Reviewers comments and author's responses of the manuscript *Brain organization into resting state networks emerges at criticality on a model of the human connectome*

Haimovici, Tagliazucchi, Balenzuela and Chialvo, Phys. Rev. Letters (2013)

1 First Round of Review

Report of Referee A – LW13389/Haimovici
COMMENTS TO AUTHORS

I enjoyed reading this concise and compelling study of neuronal dynamics on connectivity structures. As I understand it, you demonstrate that critical dynamics (operationally determined in terms of a threshold for activation) are necessary to account for the divergence of correlation lengths and variance in short-term correlations observed empirically in fMRI time-series. In nearly every respect, I thought your report and its motivation were very clear. I have a few suggestions that might improve the presentation of this work:

1) At the bottom of page 1, I would say:

"Resting state networks are associated with specific neuronal systems that have been identified with sensory, cognitive and behavioural functions. Furthermore, the pattern of correlations in these networks has been shown to change with various cognitive and pathophysiological conditions."

2) On page 2, I was a bit confused by the phrase "the correlation length of brain activity diverges with size". Your results suggest that the correlation length increases with cluster size. The term 'diverges' suggests an increase in the dispersion or variance of correlation length with size. Perhaps you could replace 'diverge' with 'increase' or qualify your terminology more precisely?

3) In the legend to Figure 2, I would insert "the cluster size (N)".

4) On page 3, in the Figure Legend and in the main text, you suggest that the variance of the mean correlation is constant in the critical regime. This is a bit confusing because it clearly decreases with cluster size. Perhaps you could say "roughly constant (showing a small decrease)".

5) At the end of page 3, I think you need to make it clearer that the maximal correlations with the spatial location of the resting state networks are over regions. In other words, they are not (as you state in your Figure legend) correlation between the spatial location -they are the correlations over voxels in the amplitude or weights of the independent components.

I hope that these comments help should any revision be required.

Report of Referee B – LW13389/Haimovici

The article 'Brain organization into resting state networks emerges from the connectome at criticality' by Ariel Haimovici et al. Explores the relationship between the structural connectivity of the brain and the experimentally found resting state networks in humans. The hypothesis that a critical dynamic is necessary to produce resting state data from the structural brain networks is illustrated by choosing a discrete excitable model at its critical point, which reproduces certain characteristics linked to criticality and activity patterns which correlate with functional resting state networks (RSNs). The paper offers an intuitive approach to comprehending emergent behavior of a complex system such as the brain. However, it still needs to be shown that this dynamical approach offers deeper insights than a purely structural analysis of the brain. Moreover, we have concerns about the validity of the claimed results. Criticality is a universal principal in physics and new applications are of interest to the community. In this model, however, the proof of criticality was not actually given in the traditional sense. Thus, the work would need to be revised thoroughly in order to be acceptable.

MAJOR ISSUES

- The statement (page 3) that 'at the critical state, the variance of ¡ C ¿ is of the same order as observed in the experiments for different cluster sizes' as well as the statement that the fluctuations remain constant at different cluster sizes is not actually reflected in Figure 3. More specifically, the first statement holds for the cluster size 12 (Figure 3 panel A), whereas the fluctuations of the model and the experiment for the cluster sizes 47 and 71 look significantly different (while in the authors argument they are claimed to be the same). Having a closer look at the gradients in Figure 3 panel B shows that the absolute value of the exponent of the red line which fits the data obtained by simulations at the critical point (which should be zero) is actually larger tan the absolute value of the exponent of the data in Figure 2 which documented the divergence of the correlation length with system size.

MINOR ISSUES

- The introduction of the model is very condensed. Particularly for readers not familiar with this type of model it would be helpful to have a few figures in the supplementary material illustrating the activity levels in the model, e.g. in the form of time series or with regards to the aspect of criticality in the form of an analysis of the avalanche statistics.

- Figure 1C shows the behavior of the order parameter depending on the control parameter. Even though the black solid curve could be the finite size relict of a discontinuity of the first derivative of the order parameter at the critical value, the point should be strengthened by showing an increase in the gradient with increasing system size. Another hint towards criticality would be the emergence of clusters of all sizes distributed according to a power law.

- According to page 2, nodes further than 1cm away from an RSN cluster were discarded when reproducing experimental results. It is not clear why this simplification has been chosen, since running the dynamic on the whole network and only reading out the RSN-activity could give significantly different results than running the dynamic on a reduced network. Generally, it would be interesting to show the results of the analysis for the entire system (without filtering or restriction to the RSNs.) In addition it would be helpful to state the percentage of nodes that were taken into the RSN analysis.

- Figure 2 shows the divergence of the correlation length with system size. A

stronger sign of criticality would be the demonstration of the divergence of the correlation length close to the critical value of the threshold by producing the power law for values just under and just over the critical value of the control parameter. - The title of the article implies causality between the connectome, the criticality and the RSNs. However, (i) the paper demonstrates only correlational not causative relationships, and (ii) the RSNs correlate only to a limited extent (correlation coefficient around 0.3) with the outcome of the simulations (Figure 4). Thus, the title should be formulated more appropriately.

Instead of showing the emergent behavior for all possible/likely critical dynamics, the results were just given for one specific exemplary model. Therefore, to motivatethe model, it might beworthwhile to refer to the biological relevance of the model parameters.

- It would be telling to see whether this model predicts the RSNs better than a pure structure analysis, ie, correlating the structural matrix with the observed RSNs in the same manner as done here for the simulated dynamics.

2 Authors response to First Round of Review

We thank both reviewers for their helpful comments and critiques. We have addressed all the points raised by the reviewers by performing new analyses whenever required, resulting in manuscript changes and additional figures in the supplementary information.

Summary of major changes:

1. Title was changed (as required by reviewer B)
2. Figure 2 was changed (to include new calculations as required by reviewer B)
3. Figure 3 was changed (includes new calculations as required by reviewer B)
4. Figure 4 was changed (incorporates new calculations as required by reviewer B)
5. Supplementary material was added to answer reviewer B' concerns including:
   - further details of the model,
   -a description of additional measures of criticality
   -an analysis of the scaling relation without exclusion of any nodes
   -a comparison at the level of structural and functional connectivity matrices.

Minor changes include adjusting the language, as requested by reviewer A, concerning correlation divergence as well as changing the wording to describe the roughly constant value of the mean correlation.

We thank again the reviewers for their suggestions and hope that our arguments and new results are able to satisfy their concerns. Detailed responses are provided in the next paragraphs.

3 Detailed response to reviewers:

4 Referee A

Q. 1) At the bottom of page 1, I would say: "Resting state networks are associated with specific neuronal systems that have been identified with sensory, cognitive and behavioral functions. Furthermore, the pattern of correlations in these networks has been shown to change with various cognitive and pathophysiological conditions."

We have performed the suggested change. We thank the reviewer for this suggestion, which helped to increase the readability of our manuscript.

Q. 2) On page 2, I was a bit confused by the phrase "the correlation length of brain activity diverges with size". Your results suggest that the correlation length increases with cluster size. The term 'diverges' suggests an increase in the dispersion or variance of correlation length with size. Perhaps you could replace "diverge" with "increase" or qualify your terminology more precisely?

We have re-phrased this passage to avoid confusion (*"the correlation length of brain activity increases with size (as expected by the divergence of correlation length)"*.

Q. 3) In the legend to Figure 2, I would insert "the cluster size (N)".

We performed the suggested change.

Q. 4) On page 3, in the Figure Legend and in the main text, you suggest that the variance of the mean correlation is constant in the critical regime. This is a bit confusing because it clearly decreases with cluster size. Perhaps you could say "roughly constant (showing a small decrease)".

We agree that the mean correlation variance at the critical point in fact decreases slightly with cluster size, and we have thus changed the wording accordingly (*"approximately constant"*). Please notice that this decrease is, however, small relative to that observed at the sub- and super-critical regimes.

Q. 5) At the end of page 3, I think you need to make it clearer that the maximal correlations with the spatial location of the resting state networks are over regions. In other words, they are not (as you state in your Figure legend) correlation between the spatial location - they are the correlations over voxels in the amplitude or weights of the independent components.

We have re-phrased this section of the manuscript to highlight the fact that we are performing spatial correlations between both ICA maps (fMRI and

model-derived).

5 Referee B

Q. - The statement (page 3) that 'at the critical state, the variance of $< C >$ is of the same order as observed in the experiments for different cluster sizes' as well as the statement that the fluctuations remain constant at different cluster sizes is not actually reflected in Figure 3. More specifically, the first statement holds for the cluster size 12 (Figure 3 panel A), whereas the fluctuations of the model and the experiment for the cluster sizes 47 and 71 look significantly different (while in the authors' argument they are claimed to be the same).

In the original version of the manuscript, we claimed that fluctuations in $< C >$ were of the same *order of magnitude* for the model and the experimental fMRI data which, strictly speaking, is true. Furthermore, the results show that the similarity between the experiment and the model at the critical point is high relative to that observed at the other regimes.

Nevertheless, motivated by the reviewer's legitimate concerns we conducted further explorations of the model which resulted in an even more striking similarity between experimental data and numerical simulations.

The key issue is to use a relatively wider Hemodynamic Response Function (HRF) in the process of building a synthetic BOLD signal from the model. Without changing any other parameter, by modifying the sampling frequency of the HRF it is possible to change its relative width. In the original manuscript we assumed a sampling rate of 2 s. for the HRF. Changing it to 1 s. results in a much wider shape (see Fig. R1). Convolving with a wider HRF gives a much closer agreement for $< C >$ variance between the model and the experimental fMRI data (see the new version of Figure 3 in the revised manuscript). Furthermore, the gap between the super critical model and the experimental data is even larger.

To demonstrate the robustness of the results, we also included in the Supp. Info. the $< C >$ time series for all subjects and cluster sizes (see new Figure S5), in which a close agreement between simulated data at the critical point and experimental data can be verified even by simple visual inspection.

Q. Having a closer look at the gradients in Figure 3 panel B shows that the absolute value of the exponent of the red line which fits the data obtained by simulations at the critical point (which should be zero) is actually larger than the absolute value of the exponent of the data in Figure 2 which documented the divergence of the correlation length with system size.

Please note that while both exponents can or not be similar in their absolute magnitude, they are of different and unrelated nature. Then, it is necessary to separately consider their meaning and the evidence favoring their interpretation in each case.

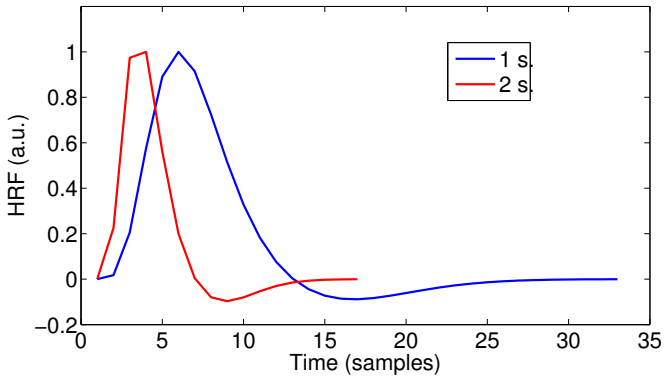


Figure 1: HRF shape for two different sampling rates (1 and 2 s)

Exponent on Figure 3: The exponent fitted in Fig. 3 is expected to be zero (at the infinite size limit) as described in detail elsewhere [3]. It deviates from zero due to finite size effects. Downsampling to 998 regions has the effect of decreasing the variance for large cluster sizes. This is easy to verify comparing these results to those reported in [3], in which this analysis was performed without any downsampling (i.e. voxel-wise) and this decrease for large cluster sizes was not observed. Also, in spite of a non-zero exponent for the fMRI data as well as for the model, the exponents are very small compared to that of the super critical regime. Importantly, this is expected due to theoretical arguments presented elsewhere [3].

Exponent on Figure 2: On the other hand, the scaling observed in Fig. 2 is of a geometrical nature. For a finite system, the divergence of the correlation length cannot exceed the actual system size. If V is the volume of the system in 3D and L is the diameter (which corresponds to the correlation length cutoff) then for a finite system $L \sim V^{\frac{1}{3}}$. Since here $N \sim V$, the scaling relationship follows. As clearly explained by Lesne & Laguës [6]:

The behavior of the system is then determined by the values of L and the coherence length ξ:

- *If $L > \xi$, the system behaves as if it was infinite.*
- *If $L < \xi$, then the boundaries of the system truncate the transition.*

An exponent of $\frac{1}{3}$, as predicted, was observed both for the experimental and simulated fMRI data at the critical regime (Fig. 2 of the manuscript).

The fact that this scaling exponent is related to the divergence of correlation length is also supported by the functional form of the $C(r)$ decay. This decay for all regimes can be described by the following expression,

$$C(r) = \frac{1}{r^{d-2+\eta}} exp\left(-\frac{r}{\xi}\right) \tag{1}$$

where d is the system dimension, η a critical exponent and ξ is the correlation length. According to this expression, for finite ξ, $C(r)$ decays exponentially with a decay constant of $1/\xi$. At the critical point, ξ diverges as $\xi \sim |T - T_c|^{-\nu}$. The exponential contribution to Eq. 1 is suppressed if (and only if) ξ diverges, turning into a power law decay with exponent $d - 2 + \eta$. We fitted the decay of $C(r)$ with a straight line in logarithmic coordinates and obtained the goodness of fit (R^2) as a function of T. Results presented in the Supp. Info. (Figure S3) show that the best fit is obtained around $T = 0.05$, which matches the critical point of the model. This is further evidence supporting that the scaling reported in Fig. 2 of the manuscript is related to the divergence of ξ.

We hope that this is sufficient clarification for the proper interpretation of both scaling exponents.

Q. The introduction of the model is very condensed. Particularly for readers not familiar with this type of model it would be helpful to have a few figures in the supplementary material illustrating the activity levels in the model, e.g. in the form of time series or with regards to the aspect of criticality in the form of an analysis of the avalanche statistics.

We appreciate this suggestion and we have included a more detailed introduction of the model in the Supp. Info. Since raw time series are not very informative by themselves, we have decided not to include them in the Supp. Info. We have, nevertheless, expanded the introduction of model by computing the lifetime (or "persistence", as termed elsewhere [2, 8]) of the model as a function of T. Given an initial randomly excited configuration, the lifetime is defined as the time elapsed until the activity dies out in the model. Since for high T activity dies out quickly and for low T activity is permanent and fails to die out, the lifetime has been identified as an order parameter for the model [2, 8]. We computed the lifetime for different r values, which measure the probability of an spontaneous excitation occurring in the system. Results are presented in the Supp. Info, Fig. S1. For $r = 0.001$ (the value used in our model) a sharp transition is observed between $T = 0.045$ and $T = 0.05$, close to the critical point identified by the size of the second largest cluster of activity (this transition is however more abrupt than the transition presented in Fig. 1 of the manuscript). The lifetime variability also peaks close to $T = 0.05$. The computation of lifetimes as an order parameter helps to put our results in the framework of previous works discussing proofs of critical behavior in the model here employed.

As suggested by the reviewer, a generic feature of criticality is the scale invariance exhibited by the sizes of clusters of activity (closely related to scale-free avalanche distributions [7]). This is only seen near the critical point, since as the system is moved away from criticality this scale invariance is lost and characteristic scales show up. Calculations in the model (see Fig. S2 of the Supp. Info) show that the distribution of cluster sizes obtained only at T_c matches the scale-free distribution computed from the fMRI data.

Q. - Figure 1C shows the behavior of the order parameter depending on the control parameter. Even though the black solid curve could be the finite size relict of a discontinuity of the first deriva-

tive of the order parameter at the critical value, the point should be strengthened by showing an increase in the gradient with increasing system size. Another hint towards criticality would be the emergence of clusters of all sizes distributed according to a power law.

First, we wish to clarify that the black solid curve depicted in Fig. 1 **IS NOT** the first order derivative of the order parameter, but the **order parameter** itself, as indicated in the text. Also, the dotted black line in Fig. 1 **IS NOT** computed as the first order derivative of the order parameter, but as the size of the second largest cluster (which incidentally resembles the first order derivative).

Increasing system size is a good suggestion, however is impractical since implies adding new nodes, and the only available connectome data is the one being used. The issue of increasing the resolution and accuracy of whole brain anatomical connectomes is a very interesting problem by itself and will surely contribute to the construction of more precise and extended large-scale brain models. However, we take as a starting point this connectome, which is state-of-the-art and also a well accepted and validated standard.

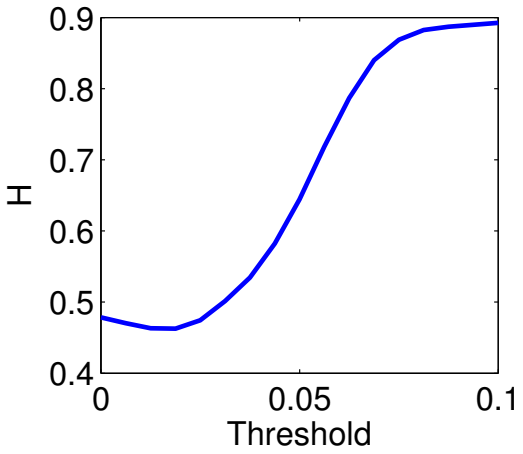


Figure 2: Mean Hurst exponent (H) as a function of T

Concerning cluster size distributions, we now include the results in Figure S2 (Supp. Info) which shows the three types of densities as the model passes trough the critical point: at the subcritical regime a giant cluster dominates the PDF; at the critical point a scale invariant distribution is observed and at the supercritical regime we see the exponential distribution of (relatively small) cluster sizes.

Given the relatively coarse spatial resolution of the connectome data (which might limit the consideration of spatial measures of criticality) we resorted also to inspect measures at the temporal domain, since arbitrarily long time series can be simulated. At the super critical point ($T < T_c$), we expect exponentially decaying temporal autocorrelations (as in white noise). Closer to the critical point, the temporal correlation length diverges and, similar to what happens

for the spatial correlation length, temporal correlations decay as a power law. This behavior can then be captured by the Hurst exponent H, which relates to the autocorrelation function $A(k) = Ck^{-\alpha}$ by $H = 1 - \frac{\alpha}{2}$. Thus, a value of $H = \frac{1}{2}$ corresponds to a random walk (i.e. pure Brownian motion). As H increases above 0.5, long-term temporal correlations appear in the system. Using Detrended Fluctuation Analysis (DFA) we obtained the mean Hurst exponents as a function of T. In Fig. R2 we show the plot of mean H (across all 998 nodes) vs. T. Clearly, H departs from $\frac{1}{2}$ around $T = 0.05$.

Q. - According to page 2, nodes further than 1cm away from an RSN cluster were discarded when reproducing experimental results. It is not clear why this simplification has been chosen, since running the dynamic on the whole network and only reading out the RSN-activity could give significantly different results than running the dynamic on a reduced network. Generally, it would be interesting to show the results of the analysis for the entire system (without filtering or restriction to the RSNs.) In addition it would be helpful to state the percentage of nodes that were taken into the RSN analysis.

Of all 998 nodes, $\approx 19\%$ were excluded from the analysis following the criteria specified in the manuscript. This procedure is not an arbitrary simplification, but a necessary one to guarantee the membership of the nodes to the different RSN under study. Otherwise, it becomes difficult to analyze the relation between the dynamics of the system and the different RSN.

Nevertheless, we consider that the reviewer's concern can be dissipated by repeating the simulations without reducing the number of nodes. Each node was thus assigned to the *closest* RSN, regardless of anatomical distance. We show these results in Figures S4 and S6 of the Supp. Info. which demonstrate that the core of our results holds perfectly when the dynamics are simulated in the complete connectome.

Q. - Figure 2 shows the divergence of the correlation length with system size. A stronger sign of criticality would be the demonstration of the divergence of the correlation length close to the critical value of the threshold by producing the power law for values just under and just over the critical value of the control parameter.

In responding, we would like to ask the reviewer to consider first the validity of our viewpoint here, concerning his/her suggestion of a *stronger* sign of criticality. After that we will meet the reviewer half way showing some computations in the spirit of his/her suggestion.

As far as we understand, is a *fact* that the model crosses a critical point. This was illustrated in the original version of the paper and the supplementary information by a number of different qualitative changes in the dynamics as a function of the control parameter T. We added now a number of other evidences to complement the description of these bifurcations. While the reviewer's suggestion seems in principle suitable for model systems with arbitrarily large size, in the case of the connectome recurring to a single spatial statistic (such as correlation length at both sides of the point) will not be per se a proof stronger

than the consistent concurrence of all the statistics we already presented. This is so because of the heavy under-sampling to 998 nodes given by the human connectome, which limits a straightforward computation of these distributions.

In particular, the suggestion to study the scaling properties of correlation length ξ around the critical point of the second order phase transition is discouraged *by the well known change in the functional form* of $C(r)$ as T moves away from the critical point. Following Eq. 1, $C(r)$ will decay exponentially outside the critical regime. Thus a continuous transition between these two types of decays of the correlation function prevents (in a relatively small system) an unambiguous determination of ξ, the length at which $C(r)$ changes from positive to negative correlations. Of course, one could set some arbitrary rules to parametrize the location of ξ, but that will open a number of new questions. For these technical reasons, we submit to the reviewer that, instead of strengthening the claim of criticality, the practical implementation of the suggestion in this small system will be easily criticized as an ill-defined problem.

Instead, we suggest the reviewer to inspect Figure S3, now included in the Supp. Info, which shows the best regression of $C(r)$ to the power law term in Eq. 1. These results are able to demonstrate, without any additional assumptions, that the best agreement is at T_c. In addition, in inspecting this figure, please note that in the examples of $C(r)$ the determination of the zero crossings is trivial in the critical regime while in the supercritical regime is not.

Q. The title of the article implies causality between the connectome, the criticality and the RSNs. However, (i) the paper demonstrates only correlational not causative relationships

We agree with this observation. We do not intend to claim causal relation between the RSN and the critical dynamics in the human brain, only on a particular model, therefore we changed the title to "Brain organization into resting state networks emerges at criticality on a model of the human connectome". We believe that this wording reflects what we report: that a model of the human connectome shows the RSN emerging only at criticality.

Q. The RSNs correlate only to a limited extent (correlation coefficient around 0.3) with the outcome of the simulations (Figure 4).

The limited correlations between fMRI RSN and those derived from the model are, in part, to be expected given the way in which the model activity is mapped into brain gray matter. Since simulated time series are mapped into "patches" grown from the discrete ROI placed throughout the brain, we think that it is difficult to expect a perfect correlation with the fMRI-derived RSN (which are obtained voxel-wise).

Please note that the correlation values reported in our paper are close (≈ 0.3) to those previously reported for the correlation between structural and simulated functional connectivity in which a $r \approx 0.32 - 0.52$, was reported [5] for a much larger N (the entire brain).

Nevertheless, to account for the reviewer interest and to properly gauge the significance of these correlations, we constructed null models and compared the correlations at the critical point obtained from the human connectome with

those obtained in the aforementioned models. These calculations are now included in the revised Figure 4.

Considering the sub- and super- critical regimes is a way to prove that the critical regime is a key factor in the emergence of spatially correlated structures which resemble the RSN. To further study whether the observed correlations can be considered high relative to those obtained from a null model, we simulated the model on a randomized version of the human connectome. Degree-preserving randomization was performed using the Brain Connectivity Toolbox (http://sites.google.com/site/bctnet/). After randomization, we repeated all computations and obtained the correlations with the RSN both for the real and randomized versions of the connectome. The average correlations are reported in the insets of the Fig. 4 of the revised manuscript. To compare the distributions of correlation values using both connectomes (real & randomized) we obtained the T-statistic for the difference in their means and plotted the values in the new version of Fig. 4. Here is shown that around the critical point, correlations obtained using the real human connectome are significantly greater than those obtained using the randomized version ($p < 10^{-3}$, multiple comparisons corrected). Thus, even though the absolute value of the correlations is limited, we can demonstrate that both the critical regime and the structural connectivity provided by the connectome are necessary factors to achieve these correlations. Future studies should benefit from connectomes obtained at higher spatial resolutions and thus be able to obtain correlations with higher absolute values.

Finally, the examples provided in the original version of Fig. 4 were individual components. As such, they were clearly noisy and it could be difficult to appreciate how the spatial organization of each model-derived RSN matched its experimental counterpart. In the new version of Fig. 4 we plot, for all eight RSN, the average components across all trials. These new maps are smoother and facilitate the identification of the similitudes and differences with the fMRI-derived RSN.

We consider that these new results should dissipate the reviewer's concern about the statistical significance of the correlations.

Q. Instead of showing the emergent behavior for all possible/likely critical dynamics, the results were just given for one specific exemplary model. Therefore, to motivate the model, it might be worthwhile to refer to the biological relevance of the model parameters.

We disagree with the reviewer's take on this. The approach of the paper is valid in the sense that follows a long tradition in studying critical phenomena, where one of the most powerful results is that the generic features of the critical state are independent of their actual realization. These features include the divergence of the correlation length, the emergence of scaling laws characterized by different (but interrelated) critical exponents, the abundance of metastable states, the alternation of synchronized states with periods of global desynchronization, etc. Surprisingly similar behavior can thus be achieved by very dissimilar systems posed at the critical state (a property termed *universality*). As stated in Lesne & Laguës [6]:

Critical behavior (and for example critical exponents) does not depend on the

microscopic details of the model (...) Critical exponents are universal quantities, which principally depend only on two "relevant" geometric parameters: the dimension d of space and the number of components n of the order parameter. Examples of "irrelevant" parameters are the symmetry of the lattice and the nature of the interaction range introduced in the model (on the condition that it decays reasonably fast with distance).

Universality legitimizes the use of simple models, since only the presence of these very few key parameters allows to characterize all systems in a given universality class. In our work, we showed that a simple model suffices to characterize different empirical results on brain activity dynamics measured with fMRI and (with the incorporation of realistic anatomical connectivity) that the metastable states of the model allow to differentiate sets of regions corresponding to well-described RSN.

The strength of our approach, thus, is to show that *all models* are bound to reproduce these results provided that:

- They are posed at the critical point of a second order phase transition.
- This transition can be described by a scalar order parameter
- The model connectivity matches that of the (realistic) network of anatomical connections (i.e., the connectome), which sets the dimensionality of the model (and so the universality class) and constraints the possible metastable states of the system.

Of course, an important next step will be to identify the biophysical mechanisms by which a critical state compatible with these requirements can be achieved. But detailed biophysical modeling is not necessary to prove that large-scale human brain dynamics are critical and belong to a certain universality class. This can be achieved by comparison with suitable (but simple) models tuned to the critical point.

Q. It would be telling to see whether this model predicts the RSNs better than a pure structure analysis, i.e, correlating the structural matrix with the observed RSNs in the same manner as done here for the simulated dynamics.

The reviewer shall agree that this concern is rather open; and after debating among ourselves how to best define "predict better" we come up empty handed (but see below). The reason is simple: of course structure and dynamics must agree in the long term averages, in the same way that highways (structure) and traffic (dynamics) are correlated - cars always travel through the highways. However, The subtle (but important) point is that shorter term changes (traffic jams, for instance) cannot be predicted from the highways maps. To investigate that, one has to explore different densities of cars circulating over a given "structure". In the case of the brain, we do not even have detailed information on the "jams", but only spatial patterns identified by ICA (which represent relatively long temporal averages). Thus, alternatively, we can investigate which dynamical regime is observed when the empirical and simulated neural dynamics agree, which is the objective of the paper. Note that this comparison is not

limited to the RSN, it could well be any other suitable and well characterized spatiotemporal pattern.

We are not alone in this view, as expressed recently by a well respected colleague: "like genes, structural connections alone are powerless", thus "the connectome must be expressed in dynamic neural activity to be effective in behavior and cognition" [9].

Among the alternative comparisons we discussed in relation with the reviewer request, we decided to study the similitude between functional connectivity matrices obtained from the model and from the empirical fMRI data, and to assess whether the correspondence between them is greater than the correspondence with the underlying structural connectivity matrix. Please notice that we already disclosed our reluctance to do this, but in the interest of the discussion we include it here.

In Fig. S8 of the Supp. Info (panel A) we show the average fMRI connectivity matrix obtained for all subjects. In panel B we show the connectivity matrix for the model at three different regimes: supercritical, critical and subcritical. In Panel C we plot the correlation between the connectivity matrices of the model and the average empirical connectivity matrix (empty circles) as a function of T. The correlation peaks around the critical T. We also simulated the dynamics using a randomized version of the connectome (empty squares), which gives ≈ 0 correlation for all the range of thresholds considered.

To study whether the model fits the empirical functional connectivity better than just the anatomical connections, we computed the average correlation between the connectome adjacency matrix and the empirical functional connectivity matrix (displayed in Panel A).

The obtained value is ≈ 0.11 and is denoted by the red horizontal line in Panel C. Clearly, the functional connectivity of the simulated dynamics around the critical point predicts the empirical functional connectivity better than just the anatomical connections.

6 Second Round of Review

Second Report of Referee A – LW13389/Haimovici

This revision has addressed my previous concerns and suggestions, thank you.

Second Report of Referee B – LW13389/Haimovici

I appreciate the considerable efforts made by the authors to strengthen and clarify their results. As a consequence, the revised version of the paper is much improved and more convincing. Below are point-by-point comments on the responses by the authors. My principal concern remains the demonstration of criticality in the model.

1) Changing the sampling rate did improve the outcome presented in Figure 3 and the exponents are now plausibly of the same order of magnitude.

2) The comparison in my question may have been misleading. This point was only intended to underline the concerns of point 1), it was not my intention to compare the nature of the two exponents mentioned.

3) I appreciate the figures added to the supplementary. They provide an intuitive insight to the critical nature of the model.

4) Thank you for the long answer although it slightly missed the point of my suggestion. As stated in the question I am aware that the order parameter is plotted and I was referring to the slope (the first derivative) at the critical point, which in an infinitely large system should show a discontinuity (it should jump from zero to infinity). In order to show that this system really is critical, the slope should increase for larger system size and decrease for smaller systems. With my comment I was intending to suggest to artificially increase (decrease) the system in a manner which keeps the structural properties. I do understand that this might be a difficult undertaking, however, I would consider that approach the strongest support for the claimed criticality. Alternatively, it should at least be stated explicitly in the paper that such a demonstration of criticality is impractical, and that therefore a range of alternative indicators are provided instead.

5) Ok.

6) The argument of the authors is valid. However, for criticality to be taken as fact, the demonstration suggested in 4) would be most convincing.

7) Ok.

8) Ok.

9) The suggestion was intended to raise the question of how a critical system could be built on the connectome and how the parameters of the model relate to the connectivity (since the same parameter choices would presumably not define the critical point if the dynamic were run on a random or all-to-all network) and the neural dynamics. I do agree with the author that this analysis might go beyond the scope of this paper.

10) The introduction of the null model and the correlation with structure helps to capture the significance of the interplay between the dynamics and structural connectivity.

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