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**Trial-by-trial variability in cortical responses exhibits scaling in spatial correlations  
predicted from critical dynamics**

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Pages/Figures: 33 pages, 5 figures

Suppl. Material: 5 pages, 3 figures

Running Title: Scale-free correlations in neuronal activity

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Keywords: mouse, primary cortex, cortex, 2-photon imaging, nonhuman primate, prefrontal and premotor cortex, high-density microelectrode array, local field potential, correlation functions, neuronal avalanches, network simulations, criticality

## 1 **Abstract**

2 Simple sensory stimuli or motor outputs engage large populations of neurons in the mammalian cortex.  
3 When stimuli or outputs repeat, the robust population response contrasts with fluctuating responses of  
4 individual neurons, known as trial-by-trial variability. To understand this apparent discrepancy, a detailed  
5 identification of the underlying spatiotemporal correlations is required. Here, we analyze spatial  
6 correlations in the instantaneous fluctuations between neurons relative to the neuronal population. Using  
7 2-photon imaging of visual and auditory responses in primary cortices of awake mice, we show that these  
8 correlations grow linearly with the size of the observed cortical area. We extend these observations to the  
9 cortical mesoscale by analyzing local field potentials in behaving nonhuman primates. In network  
10 simulations, we demonstrate this linear growth in spatial correlation to emerge at criticality. Our findings  
11 suggest that trial-by-trial variability is a signature of critical dynamics in cortex maintaining robust, long-  
12 range spatial correlations among neurons.

13

## 14 **Introduction**

15 Even simple stimuli or movements engage large numbers of neurons in the mammalian cortex. These  
16 robust population responses are contrasted by the heterogeneity and fluctuations of single neuron  
17 responses observed during repeated stimuli or motor outputs. This response variability or trial-by-trial  
18 variability has been consistently found *in vivo* for neurons that are non-selective to a particular stimulus  
19 feature (Deweese & Zador, 2004) as well as highly selective neurons (Heggelund & Albus, 1978; Tolhurst  
20 *et al.*, 1983; Vogels *et al.*, 1989; Shadlen & Newsome, 1998) and *in vitro* under network and stimulus  
21 conditions of reduced complexity (e.g. (Haroush & Marom, 2019)). While part of the variability has been  
22 attributed to single neuron properties, e.g. through a non-linear transfer between the membrane potential

23 and firing rate (Carandini, 2004; Charles *et al.*, 2018), numerous findings point to a significant role of the  
24 network dynamics to the observed variability. In particular, response variability is shared among neurons  
25 (Cohen & Kohn, 2011) through shared gain (Goris *et al.*, 2014), includes the interactions between selective  
26 as well as non-selective neurons (Kotekal & MacLean, 2019), is supported by local cortical motifs such  
27 as fan-in (Dechery & MacLean, 2018) and depends on the balance of excitation and inhibition (Haroush  
28 & Marom, 2019). This potential role in network dynamics is in line with early findings that response  
29 variability strongly correlates with ongoing synaptic activity preceding a stimulus (Arieli *et al.*, 1996).

30       The diversity and variability encountered in single neuron responses to even simple, repeated stimuli  
31 raises the question whether there exist certain principles that underlie this variability in the face of coherent  
32 network responses. These principles in order to be general should be independent from the specific  
33 stimulus given or motor output achieved, which translates into the general question of how individual  
34 elements, by interacting locally, can achieve a coherent, global population response. Correlation length  
35 measures can be used to identify the relationship between global, coherent system responses and  
36 fluctuating system components (Wilson, 1979). By studying the correlation in the fluctuations of system  
37 components, one can determine the distance at which they behave independently. It is well-established  
38 that the correlation length diverges at criticality (Wilson, 1976) in the thermodynamic limit. For finite  
39 systems, however, this asymptote behavior can be demonstrated by showing that the correlation length  
40 grows with system size. This relationship between correlation length and system size has been identified  
41 in the context of bird flocks, where a flock still maintains a coherent trajectory in space despite fluctuations  
42 in single bird trajectories (Cavagna *et al.*, 2010; Bialek *et al.*, 2012; Bialek *et al.*, 2014). It was also  
43 demonstrated for resting activity of the human brain that the correlation length of the blood oxygenated  
44 level dependent (BOLD) signal scales linearly with the size of the brain region measured (Fraiman &  
45 Chialvo, 2012), a finding in line with expectations that the brain at rest maintains a critical state.

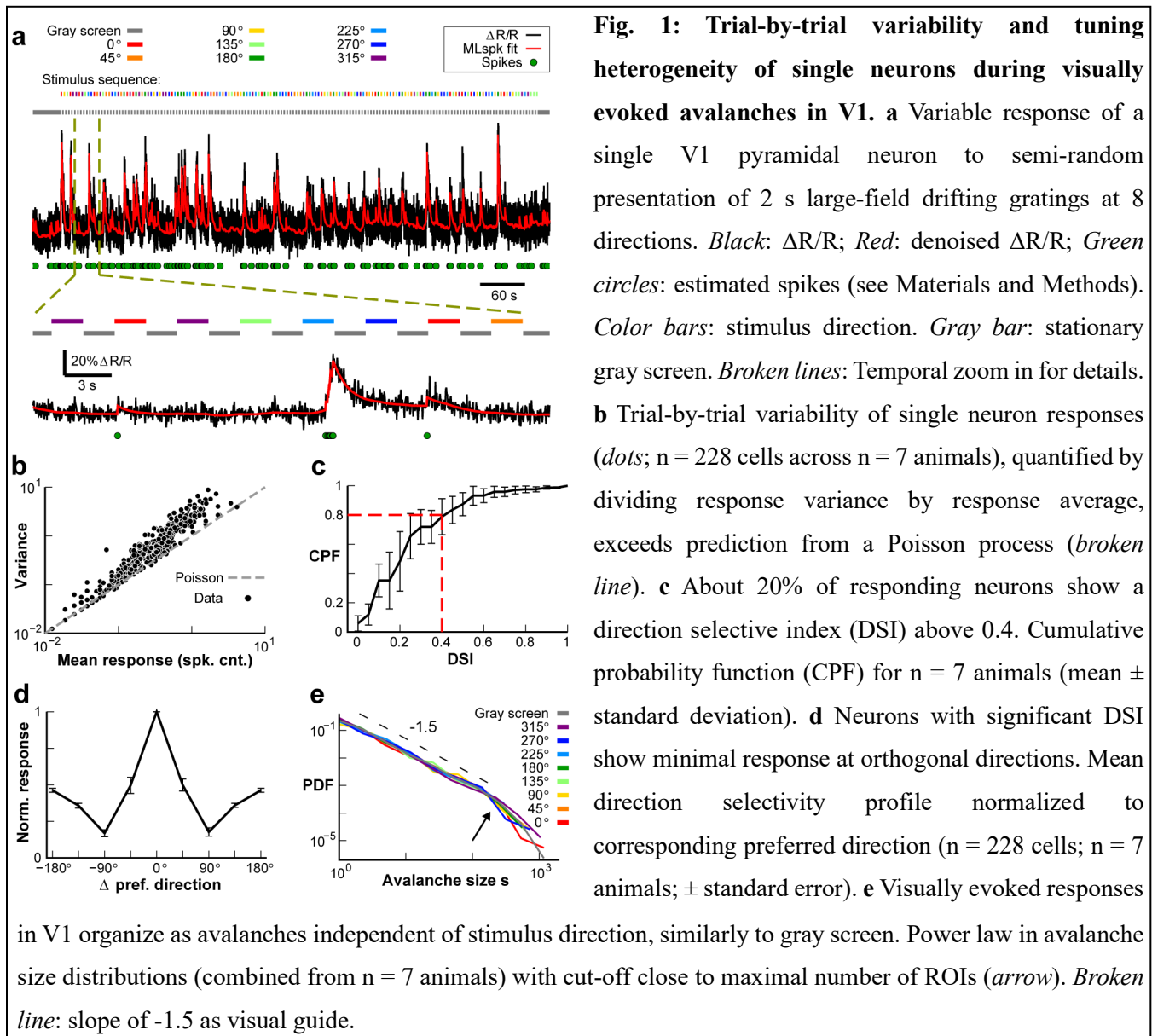
46 It has been argued (Chialvo, 2010) and shown experimentally (Shew & Plenz, 2013) that neuronal  
47 networks confer multiple benefits for being in the critical state, such as high dynamic range and maximal  
48 information capacity. For the bird flock, the critical state has been suggested to confer fast and coherent  
49 changes in flight direction in response to external perturbations, such as a predator attack (Bialek *et al.*,  
50 2014). For the brain, one might expect that external perturbations from sensory input or internal  
51 perturbations such as self-initiated motor commands lead to population responses that maintain the critical  
52 state. If this was correct, the correlation length for sensory and motor responses in the brain should scale  
53 with the size of the observed population of neurons and should be independent of feature selectivity. Here,  
54 we show experimentally a linear scaling in correlation length in the fluctuations of neuronal evoked  
55 responses in cortex. Using numerical simulations of a network model, we demonstrate this scaling to be  
56 found when the model is tuned to be critical. Our results identify a specific form of scaling in the trial-by-  
57 trial variability for sensory and motor responses in cortex *in vivo* and suggest this variability is a signature  
58 of critical dynamics that maintains robust, long-range correlations between neurons. Finally, by comparing  
59 experimental and numerical correlation functions, we are able to estimate the interaction length (i.e. the  
60 distance at which neurons interact physically) in visual cortex.

## 61 **Results**

62 We investigated the extent in the spatial correlation of neuronal activity at the cellular and mesoscale level  
63 in cortex using two different experimental approaches. At cellular resolution, we studied pair-wise  
64 correlations between individual neurons using 2-photon imaging (2PI), whereas at the mesoscale in  
65 nonhuman primates we measured the local field potential (LFP) using high-density microelectrode arrays.  
66 We analyzed ongoing as well as activity obtained during sensory/motor processing for each scale. We will  
67 first present results obtained at the cellular level in awake mice followed by a comparison at the mesoscale

68 in behaving nonhuman primates. Simulations of neuronal activity position our results in the context of  
69 subcritical, critical and supercritical dynamical regimes.

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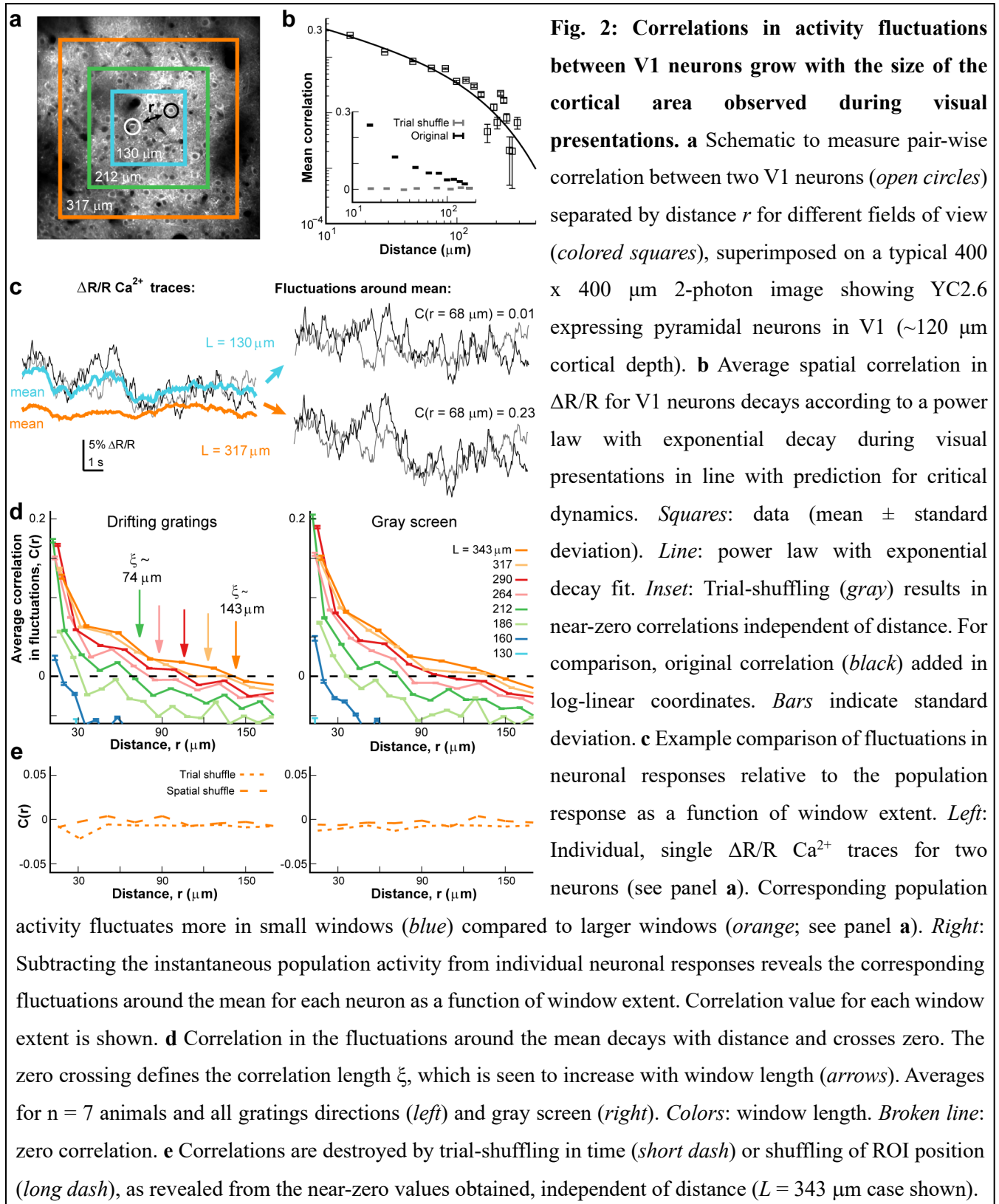


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72 **Linear scaling of correlation lengths in mouse primary cortex**

73 For cellular analysis, spiking activity in pyramidal cells of mouse primary visual cortex (V1;  $n = 7$  mice)  
74 was recorded using 2PI over an area of  $L \times L = \sim 400 \mu\text{m} \times 400 \mu\text{m}$  in superficial cortical layers at a depth  
75 of  $\sim 100 - 150 \mu\text{m}$  from the cortical surface. Mice were quietly resting during recording while 2 s-lasting  
76 drifting gratings were presented every 4 s (Fig. 1a). As can be seen in the variance over average response  
77 plot (Fig. 1b), the Fano factor was above one for most cells, indicating high response variability in single  
78 neuron responses. About 20% of neurons were tuned to stimulus direction with a selectivity index (DSI;  
79 Fig. 1c; see Materials and Methods) larger than 0.4 and an average response profile (Fig. 1d) depicting  
80 minimal response to the orthogonal orientation. Importantly, all single neuron responses were embedded  
81 in spatio-temporal clusters of activity that distributed in cluster size according to power laws, the hallmark  
82 of neuronal avalanches (Beggs & Plenz, 2003; Bellay *et al.*, 2015). This scale-invariant organization in  
83 activity clusters was found during stimulation regardless of the directional drift as well as during  
84 luminance-matched gray screen presentation (Fig. 1e;  $p < 0.05$  for power law test; see Materials and  
85 Methods).

86 The response variability encountered in single neurons, their tuning diversity and scale-invariant  
87 grouping in the form of avalanches points to a fluctuation-dominated dynamic regime of cortex, in which  
88 individual elements seem to be difficult to relate to stable population responses. One potential answer to  
89 this problem could lie in critical dynamics, which maintain some order in the presence of strong  
90 fluctuations (Chialvo 2010). Therefore, to gain deeper insight into the dynamical regime of the cortex  
91 during the relatively short-lasting (compared to the scale of large avalanches) evoked responses and, at



92

93

the same time, avoid the statistical influence of the strong drive created by the stimulus, we needed an

94 alternative approach to the statistical distribution of observed activity patterns. Here we assessed the  
95 dynamics of the cortical network by analyzing how correlations in the evoked responses scale with the  
96 size of the observed system. We first directly calculated how the average pairwise correlation between  
97 neurons changes as a function of cortical distance  $r$  for the full recording window. This correlation was  
98 well described by a power law with exponent close to -1 and exponential cut-off, in line with expectations  
99 for critical dynamics (Cavagna *et al.*, 2010) measured within a finite size window (Fig. 2b;  $p < 0.05$  for  
100 power law test). Importantly, when activity from each of the trials for a given stimulus angle was randomly  
101 shuffled for each cell independently (trial shuffling; see Materials and Methods), the correlations dropped  
102 to zero regardless of the distance between the cells. This indicates that the total activity induced by the  
103 stimulus does not contribute to the distance related decay in correlations. We then assessed how the  
104 fluctuations of neuronal responses around the instantaneous population mean change with distance  $r$   
105 between cells, by subtracting the population average as a function of time from each neuron's time series  
106 (Fig. 2c). The correlation in fluctuations as a function of distance  $r$ ,  $C(r)$ , was assessed for varying length  
107  $L$  of the observation window (Fig. 2d). This variation in  $L$  systematically changes the population mean as  
108 exemplified in Fig. 2c for two window lengths. Indeed, nearby neurons deviate in similar fashion from  
109 population activity and  $C(r)$  decayed similarly, both for drifting gratings as well as during gray screen. At  
110 a certain distance, defined as the correlation length,  $\xi$  (Fig. 2d, arrows) (Cavagna *et al.*, 2010; Fraiman &  
111 Chialvo, 2012),  $C(r)$  turns negative. We found that  $C(r)$  decayed similarly with distance for different  $L <$   
112 400  $\mu\text{m}$  (Fig. 2d, different colors) and  $\xi$  was shorter for smaller windows.

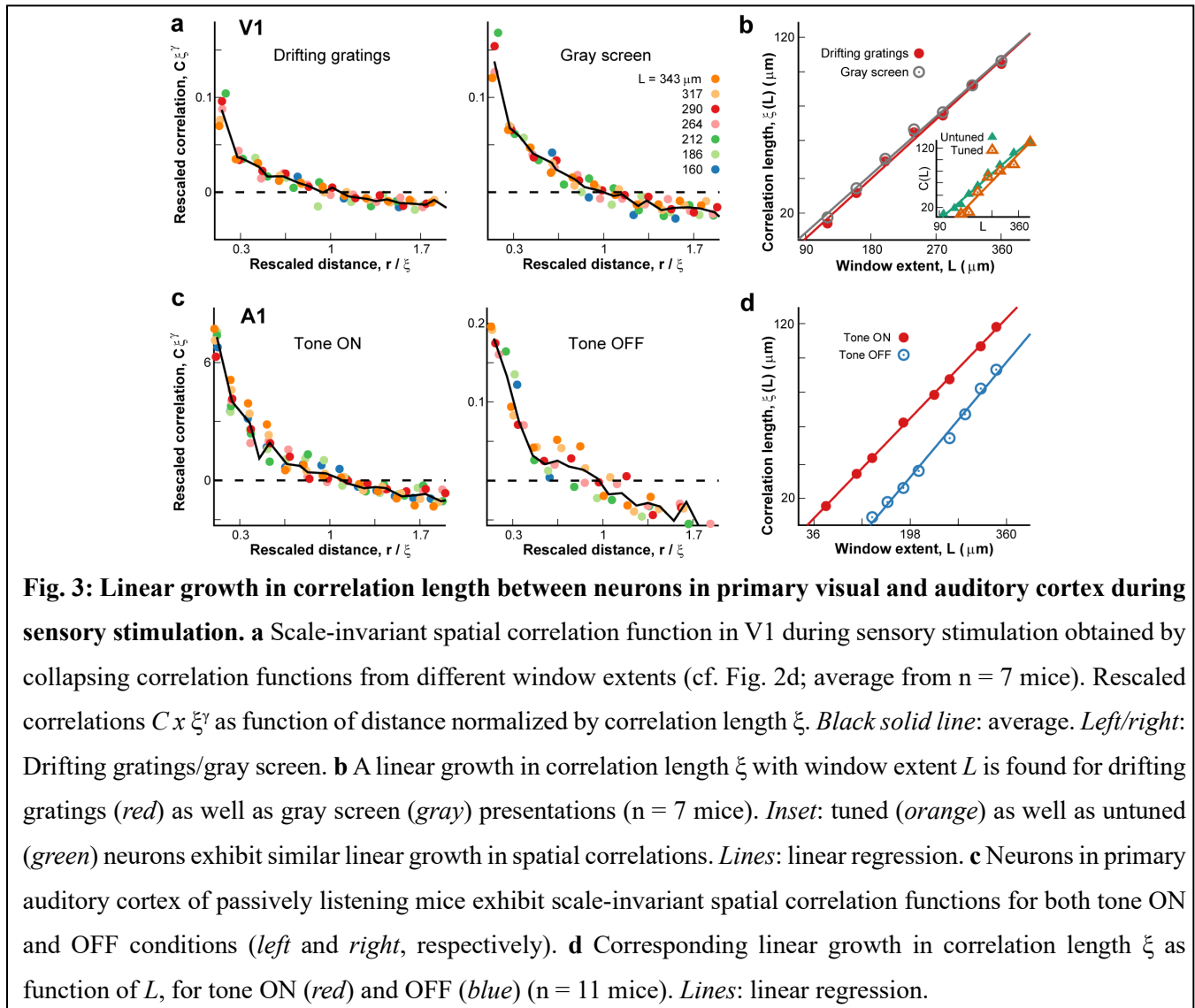
113 Deviations from the population average of cells further apart than  $\xi$  were found, on average, to be anti-  
114 correlated for any window size. This anti-correlation is to be expected to a certain degree as by definition,  
115 at any given time some cells will exhibit activity above the population mean, while others will be below  
116 it. This fact and the general drop in correlations with distance will lead to a crossing through zero



117 correlation, allowing to estimate  $\xi$ . We used trial shuffling as a control to demonstrate that  $\xi$  indeed  
118 captures emergent correlations in trial-by-trial fluctuations among neurons and does not reflect an artificial  
119 position due to subtracting the instantaneous mean. Trial shuffling maintains the common input introduced  
120 by the stimulus and distances among neurons, while removing coordinated changes of individual neuronal  
121 response around the population response. Trial shuffling results in  $C(r)$  being close to zero regardless of  
122 distance between neuron pairs, and therefore  $\xi$  cannot be estimated. This is true for both drifting gratings  
123 stimulus and gray-screen periods (Fig. 2e). Similarly,  $\xi$  is not defined after randomly permuting cell  
124 positions while keeping instant trial-by-trial correlations intact. These controls carried out for the full  
125 window size confirm  $\xi$  as a correlation length measure for neuronal activity that emerges from interactions  
126 between the observed neurons.

127 We note that a common way to obtain correlation length estimates from a system is precisely with the  
128 fit performed in Fig. 2b, by measuring how quickly correlations (without the population subtraction) drop  
129 with distance between system components after the power law regime. More specifically, the characteristic  
130 decay of the exponential portion of such a correlation spatial function can be used as a measure for the  
131 correlation length. However, as can be seen in Fig. 2b, the correlation function becomes very noisy for  
132 larger distances, reflecting the small number of pairs of neurons that far apart. Consequently, our estimates  
133 for the correlation length using that method become very unreliable ( $\xi \sim 110.97 \pm 58.55$ ; 95% confidence  
134 interval). With the alternative method (Cavagna *et al.*, 2010), which has previously been employed in  
135 neuronal activity data (Fraiman & Chialvo, 2012), we achieved a full collapse for all  $L$  by rescaling  $C(r)$   
136 with its corresponding value  $\xi$  (Fig. 3a;  $p < 0.05$ ; see Materials and Methods) and obtained a linear  
137 relationship for  $\xi$  over  $L$  (Fig. 3b), i.e. spatial correlations in V1 grow linearly with the observed cortical  
138 area. This increase holds regardless of sensory stimulus presented (Fig. 3b, different colors;  $p < 0.05$  chi-  
139 square test for both cases; see Materials and Methods) and for subsets of cells responsive to the stimulus

140 as well as those that are not (Fig. 3b, inset;  $p < 0.05$  chi-square test for both cases), indicating that all cells,  
 141 independent of their tuning-selectivity, follow the same correlation principles. Linear scaling with  
 142 window size is also obtained when spike density estimates are being used (Suppl. Fig. S1). Our findings  
 143 suggest that fluctuations around the mean between V1 neurons are scale-invariant, a hallmark of criticality.



144  
 145 We extended these findings from V1 to the primary auditory cortex in awake mice. Mice passively listened  
 146 to short (1 s) auditory tones semi-randomly presented from 8 different frequencies and 3 different volume  
 147 levels every 3 – 5 s (Bowen *et al.*, 2019). Evoked responses were recorded using 2PI in pyramidal neurons

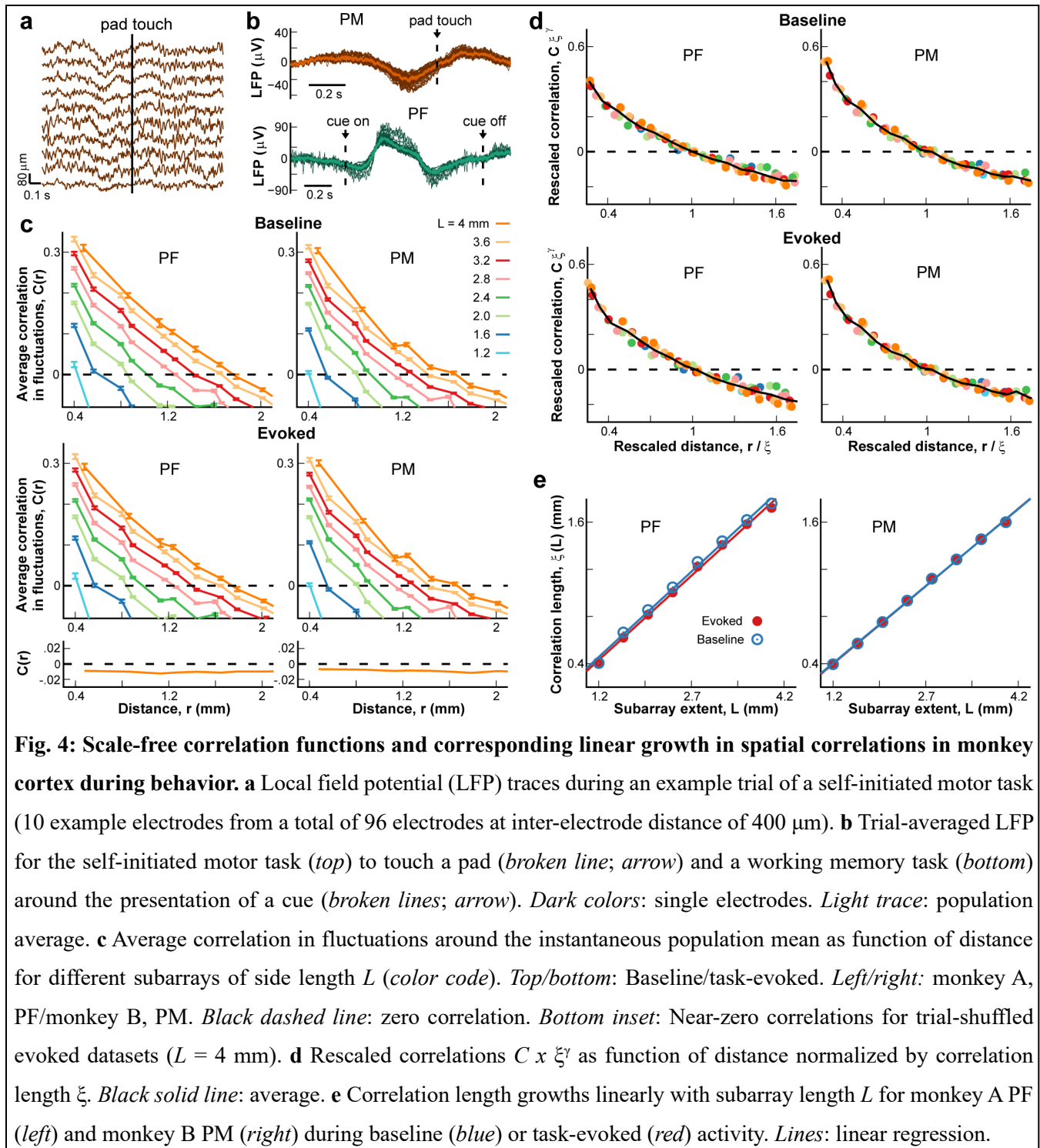
148 from superficial layers ( $n = 11$  mice). Evoked neural responses were analyzed as described for visual  
149 cortex. Correlation functions  $C(r)$  were collapsed based on correlation length  $\xi$  and recording window size  
150 (Fig. 3c). In line with what was found for V1,  $\xi$  grew linearly with  $L$  for both tone ON and tone OFF  
151 conditions in auditory cortex (Fig. 3d;  $p < 0.05$  chi-square test for both cases).

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### 153 **Linear scaling of correlation lengths in nonhuman primates at cortical mesoscale**

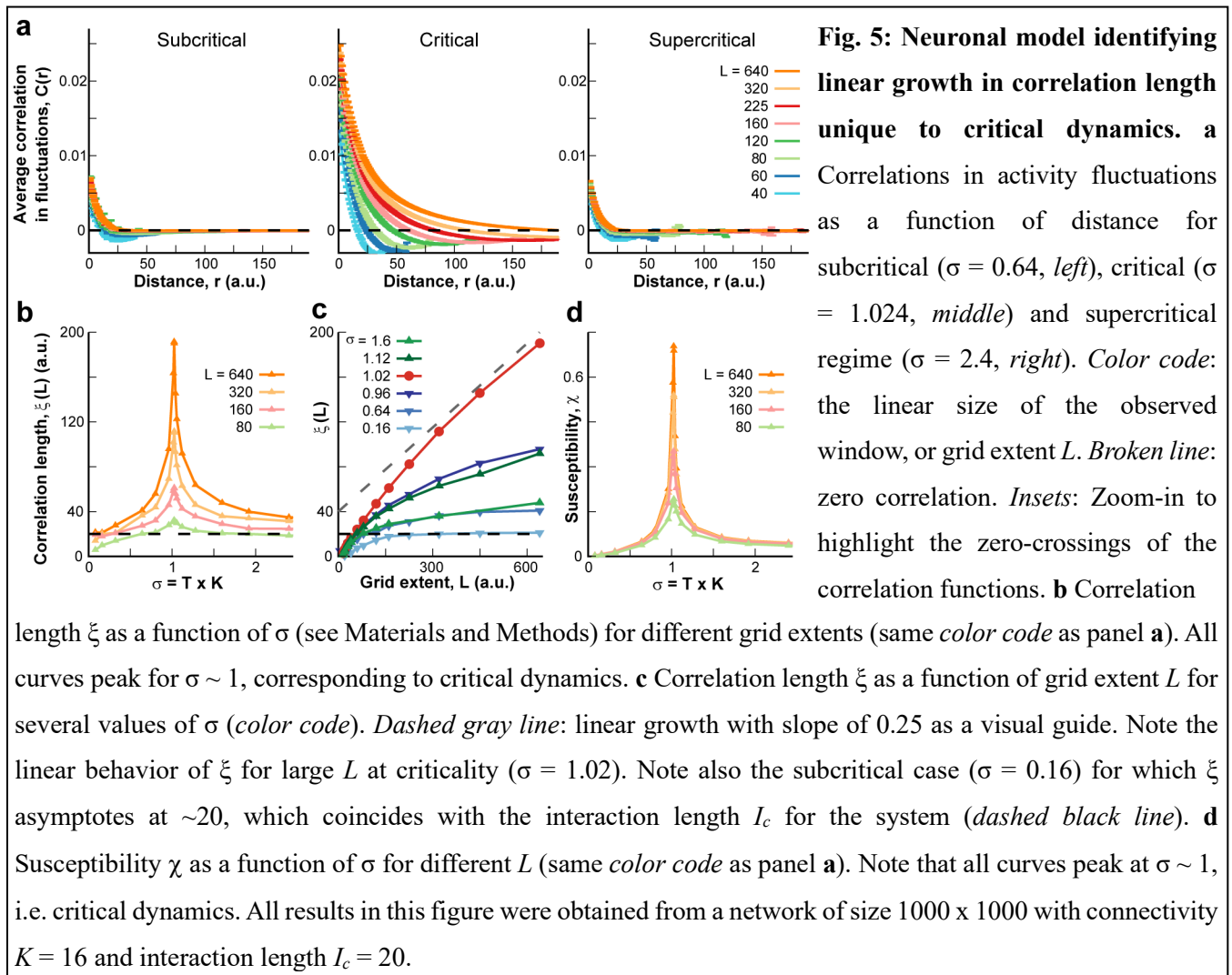
154 For the mesoscale level, i.e. analysis beyond several hundred  $\mu\text{m}$ , we employed microelectrode arrays  
155 (MEAs; 10 x 10 electrodes without corners; 400  $\mu\text{m}$  interelectrode distance) and recorded the local field  
156 potential (LFP) in prefrontal (PF; monkey A) and premotor (PM; monkey B) cortex over an area of  $\sim 4$   
157 mm x 4 mm (Fig. 4a; for details see (Yu *et al.*, 2017)). Monkey A was trained in a visual-motor mapping  
158 task (Fig. 4b, bottom; see Materials and Methods), while monkey B performed a self-initiated movement  
159 task (Fig. 4b; top). We applied the methods described in the previous section to investigate whether the  
160 same results could be observed in this larger scale. Amplitude fluctuations in the LFP were obtained by  
161 subtracting the instantaneous average on the squared subarrays of width  $L$  from each electrode LFP. We  
162 then obtained  $C(r)$  between pairs of electrodes for the subarray of width  $L$  in multiples of the inter electrode  
163 distance (400  $\mu\text{m}$ ).  $C(r)$  decayed with distance (Fig. 4c) in remarkably similar shapes for different  $L$ ,  
164 allowing for successful collapse of the curves (Fig. 4d). The collapsed functions were similar among both  
165 monkeys (Fig. 4d, left vs. right), during baseline or task-evoked activity (Fig. 4d, top vs. bottom). As found  
166 for primary visual and auditory cortex,  $\xi$  grew linearly with  $L$  for both cortical regions and was similar  
167 between baseline and motor/sensory processing epochs (Fig. 4e;  $p < 0.05$  chi-square test for all cases).  
168 Importantly, this is not the case when trial shuffling is employed, as that procedure leads to a non-decaying  
169 near-zero correlation function (Fig. 4c, bottom), also in line with results obtained from mice.

170



172 **Neuronal network model demonstrates linear growth of correlation lengths unique to critical**  
 173 **dynamics**

174 We simulated a neural network (see Materials and Methods and refs. (Kinouchi & Copelli, 2006; Ribeiro  
 175 et al., 2014) for more details) to establish to which extent the results obtained in the experimental data can  
 176 be used as an identifier for criticality. Specifically, we explore the impact of windowed access to a larger  
 177 system, as this is currently the only way to examine finite-size effects on brain activity measures.



178  
 179 Furthermore, given the less than an order of magnitude spatial range we were able to access with 2PI and  
 180 high-density microelectrode arrays, we estimated the expected deviation in correlation length estimates

181 when networks move away from criticality. In the simulations we performed the correlation analysis  
182 exactly as described for the experimental data using a network of  $1000 \times 1000$  units, with neurons  
183 interacting up to a distance  $I_c = 20$ . As can be seen in Fig. 5a, the correlations in the fluctuations were  
184 highest and extended for the longest distance in the critical regime (Fig. 5a, middle). Furthermore, the  
185 growth of  $\xi$  with the observed grid extent  $L$  was bounded for sub- and supercritical regimes (Fig. 5a, left  
186 and right), while in the critical regime, it increased with  $L$ . In fact, Fig. 5b shows that  $\xi$  peaked at criticality  
187 ( $\sigma \simeq 1$ ; see Materials and Methods), regardless of the extent of the observed grid (Fig. 5b, different colors).  
188 We note that the absolute difference in the value of correlations from our simulations compared to  
189 experimental data simply results from the smoothing procedure employed in the latter (see Materials and  
190 Methods). In summary, the linear scaling of  $\xi$  as a function of  $L$  was unique to criticality, with sub- and  
191 supercritical systems presenting asymptotic behavior for  $\xi$  over  $L$  (Fig. 5c, different colors) and our  
192 simulations support our use of observation windows of different size as a proxy of system size in the  
193 analysis of correlations of critical systems. This approach was important so that the simulations properly  
194 mimic what is observed from the brain: only a small subset of the full network is then further subsampled  
195 in order to obtain the scaling of the correlation length. In Supplemental Figure S2, we provide further  
196 demonstration that this windowing approach (as opposed to measuring the correlation length as function  
197 of system size) is a valid method using the paradigmatic Ising model. Finally, in Fig. 5d we demonstrate  
198 that the susceptibility  $\chi$  also peaks at criticality.

199 Altogether, these results demonstrate that at the critical regime, the range at which the fluctuations  
200 from two units in the network are correlated extends much further than the range at which units are  
201 connected, the interaction length  $I_c$  (see Materials and Methods). In contrast, for a system far away from  
202 the critical point, correlations cannot extend significantly beyond  $I_c$  (Fig. 5c, dashed line at 20 coincides

203 with asymptote value for  $\xi$  at  $\sigma = 0.16$ ). However, as can be seen in Fig. 5c, even near the critical regime  
204 the linear growth of the correlation length is not present at smaller scales.

205 Finally, we studied how  $\xi(L)$  changed as a function of  $L_c$  for critical systems. Linear scaling was not  
206 obeyed for grid extents shorter than  $L_c$ , for which the curve abruptly changed from the asymptotic slope to  
207 a sharper decay (Suppl. Fig. S3a, *left*; see also Supplementary Materials). Indeed, scaling  $\xi$  and  $L$  by  $L_c$ ,  
208 we obtained a collapse of all curves (Suppl. Fig. S3a, *right*). This scaling function clearly identified two  
209 regimes: scale free behavior took place for  $L > L_c$ , while  $\xi$  increased much more abruptly for increasing  $L$   
210  $< L_c$ , due to direct connections between units. We observed similar trends for individual mice in V1 when  
211 replotting the correlation lengths as a function of window extent with the linear regime being preceded by  
212 a steeper increase (Suppl. Fig. S3b, *left*). We estimated the point where the scaling abruptly changed for  
213 each mouse. They ranged from  $\sim 100$  to  $180 \mu\text{m}$  for V1 networks. These estimates were used to  
214 successfully collapse all data (Suppl. Fig. S3, *right*).

## 215 Discussion

216 Here, we used a correlation approach to assess the dynamical regime of the cortex during information  
217 processing epochs. The correlation length, a measure of how far apart neurons in cortex are positively  
218 correlated was shown to scale approximately linearly with the size of the observed window. If the distance  
219 over which neuronal activities correlate were to be finite, e.g.  $200 \mu\text{m}$ , our approach would have revealed  
220 an upper bound in window size, or cortical area, for which the correlation length saturated. Instead, both  
221 of our experimental approaches, first, for up to  $400 \mu\text{m}$  at the level of individual neuronal firing in primary  
222 visual and auditory cortex using 2-photon imaging and second, for up to  $4 \text{ mm}$  in the local field potential  
223 in awake nonhuman primates using high-density arrays, demonstrated that correlation length simply grows  
224 linearly with the size of the cortical area observed. Our simulations confirmed that our approach using

225 windowing identifies linear growths in networks with critical dynamics, for which correlation length  
226 growths unbounded up to the final observed size.

227 We evaluated the correlation length as function of subsamples of the recorded region, i.e. compact  
228 windows, and not as a function of system size, which is the more common approach in physics. While it  
229 is known that windowing differs to a certain degree from finite size effects (Chen *et al.*, 2011), we  
230 demonstrated for two different models that our method leads to the similar results. Given that the finite-  
231 size changes cannot be executed for real brains, windowing is therefore a realistic, alternative approach.  
232 Further support of our windowing method has been provided in BOLD fMRI recordings for the whole  
233 brain. In that study (Fraiman & Chialvo, 2012) it was shown that the linear growth in correlation length  
234 with the size of separate functional areas of the brain also describes the behavior of the correlation length  
235 when different subsets of multiple areas are added together in the analysis.

236 We used the fluctuations of local neuronal activity around the instantaneous mean of the observed  
237 network size to evaluate individual trials. The subtraction of the (observed) population average before  
238 calculating correlations has been successfully applied in the context of bird flocks (Cavagna *et al.*, 2010),  
239 where one needs to evaluate how birds move in relation to one-another, disregarding the overall movement  
240 of the flock. This approach is much more common in physics (Wilson, 1976; Wilson, 1979) and, to our  
241 knowledge, has been applied here for the first time to single neurons and local neuronal populations in the  
242 wake animal. One might reconcile this common method by realizing that during sensory input or motor  
243 output, many neurons integrate similar inputs that consequently drive the activity of the network as a  
244 whole. Accordingly, subtracting the instantaneous population average reduces this ‘drive’ component,  
245 allowing the correlation analysis to focus on how activity in neurons changes in relation to one-another,  
246 independent from the general sensory/motor responses observed. This interpretation is thoroughly  
247 supported by our trial-shuffling results, in which the specific inter-neuron relationships that differ from



248 trial-by-trial are removed and our correlation analysis correctly predicted zero correlations. We note that  
249 this method is not advisable for small number of neurons in which subtracting the average introduces  
250 dominant anti-correlations artificially decreasing correlation lengths for small windows. We mitigated this  
251 effect by imposing a minimum number of units in a given window before considering it for analysis. Small  
252 windows also suffer from the influence of the interaction length. Specifically, when the interaction length  
253 is on the order of the observed system size, the growth of the correlation length naturally is much faster  
254 with system size. We used this to our advantage, which allowed us to estimate the typical interaction range  
255 for superficial layers in the primary visual cortex.

256 That the cortical state is known to affect trial-by-trial variability (Kisley & Gerstein, 1999) and  
257 correlation among neurons (Cohen & Kohn, 2011; Rosenbaum *et al.*, 2016) has been a long-standing  
258 observation. It is also well established that part of this variability originates from the cortical network  
259 itself (Kara *et al.*, 2000; Sadagopan & Ferster, 2012; Goris *et al.*, 2014; Schölvinc *et al.*, 2015). Our  
260 demonstration of linear scaling in correlation length suggests critical dynamics as the framework that  
261 captures the intracortical correlation structure underlying this variability. Critical dynamics has been a  
262 fundamental driver in understanding optimization of information processing in complex systems in light  
263 of the evidence that fluctuations or variability are high at criticality (e.g. refs. (Shew *et al.*, 2011; Fraiman  
264 & Chialvo, 2012; Tkačik *et al.*, 2013; Karimippanah *et al.*, 2017)). Decades ago, it was suggested that  
265 critical dynamics optimize information transfer in gene-regulation networks (Kauffman, 1969; Sole *et al.*,  
266 1999; Rämö *et al.*, 2007; Nykter *et al.*, 2008). Since then, the criticality hypothesis (Beggs & Plenz, 2003;  
267 Chialvo, 2010; Mora & Bialek, 2011; Plenz, 2012; Hesse & Gross, 2014; Marković & Gros, 2014; Plenz  
268 & Niebur, 2014; Bettinger, 2017; Cocchi *et al.*, 2017; Muñoz, 2018) has gained much ground in the field  
269 of neuroscience. Highly desirable aspects of information processing have been shown to improve at  
270 criticality such as the maximization of mutual information between stimulus input and output (Kinouchi

271 & Copelli, 2006; Shew *et al.*, 2009; Shew & Plenz, 2013; Gautam *et al.*, 2015; Bortolotto *et al.*, 2016),  
272 increased information capacity (i.e. the number of possible internal states a network can establish)  
273 (Haldeman & Beggs, 2005; Shew *et al.*, 2011; Tkačik *et al.*, 2015), improved stimulus discrimination  
274 (Shriki & Yellin, 2016; Clawson *et al.*, 2017), and the ability of neurons to flexibly change synchronization  
275 while maintaining an overall robust degree of phase-locking (Jantzen *et al.*, 2009; Yang *et al.*, 2012; Kelso  
276 *et al.*, 2013; Kirst *et al.*, 2017). Accordingly, our findings support the notion that trial-by-trial variability  
277 rather than reflecting pure noise, represents an intrinsic property of cortical dynamics during information  
278 processing.

279 Previous reports relied solely on the calculation of avalanche statistics in examining how close cortical  
280 networks are to critical dynamics. Such statistics is sensitive to non-stationarities in neuronal activity as  
281 found in evoked responses (Yu *et al.*, 2017), which might explain the lack of avalanche statistics during  
282 sensory processing in *ex vivo* turtle (Shew *et al.*, 2015) and the human MEG (Arviv *et al.*, 2015). Power  
283 laws statistics as found for avalanches can in principle arise in critically balanced systems in the absence  
284 of correlations (see e.g. neutral avalanches (Martinello *et al.*, 2017) and alternative models (Williams-  
285 García *et al.*, 2014; Aitchison *et al.*, 2016; Ioffe & Berry, 2017; Touboul & Destexhe, 2017). Our present  
286 results, therefore, which are based on the scaling of spatial correlations, provide a new experimental  
287 underpinning that cortical processing is in line with critical dynamics (Chialvo, 2010; Shew & Plenz,  
288 2013).

## 289 **Materials and Methods**

290 All procedures followed the Institute of Laboratory Animal Research (part of the National Research  
291 Council of the National Academy of Sciences) guidelines and were approved by the NIMH Animal Care  
292 and Use Committee or by the University of Maryland Institutional Animal Care and Use Committee.

293

294 **Mouse surgery and preparation**

295 Wild type (C57/Bl6, Jackson Laboratory) mice were housed under a reversed 12 h-light/12 h-dark cycle  
296 with ad libitum access to food and water. Imaging experiments were generally performed near the end of  
297 the light and beginning of the dark cycle. A custom-made titanium head bar was surgically implanted onto  
298 the skull of the mice under isoflurane anesthesia (4% induction, 1-1.5% maintenance). A circular  
299 craniotomy (~3 mm) was made above the area of interest (visual or auditory cortex), followed by injection  
300 of a virus containing the genetically encoded calcium indicator (YC2.6 for V1; GCaMP6s for A1) at a  
301 depth of ~250-300  $\mu\text{m}$ . After that, a cranial window composed of two 3 mm diameter coverslips glued to  
302 a 5 mm coverslip was implanted and the entire area (except for the window) was sealed with dental cement  
303 (Goldey *et al.*, 2014; Bowen *et al.*, 2019).

304

305 **Visual stimulation and response measures**

306 Visual stimuli were prepared in Matlab using the Psychophysics Toolbox (Kleiner *et al.*, 2007) and  
307 delivered via a monitor (Dell, 60 Hz refresh rate) placed ~25 cm in front of the contra-lateral eye of the  
308 mouse. The stimulus was composed of moving gratings at 8 different directions presented for 2 s at  
309 maximum contrast, 0.04 cycles per degree and 2 cycles per sec. Stimuli were interspaced by gray screen  
310 (matched for average luminance) for 2 s. Each direction was presented 20 times in randomized order, for  
311 a total of 160 iterations. We calculated the direction selectivity index using the common definition:  $DSI =$   
312  $(R_P - R_O)/(R_P + R_O)$ , where  $R_P$  and  $R_O$  are the responses to the preferred and opposite direction,  
313 respectively. Significance of  $DSI$  for each cell was assessed by comparing the values obtained from the  
314 original data with those obtained from shuffling the inter-spike intervals.

315 **Acoustic stimulation**

316 Sound stimuli were synthesized in Matlab using custom software, passed through a multifunction  
317 processor (RX6, TDT), attenuated (PA5, Programmable Attenuator), and delivered via ES1 speaker placed  
318 ~5 cm directly in front of the mouse. The sound system was calibrated between 2.5 and 80 kHz and showed  
319 a flat ( $\pm 3$  dB) spectrum over this range. Overall SPL at 0 dB attenuation was ~90 dB SPL on average (for  
320 tones). Sounds were played at a range of sound levels (40-80 dB SPL). Auditory stimuli consisted of  
321 sinusoidal amplitude-modulated (SAM) tones (20 Hz modulation, cosine phase), ranging from 3 to 48  
322 kHz. The frequency resolution was 2 tones/octave (0.5 octave spacing). Each of these tonal stimuli was  
323 repeated 5 times with a 6 second inter-stimulus interval, for a total of 135 iterations (Bowen *et al.*, 2019).

324

325 **Two-photon imaging and analysis**

326 Images were acquired by a scanning microscope (Bergamo II series, B248, Thorlabs) coupled to a pulsed  
327 femtosecond Ti:Sapphire 2-photon laser with dispersion compensation (Vision S, Coherent). The  
328 microscope was controlled by ThorImageLS software. The wavelength was tuned to either 830 nm or 940  
329 nm in order to excite YC2.6 or GCaMP6s, respectively. Signals were collected through a 16 $\times$  0.8 NA  
330 microscope objective (Nikon). Emitted photons were directed through 525/50 nm (green) and 607/70 nm  
331 (red) band filters (for GCaMP6s) or 535/22 nm (yellow) and 479/40 nm (cyan) band filters (for YC2.6)  
332 onto GaAsP photomultiplier tubes. The field of view was ~400 x 400  $\mu$ m. Imaging frames of 512 $\times$ 512  
333 pixels were acquired at 30 Hz by bidirectional scanning of an 8 kHz resonant scanner. Beam turnarounds  
334 at the edges of the image were blanked with a Pockels cell. The average power for imaging was <70 mW,  
335 measured at the sample. The obtained images were corrected for motion using dft registration software  
336 with Matlab (Guizar-Sicairos *et al.*, 2008). Regions of interest (ROI) were identified from the average  
337 image of the motion corrected sequence using custom code. For each labeled neuron, raw fluorescence

338 signals (cyan and yellow for YC2.6; green for GCaMP6s) over time were extracted from the ROI overlying  
339 the soma. The mean ratiometric signal (R; YC2.6) or single fluorescence (F; GCaMP6s) in each ROI was  
340 calculated across frames and converted to a relative fluorescence measure ( $\Delta R/R_0$  or  $\Delta F/F_0$ ). The baseline  
341 signal  $R_0$  (or  $F_0$ ) was estimated by using a sliding window that calculated the average fluorescence of  
342 points less than the 10<sup>th</sup>-percentile during the previous 1.3-second window (40 frames).

343

### 344 **Monkey behavioral training and electrophysiological setup**

345 Experiments were described previously (Yu *et al.*, 2017). In short, two adult rhesus monkeys (*Macaca*  
346 *mulatta*) were surgically implanted with a titanium head post. After recovery, they were trained to sit head-  
347 fixed in a primate chair for behavioral performance. In the cue-initiated task, monkey A (male, 9 years  
348 old, 8 kg) had to press a bar in front of the chair upon presentation of the ‘trial-initiation’ cue on a computer  
349 screen. After ~2 s, the initiation cue was followed by an ‘instruction’ cue, for the duration of 1 s. Upon  
350 cue disappearance, monkey A had to release the bar and reach with his right arm to one of two specialized  
351 feeders, depending on which of two possible cues were presented (Mitz *et al.*, 2001). Approaching the  
352 incorrect feeder rapidly triggered a proximity sensor to sequester the food rewards in both feeders, which  
353 prevented the monkey from obtaining a reward on that trial. The inter trial interval was 3 – 5 s. In the self-  
354 initiated motor task, monkey B (female, 8 years old, 7 kg) had to move her right arm to touch a pad placed  
355 ~30 cm in front of the monkey chair after which a food reward was given. After the monkeys learned their  
356 respective tasks, a multi-electrode array (MEA; 96 channels - 10×10 without corners, inter-electrode  
357 distance: 400  $\mu\text{m}$ ; electrode length: 1 mm for monkey A and 0.55 mm for monkey B; BlackRock  
358 Microsystems) was chronically implanted in the arm representative region of the left prefrontal area (area  
359 46, monkey A) or the left premotor cortex (monkey B). The LFP (1 – 100 Hz band pass filtered; 2 kHz  
360 sampling frequency) was obtained from the implanted MEA. Electrophysiological signals as well as the

361 timing of behaviorally relevant events, e.g. touching the pad, presentation of visual cues, etc., were stored  
362 for off-line analysis.

363

### 364 **Numerical simulations**

365 We simulated a neural network, as described previously (Kinouchi & Copelli, 2006; Ribeiro *et al.*, 2014).

366 In short, each neuron can be in one of three states at each time step: 0 for resting, 1 for active, and 2 for

367 refractory. The model considers  $S^2$  neurons on a square lattice. Each neuron outputs to  $K$  other neurons,

368 selected with an exponentially decaying probability function of the Euclidian distance  $r$  between them

369 ( $P_{Conn} \sim e^{-r/R_0}$ , with  $R_0 = 5$ ). A spatial cutoff is set in the interaction distance: neurons cannot directly

370 connect at distances greater than  $I_c = 4R_0$  spatial units (thus, defining an interaction length  $I_c$ ).

371 Furthermore, to reduce small  $S$  effects, we employed periodic boundary conditions. Results were

372 computed on a square grid of length  $L$ . Simulations parameters were always such that  $S$  was much larger

373 than  $L$  to reduce finite-size artifacts and to better mimic experimental data. A small Poisson drive ( $h = 10^{-7}$

374 per time step) to each neuron determined the overall rate of firing activity. The present results were robust

375 over a wide range of  $h$  values (e.g.,  $h = 10^{-9}$  to  $10^{-4}$  per time step). The control parameter of the model

376 determines the branching of the neural activity and was defined as  $\sigma = K \times T$ , where  $T$  is the probability

377 that an active neuron (i.e., in state 1) can excite each one of the  $K$  neighbors that it connects to. Therefore,

378 as shown previously, the model can be made critical by selecting a transmission probability  $T$  such that  $\sigma$

379  $\sim 1$ , for any given  $K$ . Susceptibility was defined as the area under the correlation vs. distance curve, for a

380 given window size observed, up to the correlation length.

381 Considering the focus of the present study, we note that there are four length scales in the model. The

382 *interaction length* (here called  $I_c$ ) is the scale at which neurons can interact via direct connections. *System*

383 *length* (called  $S$ ) determines system size (the network is composed of  $S^2$  neurons). The third one is the

384 window length  $L$  ( $L \leq S$ ), called *grid length*, which determines how many neurons we will measure from  
385 (i.e.,  $L^2$  neurons). The last scale is the *correlation length*  $\xi$ , the longest distance at which on average the  
386 activity of any two given neurons may remain positively correlated. It is calculated from fluctuations on  
387 activity, following Cavagna's work (Cavagna *et al.*, 2010) (see section below). To avoid confusions, we  
388 remark that the term *interaction* is reserved here to denote *direct connections* and *correlations* to the  
389 mathematical result from computing *correlations of neural activity*. Simulations for varying interaction  
390 length ( $I_c$ ) were carried out using the same model described above. When changing  $I_c$ , the decaying  
391 parameter used for making connections  $R_0$  was changed accordingly (such that the relation  $I_c = 4R_0$  still  
392 holds).

393

#### 394 **Avalanche analysis**

395 Avalanche analysis for the 2PI data was performed as described previously (Beggs & Plenz, 2003; Bellay  
396 *et al.*, 2015). In short, estimated spikes (Deneux *et al.*, 2016) from all neurons were pooled together to  
397 create a population activity series. Avalanches are defined by contiguous non-zero population activity  
398 preceded and followed by blank frames (frames with zero population activity). Avalanche sizes were  
399 defined by the total number of spikes throughout their lifetime. Power-law goodness of fit was evaluated  
400 through a p-value calculated from the log-likelihood ratio when comparing power law, exponential and  
401 lognormal fits, as described previously (Clauset *et al.*, 2009; Klaus *et al.*, 2011; Bellay *et al.*, 2015).

402

#### 403 **Correlation analysis**

404 The correlation of the fluctuations as function of distance (Cavagna *et al.*, 2010) was calculated as

405 
$$C(r) = \frac{1}{c_0} \frac{\sum_{i,j} u_i u_j \delta(r-r_{ij})}{\sum_{i,j} \delta(r-r_{ij})}, \quad (1)$$

406 where  $\delta(r - r_{ij})$  is a smoothed Dirac  $\delta$  function defining all pairs of neurons located at mutual distance  $r$ ,  
407  $r_{ij}$  is the Euclidean distance from the  $i$ -th neuron's spatial location to the spatial location of neuron  $j$ , and  
408  $u_i$  is the value of the signal  $v$  of neuron  $i$  at time  $t$ , after subtracting the overall mean of signals  $v$  from  
409 neurons inside the observation window of size  $L$  at that time  $t$ :  $u_i(t) = v_i(t) - \bar{v}(t)$ . To ensure that  $C(r =$   
410  $0) = 1$ , the normalization factor  $1/C_0$  was used. We note that since the instantaneous average is subtracted,  
411  $C(r)$  is not equivalent to the most commonly used pairwise Pearson correlation function.

412 The objective of computing the  $C(r)$  is to determine the correlation length  $\xi$ , which is defined as the  
413 point where the correlations of the fluctuations reaches zero, i.e.  $C(\xi) = 0$ . Since system size, i.e. cortex  
414 size in our experimental data, was fixed, we investigated how  $\xi$  changes with system size subsampled by  
415 our recordings and considered neurons/electrodes within a window of length  $L$  (this proxy is validated by  
416 computing correlation lengths both as function of increasing system and window sizes in a model (Suppl.  
417 Fig. S2). More specifically, for the 2PI data in mice, fields of view ranging from  $\sim 40 \times 40 \mu\text{m}$  (windows  
418 with fewer than 5 units were ignored to avoid bias introduced by the average subtraction procedure when  
419 the number of units is too small) to the maximum possible size were considered, while for the monkey  
420 LFP data the smallest subarray considered was  $3 \times 3$ . To reduce noise effects, results were averaged across  
421 all possible subregions for any given size. The time series were smoothed in the time domain (using Matlab  
422 routine *medfilt1.m* with 20 samples for the mice 2PI data, 8 samples for the monkey LFP data). This  
423 smoothing procedure improved statistics without changing the results qualitatively. In order to more  
424 precisely estimate the zero-crossing point for the experimental data, we fit 3<sup>rd</sup> order polynomial functions  
425 to the  $C(r)$  curves around the zero-crossing.

426 To quantify linear growth in correlation length  $\xi$  as function of window length  $L$ , we first obtained a  
427 linear regression of the  $\xi(L)$  data followed by chi-square statistics  $\chi_c^2 = \sum_i [\xi(L_i) - R(L_i)]^2 / R(L_i)$ , where  
428  $L_i$  is the  $i^{\text{th}}$  measured value of  $L$  and  $R(L_i)$  is the linear regression value at  $L_i$ .  $\chi_c^2$  can be used to obtain a p-



429 value that estimates how likely the data fit the linear regression that well by chance from the chi-square  
430 distribution. We rescaled the correlation *vs.* distance curves by normalizing the distances by the correlation  
431 length and by rescaling the correlations by the correlation length to the power of  $\gamma$ , defined as the slope of  
432 the curves at zero-crossing (Cavagna *et al.*, 2010).

433

#### 434 **Trial shuffling and spatial shuffling**

435 Trial shuffling for the V1 data was obtained by randomly permuting the responses from each of the 8  
436 presented directions separately. This was done for each neuron independently. Therefore, in each trial of  
437 the trial shuffled dataset activity from each cell corresponds to a response to the same stimulus presented  
438 in the original data but taken from different presentations of that stimulus. For example, suppose we  
439 presented stimulus 5 in trial 1. In the shuffled data, the response of neuron 1 in that trial may be taken  
440 from the 10<sup>th</sup> presentation of stimulus 5, while response of neuron 2 may be taken from the 3<sup>rd</sup> presentation.  
441 Spatial shuffling was performed by randomly permuting cell positions, leaving everything else unchanged.

442

#### 443 **Acknowledgements**

444 We thank members of the Plenz lab for lively discussions. This research was supported by the Division of  
445 the Intramural Research Program (DIRP) of the National Institute of Mental Health (NIMH), USA, ZIA  
446 MH00297 and the BRAIN initiative Grant U19 NS107464-01. D.A.M. acknowledges financial support  
447 from ANPCyT Grant No. PICT-2016-3874 (Argentina). This research utilized the computational resources  
448 of Biowulf (<http://hpc.nih.gov>) at the National Institutes of Health (NIH), USA, and UnCaFiQT-INIFTA  
449 (SNCAD), Argentina.

450

451 **Contributions**

452 T.L.R., D.R.C. and D.P. conceived and planned the study; T.L.R., S.Y., D.W., P.K. and D.P. oversaw and  
453 carried out experiments; T.L.R., D.A.M., D.R.C and D.P. designed the models and carried out the  
454 simulations; T.L.R. took the lead in the analysis; T.L.R., D.R.C. and D.P. wrote the paper.

455

456 **Conflicts of Interest**

457 The authors declare no competing financial interests.

458

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1 **Trial-by-trial variability in cortical responses exhibits scaling in spatial correlations**  
2 **predicted from critical dynamics**

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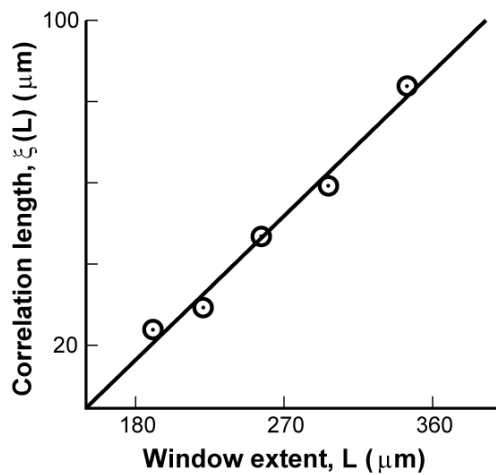
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5 **Supplementary Material**

6 **Scaling of correlation lengths in mouse V1 based on spike density estimates**

7



Supplemental Figure S1: **Correlation length scales linearly with window extent for spiking data.** Correlation as a function of window extent obtained from estimated spike times from V1 in mice. *Line* represents a linear regression.

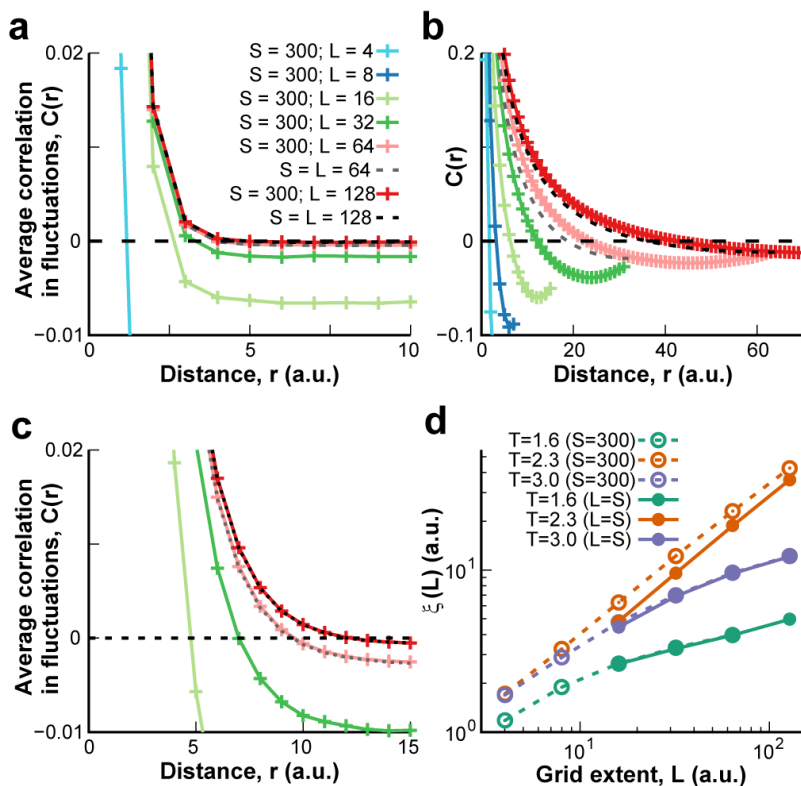
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12 **Correlation length scaling for increasing window size in the Ising model**

13 In critical systems, the correlation length is known to scale with system size. Because in biological systems  
14 changing system size is often impractical, in this work we introduce a proxy which uses windows of  
15 different sizes. In order to validate that approach, we test the concept in the paradigmatic 2D  
16 Ferromagnetic Ising model, which undergoes a critical transition at temperature  $T \approx 2.3$ . The simulations

17 (lasting at least  $10^5$  Monte Carlo steps) used two setups: in the first, the correlation function was computed  
 18 in the standard way, from a model running on square lattices of increasing  $S = 16, 32, 64$  and  $128$ . In the  
 19 second setup, a relatively large  $S = 300$  square lattice (i.e.  $300 \times 300$  spins) was simulated, and the  
 20 correlation function was computed from square windows of smaller sizes  $L = 4, 8, 16, 32, 64$  and  $128$ .  
 21 Representative results for three different temperatures are shown: subcritical ( $T = 1.6$ , Fig. S2a), critical  
 22 ( $T = 2.3$ , Fig. S2b) and supercritical ( $T = 3.0$ , Fig. S2c). Fig. S2d shows the correlation lengths computed  
 23 from both setups are very similar. Therefore, the curves obtained changing system size  $S$  or changing  
 24 window size  $L$  produce similar correlation lengths. These results validate the use of window size as a  
 25 proxy of system size in the analysis of correlations of critical systems.

26



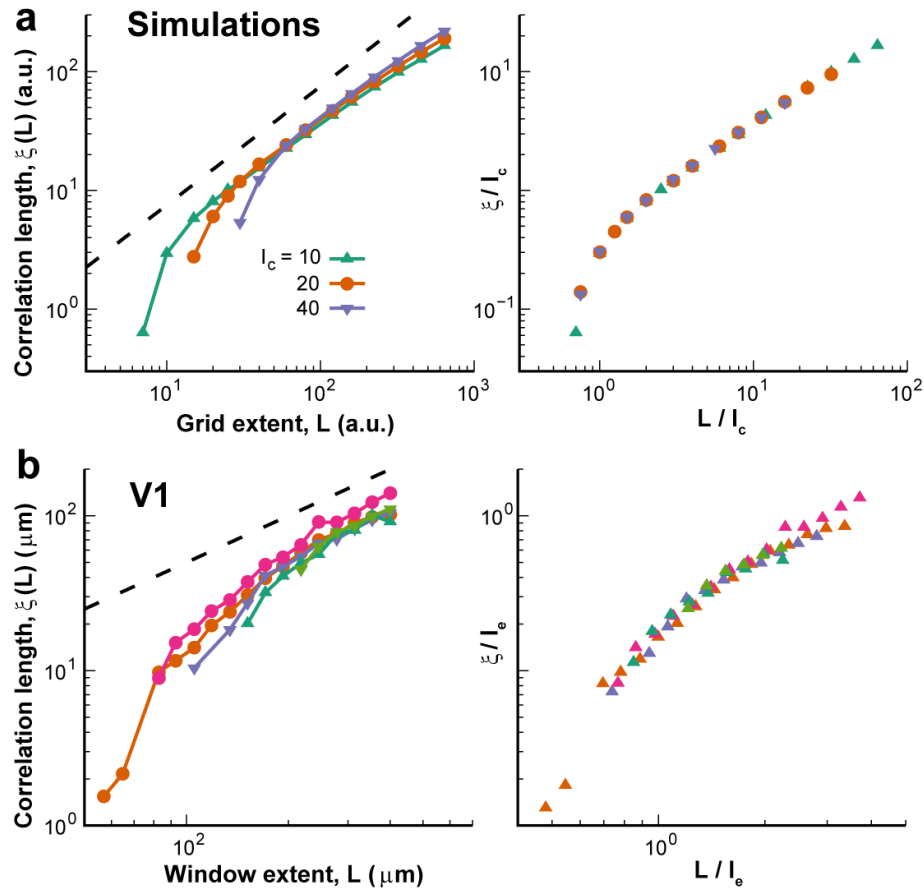
**Supplemental Figure S2: The ferromagnetic 2D Ising model.**

**a** Correlation as a function of distance for the subcritical regime ( $T = 1.6$ ). Color code: different window sizes ( $L$  from 4 to 128) in a system of size  $S = 300$ . Dotted lines: fixed  $S = L = 64$  and  $128$ , as indicated. **b** Results for the critical regime ( $T = 2.3$ ). **c** Results for supercritical regime ( $T = 3.0$ ). **d** Correlation length as a function of distance for  $T = 1.6, T = 2.3$  and  $T = 3$  and different conditions. Empty circles and dashed lines are used for systems with  $S = 300$ . Filled symbols with continuous lines are used for systems and windows of sizes  $S = L$ .

## 28 **Estimating the interaction length from experimental data**

29 We studied how the scaling law changed as a function of the interaction length for critical systems. We fit  
30 a power law of exponent 1 with an extended exponential part to the data as follows  $\xi(L) = CL\{1 -$   
31  $\exp[-(L/L_0)^\varepsilon]\}$ , where  $C = 0.27$  is a constant that controls the slope of the curves (in linear coordinates),  
32  $\varepsilon = 3$  is a constant that controls how sharp the decay for small  $L$  is and  $L_0$  is the cross-over point where  
33 the behavior changes from the exponential to the linear growth, our estimate for the interaction length.  
34 The values for  $C$  and  $\varepsilon$  were found empirically and represent a good match for the curves obtained in the  
35 simulations.

36 As shown in Fig. S3a (left), the linear scaling was not obeyed for grid extents shorter than  $I_c$ , for which  
37 the curve abruptly changed from the asymptotic slope to a sharper decay. If this change in behavior was  
38 solely due to the influence of direct connections between units (as opposed to influence of critical  
39 dynamics) then we should be able to obtain a universal curve that is invariant to the range at which units  
40 can be connected. Indeed, scaling  $\xi$  and  $L$  by  $I_c$  we obtained a collapse of all curves (see Fig. S3a, right).  
41 This scaling function clearly identified two regimes: scale free behavior took place for  $L > I_c$ , while  $\xi$   
42 increased much more abruptly for increasing  $L < I_c$ , due to direct connections between units. We observed  
43 similar trends for individual mice in V1 when replotting the correlation lengths as a function of window  
44 extent with the linear regime being preceded by a steeper increase (Fig. S3b, left). The point where the  
45 scaling abruptly changed differed between mice (Fig. S3b, different colors) and we used a function that  
46 mimics the behavior observed for the collapsed curve in Fig. S3a (right) to estimate the interaction length  
47 for each mouse (see Materials and Methods). These estimates were used to collapse all functions (Fig.  
48 S3b, right). They ranged from  $\sim 100$  to  $180 \mu\text{m}$  among mice and are a good estimate for the local distance  
49 at which pyramidal cells typically connect in superficial layers in V1 (Levy & Reyes, 2012; Seeman *et*  
50 *al.*, 2018).



51

**Supplemental Figure S3: Interaction length in experimental data can be estimated from correlation length growth with observed window size.** **a Left:** Correlation length  $\xi$  as a function of  $L$  for simulations at criticality for 3 different values of interaction length  $I_c$  (color code) in log-log coordinates. *Dashed line:* linear growth as a visual guide. **Right:** After rescaling grid extents and correlation lengths by the interaction length, all curves collapse into a single scaling function that highlights the change in the linear behavior at  $L = I_c$ . In all cases, system size is  $1000 \times 1000$  with connectivity  $K = 16$ . **b** Same as panel **a**, but for correlation lengths obtained from individual mice in V1. We estimated the point where the linear growth of the correlation length breaks for each mouse (see Materials and Methods) and used those values to rescale the curves as in panel **a** (right). The collapse obtained suggests that the estimated points ( $\sim 119 \mu\text{m}$  for mouse 1 – orange;  $\sim 143 \mu\text{m}$  for mouse 2 – purple;  $\sim 108 \mu\text{m}$  for mouse 3 – pink;  $\sim 179 \mu\text{m}$  for mouse 4 – dark green;  $\sim 180 \mu\text{m}$  for mouse 5 – light green) represent well the interaction length for these mice.

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