another neuron's binarized spike train in the 630 window previous. This process is iterated over all possible neuron pairs. Information sharing 631 captures a similar metric to that of active information storage, although the key difference is that 632 information sharing captures not just the temporal ordering, but the spatio-temporal ordering of 633 spike timing, as it is computed across neuron pairs, rather than individual neurons. The resulting 634 matrix is the Information Sharing. Although these measures have only been briefly described 635 here, we suggest to the interested reader to examine the methods presented in our previous 636 work [REF] where they have been rigorously defined.

637

#### 638 Feature-Based Substate Extraction

639 State extraction for each recording were also computed using the methods of our previous work, 640 namely based around k-means clustering of each feature. The exception here, is we no longer 641 choose a stable number of K clusters in k-means. Rather we cluster our 3 raster-based computed 642 features (firing, storage, sharing) 3 separate times with K ranging from K = 3, 4, ... 10. The function 643 'kmeans' was used from the default MATLAB toolbox. More information can be found on the 644 Mathworks website. These K values were chosen as they represented a clustering range of too 645 gross to too fine based on previous findings.  $K \le 2$  would represent the same, or less, number 646 of states as global states, which was previously established to be too small (Clawson et al., 2019). 647 The clustering became too fine when  $K \ge 10$ , wherein many substates only appeared for brief 648 time periods, and never re-occurred. For each feature there are 8 different clustering results, 649 done in an unsupervised manner 3 times to ensure that our results do not rely on single instance of clustering. This gave our analysis an opportunity to compute all metrics defined below over a robust range of K, ensuring that we can investigate how our substate stable metrics and results vary with arbitrarily too little or too many substates.

653

To compute the null model for substate extraction the process detailed above was repeated with the time stamps of all firing, storage and sharing jittered. This therefore retains the global mean and variance. Then, k-means was run on this jittered dataset 3 times, to produce 3 different clustering of the randomized dataset. These were not modified after this step and were used in any instances where a null model was needed (i.e. for silhouette and contrast).

659

#### 660 Substate Tables

Our main meta-object of study is a state table, a combination of our four features into a matrix (4 x number of windows). Table generation is an iterative process, as we have 8 possible substate configurations per feature. First, k = 3 in cluster attempt 1 for firing (FIRE  $_{K3C1}$ ), k = 3 in cluster attempt 1 for storage (STORE $_{K3C1}$ ), and k = 3 in cluster attempt 1 for sharing (SHARE $_{K3C1}$ ), are used in conjunction with the clustered spectral substates to form substate table 1 (Figure 2A).

666

Then, FIRE  $_{K3C1}$ , STORE $_{K3C1}$ , and SHARE $_{K4C1}$  are used in conjunction with the clustered spectral substates to form substate table 2. After, FIRE  $_{K3C1}$ , STORE $_{K3C1}$ , and SHARE $_{K5C1}$  used in conjunction with the clustered spectral substates to form substate table 3. This process continues such that all combinations of possible k values have been saved for a total of 512 different substate tables, with the final table having FIRE  $_{K10C1}$ , STORE $_{K10C1}$ , and SHARE $_{K10C1}$ . It is important to note that all tables have the same spectral clustering, as the 2 substates of SO and THE are extremely robust
as discussed above. This entire process is then repeated for each clustering attempt, resulting in
3 sets of our 512 substate tables for each region for each recording. Where applicable, all results
are given as a function of total k states per table (i.e. for state table 1, there are 2 global states,
3 firing, 3 storage and 3 sharing for a total k<sub>total</sub> = 11).

677

678 To produce the ordered tables for the 'ordered' null model, each substate table was sorted such 679 that all substates with label '1' appeared first, label '2' was second, and so on and so forth. This 680 can easily be achieved with the MATLAB function sort. Note that there is only one possible 681 version of this type of ordering, and therefore the sample size for ordered tables is the same as 682 recordings (n = 5 for control, n = 6 for epilepsy). To produce the randomized tables, substate 683 labels were randomly permuted in time. For this process, we used bootstrapping to produce as 684 5000 randomizations to ensure the random null model was as strong as possible. To do this, 90% 685 of each table was taken, randomly permuted and saved. These resulting tables were used as the 686 random null model for relative dictionary and complexity seen in Figure 5 & 6.

687

#### 688 **Contrast**

To calculate contrast for a given feature we first calculate its global mean for each neuron (i.e., global mean firing per neuron). Here, 'global' refers to the entire recording. We then calculate the substate mean for each neuron by concatenating all periods of a given substate and calculating the mean across the 'entire' substate. The formula for contrast is then defined as the

693 difference between the substate mean firing rate and the global mean firing rate, normalized by

694 the global mean firing rate.

$$695 \qquad \qquad contrast = \frac{\mu_{substate} - \mu_{global}}{\mu_{global}}$$

This allows the contrast to be either positive or negative. This process was done for all 3 features of firing, storage and sharing such that there are contrast values for each. This process was repeated for all possible clustering, therefore a contrast value per feature per *k*.

699

# 700 Substate-Specificity

To compute the distribution of substates within periods of SO and THE we counted the number of times a substate appeared within a given epoch. Some substates exclusively appeared in only SO or THE, while others occurred in both. From these frequencies we estimated p(THE) and p(SO), i.e. the probability of a given substate occurring in either THE or SO, respectively. SSI is then:

706

SSI = |p(THE) - p(SO)|

This equation results in SSI bound between 0 and 1, where 1 represents a state who exclusively

occurs in either THE or SO and 0 represents a state that occurs equally in THE and SO.

709

# 710 Hubs & Hub Stability

In this work we define a hub neuron in the same way as our previous work. Namely, for a given feature if a neuron's activity within a given substate was higher than the 90<sup>th</sup> percentile it was marked as a hub for the feature for that state. We compute hubs for every iteration of state table as defined above, such that we have a graph, or matrix, (see FIG 4A) for each state table. These matrices are Neuron ×  $k_{total}$  where each entry is either a '0' for non-hub or '1' for hub. To compute how stable each of these matrices are as a function of k, we compute the normalized hamming distance of each matrix using the *pdist2* function in MATLAB but modified so that it gives a sense of how stable hubs are across states, where perfect similarity would result in a '1', and no similarity at all would give a '0'.

720

## 721 Coreness & Jaccard

The values for coreness & Jaccard were computed using the methods presented in Pedreschi et al. (2020). These were then analyzed using the same sliding window technique as presented in 'Feature Computation'. After, periods of THE and SO were analyzed with similar techniques as that of Figure 1.

726

## 727 Dictionary & Complexity

728 To compare sequences of substates of different types or in different regions we introduced a 729 symbolic description of substate switching. With this description, each substate label acts as a 730 letter symbol s<sup>(p)</sup>, where (p) can indicate firing, sharing or storage. For example, the firing features 731 from the example substate table 1 [FIG 2A] would have the integer labels 1, 2, 3, and 4 (they can 732 also arbitrarily be assigned letters as well, i.e. A, B, and C). We can therefore describe the temporal sequences of the visited substates of each feature as an ordered list of integers  $s^{(p)}(t)$ . 733 734 Once substate labels are thought of as letters, we define the combination of firing, storage and 735 sharing letters in each state table from a given window as 3 letter words. Using the formalism of 736 linguistics, we can then compute the *dictionary*, or the number of words expressed, of a given

recording within a region. We can also compute the *used dictionary fraction*, or the number of words found in the dictionary divided by the number of theoretically possible words given the number of substates per feature. For example, substate table 1 could have expressed 27 unique words. The used dictionary fraction was computed in an identical way to that of Clawson et al 2019. Specially, see 'Complexity of substates sequences.

742

Using these methods, we compute the complexity of the sequences expressed using the notions of Kolmogorov-Chaitin complexity and minimum description length approaches (Crutchfield, 2011). While further discussion of method can be found here (Clawson et al., 2019) – the aspects of this complexity measure that is relevant for this work is that a random sequence of letters (and words) produces a higher complexity, while an ordered sequence of letters (and words) would produce a low complexity.

749

#### 750 Ordered & Random Substate Tables

To have relevant points of reference in our measures, each substate table was ordered and randomized. For the case of ordering, all substate labels for all features were sorted in ascending order which keeps the total lifetime of any state constant, while removing the temporal organization in an *ordered* fashion. In the case of randomization, all substate labels for all features were randomized 500 times, which again keeps the total lifetime of any state constant, while removing the temporal organization in a *random* fashion.

To compute the relative minimums and maximums for comparisons between order and random
 the MATLAB function 'rescale' was used. The minimums were computed using the average (of a

- 759 given measure) of all ordered state tables for a given ktotal and the maximums were computed 760 using the average (of a given measure) of all random substate tables for a given ktotal. 761 Plotting 762 Various tools were used for plotting. While mostly done via MATLAB, other tools were also 763 used from 'Moving Beyond p-values' (Ho et al., 2019). 764 765 **Bibliography** 766 Barba, C., Barbati, G., Minotti, L., Hoffmann, D., & Kahane, P. (2007, Jul). Ictal clinical and scalp-EEG 767 findings differentiating temporal lobe epilepsies from temporal 'plus' epilepsies. Brain, 130(Pt 768 7), 1957-1967. https://doi.org/10.1093/brain/awm108 769 770 Bartolomei, F., Chauvel, P., & Wendling, F. (2008, Jul). Epileptogenicity of brain structures in human 771 temporal lobe epilepsy: a quantified study from intracerebral EEG. Brain, 131(Pt 7), 1818-1830. 772 https://doi.org/10.1093/brain/awn111 773 774 Blumcke, I., Thom, M., Aronica, E., Armstrong, D. D., Bartolomei, F., Bernasconi, A., Bernasconi, N., Bien, 775 C. G., Cendes, F., Coras, R., Cross, J. H., Jacques, T. S., Kahane, P., Mathern, G. W., Miyata, H., 776 Moshe, S. L., Oz, B., Ozkara, C., Perucca, E., Sisodiya, S., Wiebe, S., & Spreafico, R. (2013, Jul). 777 International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task 778 Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia*, 54(7), 1315-1329. 779 https://doi.org/10.1111/epi.12220 780 781 Calhoun, V. D., Miller, R., Pearlson, G., & Adali, T. (2014, Oct 22). The chronnectome: time-varying 782 connectivity networks as the next frontier in fMRI data discovery. Neuron, 84(2), 262-274. 783 https://doi.org/10.1016/j.neuron.2014.10.015 784 785 Chauvière, L., Rafrafi, N., Thinus-Blanc, C., Bartolomei, F., Esclapez, M., & Bernard, C. (2009). Early 786 deficits in spatial memory and theta rhythm in experimental temporal lobe epilepsy. Journal of 787 Neuroscience, 29(17), 5402-5410. https://doi.org/29/17/5402 [pii] 10.1523/JNEUROSCI.4699-788 08.2009 789 790 Clawson, W., Vicente, A. F., Ferraris, M., Bernard, C., Battaglia, D., & Quilichini, P. P. (2019, Jun). 791 Computing hubs in the hippocampus and cortex. Sci Adv, 5(6), eaax4843. 792 https://doi.org/10.1126/sciadv.aax4843
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# 958 Data Availability

- 959 Partial data and codes can be found here: 10.5281/zenodo.4534369
- 960 Full codes, including figure generation as well as complete dataset are available upon request.
- 961

#### 962 Competing Interests

963 The authors declare that they have no competing interests.

# 964 Supplementary Figures





- 974 and SO power in the mEC, and to a lesser extent on THE power in CA1. For all graphs, 5000
- 975 bootstrap samples were taken; the confidence interval is bias-corrected and accelerated.







# **Silhoutte Difference**

984

985 S3 – Null model with mean silhouette difference – The mean silhouette difference between a 986 randomized null clustering model and the silhouettes found using k-means on non-shuffled 987 data. Each point was calculated by computing mean silhouette values from a random selection 988 of the randomized and normal clustering and taking the difference. This was done 500 times to 989 produce error bars, but the error bars were so small that they appear to be squares on the 990 graph. The blue line is representative of control data and the red line represents epilepsy data. 991 There is a very large difference for firing and storage modalities from the null model for all k 992 values in both CA1 and mEC in control and epilepsy conditions. Of special note is the sharing 993 states found within CA1 (bottom right). We find that for both control and epilepsy conditions,

- 994 our measure crosses 0 at k=5 and k=7, respectively, but fluctuates back above 0 until k=9 states
- 995 in control and k=10 in epilepsy. This would indicate that the clustering only weakly holds in
- 996 these intermediate values of k before not separating states better than a null, shuffled model
- 997 up until the higher k values. Therefore, it may be that the states are either less definable in CA1
- 998 or, that on average there tend to be more states for sharing in both the control and epileptic
- 999 states in CA1 and would therefore require higher k, on average.



S4 – Contrast Values for Control vs Epilepsy in CA1 – Average contrast difference between
 control and epilepsy is shown with respect to both feature and number of states, *k*. The circles
 represent the mean difference, the thick blue bars represent the 25-75% quantile and the thin
 blue bars represent the 1-99% quantile. The red dotted line is to add the null hypothesis line of
 no significant difference between control and epilepsy.



S5 – Coreness and Jaccard Values – Average values and difference of differences graphs for
 data features taken from sharing networks, found using the sharing feature, for both
 control and epileptic animals. Circles and triangles represent the mean, and all bars
 represent a 99% bootstrapped confidence interval. Note the very large effect size in the
 decrease of the Jaccard index in CA1 during SO. Accordingly, the brain state specificity of
 connectivity variance is lost. Significance is shown using the symbol (\*) with their standard
 corresponding meaning (\*, p<0.05; \*\*, p<0.01; \*\*\*, p<0.001).</li>

	mEC			CA1			
Firing	mean difference	CI	P value	mean difference	CI	P value	
Control	-0.0593	[-0.0815 <i>,</i> - 0.0365]	0	-0.0475	[-0.0823 <i>,</i> - 0.0162]	0.0002	
Epilepsy	-0.0217	[-0.0432 <i>,</i> - 2.55e-05]	0.008	0.00082	[-0.0226, 0.0263]	0.00082	
Storage							
Control	-0.133	[-0.18 <i>,</i> - 0.0859]	0	-0.0828	[-0.146 <i>,</i> - 0.0214]	0.0002	
Epilepsy	-0.0584	[-0.0933 <i>,</i> - 0.0224]	0	0.0034	[-0.0452 <i>,</i> 0.0528]	0.0034	
Sharing							
Control	0.109	[0.0643 <i>,</i> 0.16]	0	0.0582	[0.0369, 0.0814]	0	
Epilepsy	0.0535	[-0.022 <i>,</i> 0.128]	0.0594	0.0285	[0.0105 <i>,</i> 0.0435]	0	

# 1013 ST1 – P value reporting: THE/SO unpaired mean difference

1014

1015The p-value reported here is from a two-sided permutation t-test with CI intervals at 99%. 50001016bootstrap samples were taken; the confidence interval is bias-corrected and accelerated. The P1017value(s) reported are the likelihood(s) of observing the effect size(s) if the null hypothesis of1018zero difference is true. For each permutation P value, 5000 reshuffles of the control and test1019labels were performed. They are included here to satisfy a common requirement of scientific1020journals. (Ho et al., 2019)

# 1021 ST2 – P value reporting: Difference of Difference Graphs

	mEC			НРС			
	Effect	CI	Р	Effect	CI	Р	
			value			value	
Firing							
Control v Epilepsy	-0.025	[-0.043, -0.007]	<0.001	-0.031	[-0.051, -	<0.001	
					0.011]		
THE v SO	-0.044	[-0.062, -0.026]	<0.001	-0.023	[-0.044 <i>,</i> - 0.003]	0.003	
Diff of Diff	0.0377	[0.001.0.0744]	0.008	0.048	[0.0072.	0.002	
	010077	[0:001) 0:07 11]	0.000		0.0889]	0.002	
Storage							
Control v Epilepsy	-0.126	[-0.161, -0.092]	< 0.001	-0.107	[-0.147, -	< 0.001	
					0.068]		
THE v SO	-0.104	[-0.138, -0.069]	<0.001	-0.041	[-0.081 <i>,</i> -	0.007	
					0.002]		
Diff of Diff	0.0783	[0.0099, 0.1467]	0.003	0.083	[0.0041,	0.007	
					0.1619]		
Sharing							
Control v Epilepsy	0.0122	[-0.032, 0.0563]	0.474	-0.033	[-0.047, - 0.018]	<0.001	
THE v SO	0.0844	[0.0443.0.1325]	<0.001	0.0433	[0.029.	<0.001	
			.0.001		0.0576]		
Diff of Diff	-0.052	[-0.141, 0.0359]	0.126	-0.03	[-058, -0.001]	0.007	
Coreness							
Control v Epilepsy	-0.003	[-0.019, 0.0124]	0.578	0.001	[-0.012 <i>,</i> 0.0143]	0.849	
THE v SO	0.0126	[-0.003, 0.0285]	0.04	0.0056	[-0.008,	0.28	
					0.0188]		
Diff of Diff	0.0099	[-0.022, 0.0416]	0.42	0.0205	[-0.006, 0.047]	0.047	
Jaccard							
Control v Epilepsy	0.0158	[0.0074, 0.0241]	<0.001	-0.046	[-0.051, -	<0.001	
					0.042]		
THE v SO	0.0615	[0.0615, 0.0782]	<0.001	0.0325	[0.028,	<0.001	
D.10. 4 - 10					0.0369]		
Diff of Diff	-0.009	[-0.026, 0.0076]	0.16	-0.084	[-0.093, -	<0.001	
					0.075]		