Recovery of neural dynamics criticality in personalized whole-brain models of stroke

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The critical brain hypothesis states that biological neuronal networks, because of their structural and functional architecture, work near phase transitions for optimal response to internal and external inputs. Criticality thus provides optimal function and behavioral capabilities. We test this hypothesis by examining the influence of brain injury (strokes) on the criticality of neural dynamics estimated at the level of single participants using directly measured individual structural connectomes and whole-brain models. Lesions engender a sub-critical state that recovers over time in parallel with behavior. The improvement of criticality is associated with the re-modeling of specific white-matter connections. We show that personalized whole-brain dynamical models poised at criticality track neural dynamics, alteration post-stroke, and behavior at the level of single participants.
The fundamental mechanisms underlying the dynamics of brain activity are still largely unknown. Interdisciplinary research in neuroscience, inspired by statistical physics, has suggested that healthy brain's neural dynamics stay close to a critical state, i.e., in the vicinity of a critical phase transition between order and disorder, or between asynchronous or synchronous oscillatory activity. In physics, critical phenomena occur at the transition of different states of the systems (also known as phase transitions) for specific values of the so-called system’s control parameter (e.g., temperature). There is mounting evidence that biological systems (or parts, aspects, or groups) operate near/at critical points. Examples include gene expression patterns, bacterial clustering, flock dynamics, as well as spontaneous brain activity. Indeed, neural systems seem to display features that are characteristic of systems at criticality. These include (i) the scaling invariance of neural avalanches reported in diverse species, through different imaging techniques, and electro-physiological signals; (ii) the presence of long-range spatiotemporal correlations in the amplitude fluctuations of neural oscillations, including the observation of 1/f power spectra from simultaneously recorded MEG/EEG signals, and cognitive responses, and (iii) the increase of the correlation length with system size.

Critical brains benefit from these emergent features to promptly react to external stimuli to maximize information transmission, hence sensitivity to sensory stimuli, storage of information, and a coordinated global behavior. If criticality is indeed a fundamental property of healthy brains, then neurological dysfunctions shall alter this optimal dynamical configuration. However, we know little about the effect of brain disorders on criticality. Some studies have reported disrupted criticality during epileptic seizures, slow-wave sleep, and electro-physiological signals, and the presence of long-range correlation length with system size.

In this work, we use stroke as the prototypical pathological dynamics. To simulate neural activity at the individual whole-brain level we employed the homeostatic plasticity model recently developed. Figure 1 illustrates the main ingredients of our modeling strategy. Individual structural connectivity matrices are the key inputs of the stochastic model (Fig. 1a). Imaging and behavioral data are taken from a large-scale stroke study described in previous publications. Structural connectivity data was available for 79 patients, acquired 3 months ($t_1$) and 1 year ($t_2$) after stroke onset. The same study includes data from 28 healthy controls, acquired twice 3 months apart. The difference in the time interval between stroke and controls is that diffusion imaging in patients was obtained only at three and 12 months since the diffusion signal is highly variable early post-injury. In contrast behavioral, structural, and functional connectivity were obtained at all three time points in both groups (see Methods sections for details about the stroke dataset, lesion analysis, diffusion-weighted imaging (DWI), and resting-state Functional magnetic resonance imaging).

The whole-brain is described as a network of $N = 324$ nodes (i.e., cortical brain regions), linked with symmetric and weighted connections obtained from DWI scans and reconstructed with spherical deconvolution. The weights of the structural connectivity matrix, $W_{ij}$, describe the connection density, i.e., the number of white-matter fiber tracts connecting a given pair of regions of interest (ROIs) normalized by the product of their average surface and average fiber length. The ROIs are derived from a functional atlas of the cerebral cortex. Fig. 1a shows the topography of structural connections, the corresponding network assignment, and the corresponding averaged structural matrices. The matrix is sparse, and contains many short-range connections and fewer long-range connections. In the control group, inter-hemispheric connections between homotopic regions of the same
Fig. 1 Overview of whole-brain modeling. a Average structural connectivity (SC) matrices (top) and their corresponding network architecture embedded in a glass dorsal view of the brain (bottom). SC matrices and brain networks are organized according to regions of interest (ROI) defined on the cortical parcellation of Gordon et al.59. b The probability distribution function of the structural connectivity weights in controls and patients after homeostatic normalization (see main text, Eq. (1)). For each group, the (non-zero) weights of all individual matrices were pooled together and then the histogram was computed leading to a representative pdf for the corresponding group. c Top. Illustration of the network dynamics with homeostatic plasticity following the transition probabilities between the three possible states: inactive (I), active (A) and refractory (R). The temporal evolution of the central inactive node (pink) is as follows: in $t_1$, it is surrounded by three active nodes (green) and one refractory node (orange); in $t_2$, the incoming excitation is propagated ($\sum W_{ij} > T$); and finally, in $t_3$, it reaches the refractory state. Bottom. Procedure used to transform node’s activity, $s_i(t)$, in functional BOLD signals, $x_i(t)$. BOLD time-series are obtained by convolving instantaneous $s_i(t)$ with a canonical hemodynamic response function (HRF). d Behavior of the neural variables, the largest ($S_1$, continuous line), and the second largest ($S_2$, dotted line) cluster size as a function of $T$ (top). The peak in $S_2$ (red dot) is identified as the critical phase transition. Blue and green dots correspond to minimal and maximal values of $T$, and corresponding activity and BOLD time-series in the lower panels. Left panel: instantaneous network activity, $A(t) = \sum s_i(t)$, for different values of the activation threshold $T$; the super-critical phase $T > T_c$ (blue time-series), the critical phase $T = T_c$ (red) and the sub-critical phase $T < T_c$ (green). Right panel: example of the simulated BOLD signals between two arbitrary ROIs and their corresponding Pearson correlation $\rho$. The highest correlation is achieved at the critical phase, where BOLD fluctuations are long-range correlated.
Abnormal neural dynamics in stroke. In this section, we shall investigate the model’s fingerprint of criticality loss. Stroke is not a binary phenomenon, thus we do not expect that all individuals will lose criticality following a lesion. While some patients neural patterns will behave similarly to controls others will significantly depart from normality. First, we show the fingerprints of criticality loss and associated recovery in a representative patient, then we quantify the variability of the neural activity patterns across groups and time points. All the statistical tests reported throughout this study met the assumptions of normality and equal variances.

Figure 2a–d shows the model’s neural activity variables for an arbitrary control-patient pair. The neural profiles for each stroke patient and healthy control can be seen in the Supplementary Fig. 10–16. To facilitate the comparison between individual control and stroke data, we also present the average and standard deviation of the healthy controls (blue dashed line and shaded area, respectively). In general, the neural dynamics in healthy participants are quite distinct from stroke patients who manifests a loss of criticality. First, let us consider one healthy participant, Fig. 2a, b (black/gray dots). The neural patterns follow the expected behavior, with a critical point $T = T_{c}$ around the maximum of $S_{2}$, or equivalently, near the sharp decrease of $S_{1}$. Moreover, as expected, the two curves have low variability across the two time points ($t_{1}$ and $t_{2}$), displaying the same $T_{c}$ (within one standard deviation), and stable shape as a function of $T$.

The pattern is dramatically different in the stroke patient. The characteristic peak in $S_{2}$ describing the critical phase transition is completely absent at 3 months post-stroke, but normalizes at 1 year, where the transition is sharper and both, $S_{1}$ and $S_{2}$, with a behavior similar to normal. The monotonic behavior of $S_{2}$ is associated with a loss of a critical phase transition (for any value of excitability $T_{c}$, as shown in a recent study by Zarepour and colleagues). Accordingly, this monotonic behaviour is encountered when the average degree or the disorder of the structural connectivity matrix $(\hat{W})$ is low. When the connectivity disorder or degree increases then criticality emerges. Therefore, the recovery of criticality at 12 months predicts a reorganization of the topology of the structural connectome, with an associated increase of both, the average degree and the connectivity disorder, as a function of time. We shall investigate the anatomical bases of brain criticality modifications in the next section.

As already observed in, the homeostatic normalization on the weights of the structural matrix decreases the inter-participant variability of neural activity patterns. More importantly, it fixes the critical point of healthy controls to a universal value, $T_{c} \sim 0.122$. In other words, thanks to the homeostatic plasticity mechanism, the critical point is independent of the individual variability in the structural connectivity matrix. However, the strength of the $S_{1}$ and $S_{2}$ peaks provides the characterization of differences in criticality. In fact, near the critical point the differences in the stroke patient at $t_{1}$ and $t_{2}$ are pronounced. The most interesting feature, as shown in Fig. 2c, d, is the recovery-like pattern: the 1 year post-stroke curve resembles, both qualitatively and quantitatively, the pattern of the healthy controls. Similar results are shown for several examples of individual stroke patients and healthy participants (see Supplementary Figs. 10–16 and Supplementary Note 4).

We next examined the variability of the neural activity patterns across groups and time points. Figure 3 summarizes the results for $S_{1}$, $S_{2}$, $A$ (the average activity) and $\sigma_{A}$ (the variability of activity), respectively (the functional connectivity (FC) and the entropy $H$ are shown in Supplementary Fig. 3). The thin solid curves represent each individual stroke patient, while the thick dashed lines (brown = stroke 3 months; green = stroke 12 months; blue = average control) represent the group average, i.e., $X_{\mu} = \sum_{i} X(i)/n$, where $n$ is the number of individuals in each group. Individual stroke patients, as expected, showed great variability of $S_{1}$, $S_{2}$ behavior at $t_{1}$ with some exhibiting loss of criticality (monotonic $S_{2}$ and flat $S_{1}$) while others showing normal curves. On average, however, the stroke group at $t_{1}$ manifested a less critical behavior as apparent both in the distribution of individual (brown) curves and the average curves. In $t_{2}$, this abnormal condition was restored, and $S_{1}$ decreased toward normal, while $S_{2}$ increased. These changes in cluster sizes reflect alterations in segregation-integration balance within/between networks. The total average activity, $A$, followed the behavior of $S_{1}$. The variability of neural activity, $\sigma_{A}$, presented a sharp peak...
Fig. 2 Fingerprints of criticality loss and associated recovery in a representative patient. Analysis of neural activity patterns, $S_1$ and $S_2$, of a healthy participant (Con. / a, b) and stroke patient (Pat. / c, d). In blue dashed line we show the corresponding control’s group average, while the shaded area corresponds to one standard deviation. For the healthy participant, $t_1$ and $t_2$ correspond at two different time points 3 months apart. For the patient, $t_1$ and $t_2$ correspond to 3 months and 12 months post-stroke. The healthy participant exhibits features of criticality at both time points with small variability across time points and within the variability of the healthy group. At the same threshold $T$, both $S_1$ and $S_2$ sharply change their size. For the stroke patient under consideration, the flattened shape at $t_1$ of both, $S_1$ and $S_2$, combined with the monotonic behavior of $S_2$ indicates lack of criticality, which, however, returns at $t_2$ as depicted by the emergence of a peak in $S_2$. The black vertical dashed line depicts the critical point of healthy controls. Source data are provided as a Source Data file.

Fig. 3 Variability of the neural dynamics criticality across groups and time points. a, b Group based analysis of neural activity patterns, $S_1$ and $S_2$, as a function of $T$ for all patients and controls. The brown lines represent patients at $t_1$ (3 months post-stroke, $n=54$), and the green lines at $t_2$ (12 months post-stroke, $n=59$). The thin solid curves indicate each individual stroke patient, while the thick dashed lines represent the group average. The group analysis reveals that on average patient’s neural activity patterns are abnormal at $t_1$, but approach control levels at $t_2$. c, d Average activity and standard deviation of activity, respectively. Note improvement of the activity and its variability across time points. Insets: Probability distribution function (pdf) of the Euclidean distances $d$ in individual age-matched-controls and stroke patients at $t_1$ (brown) and $t_2$ (green). Patients at $t_1$ show greater variability of model neural activity as depicted by the longer pdf’s tails. Note trend toward normalization from $t_1$ to $t_2$. The black vertical dashed line depicts the critical point of healthy controls. Source data are provided as a Source Data file.
at the critical point for healthy participants, but was significantly attenuated in patients. We statistically assessed how the neural variables evaluated at the critical point shown in Fig. 3 varied between groups and across the two-time points using mixed ANOVA. The group main effect was reliable for all variables (all p-values < 0.004), confirming the alterations in the neural dynamics for stroke patients with respect to healthy controls. However, the main effect of time was not significant. We expected a group by time interaction reflecting longitudinal changes restricted to the patient group, but this was only significant for the standard deviation (p-value = 0.022) due to the large variability across patients. Nevertheless, we carried out planned paired two-tailed t-tests to further assess changes in the patients' neural variables over time. We found statistically significant differences for $S_1$ (p-value = 0.03) but not for $S_2$ and $A$ (Supplementary Table 3).

The Euclidean distance, $d$, was then used to quantify the similarity between individual neural activity pattern (i.e., $X(i)$) with the corresponding control group average (see Methods section (Eq. 9)). This measure takes in consideration the behavior of the neural profile across all values of excitability $T$. A low $d$ indicates low variability of the dynamic parameters across participants and time points as observed in healthy participants (e.g. Fig. 2a, b). A high $d$ indicates high variability across participants and time points of the neural state variables implying the presence in the group of abnormal dynamics. The insets in Fig. 3 show the normalized distribution of the Euclidean distances for each variable ($S_1, S_2, A, o_b$). Each variable shows higher variability in stroke than controls, and higher variability at $t_1$ than $t_2$. Based on\textsuperscript{62} changes in criticality of the model must depend on changes in the underlying structural connectivity, a biological prediction that we will examine in more detail in the next section.

In summary, both at the level of single participants and group level, the models of stroke patients show a significant loss of the network segregation and integration\textsuperscript{64}, respectively. Further, the main effect of time was not significant. These results indicate a weak relationship between lesion size and loss of criticality.

We further characterized the brain network organization in terms of modularity (an index of network segregation) and global efficiency (an index of network integration). Healthy participants are highly clustered in the upper left region of the scatter plot and show the highest values of global efficiency and lowest values of modularity. This pattern reflects a balanced network configuration that supports functional segregation between distinct specialized brain regions while allowing for functional integration. However, stroke disrupts this balance. In fact, patients at $t_1$ show decreased global efficiency reflecting a decrement of network integration with reduced capacity for information transfer between distant brain regions. At $t_2$ global efficiency and modularity tend to normalize moving their distribution toward controls. Changes of modularity from $t_1$ to $t_2$ are negatively correlated with changes in global efficiency ($R^2 = 0.8$, $\rho = -0.9$ and p-value $< 10^{-14}$, inset of Fig. 4b). A pathological increase of network segregation therefore comes at the cost of diminished integration and vice-versa. The global efficiency presents more robust variations across time points (paired t-test: $t = 1.8$, p-value = 0.08) than modularity (paired t-test: $t = -1.2$, p-value = 0.23). In summary these analyses indicate remodeling of white-matter connections from three to 12 months post-stroke that correspond to changes in network organization. In the Supplementary Information we provide additional evidence for this remodeling (Supplementary Table 1 and Supplementary Note 1). We tested whether the structural connectivity matrices, or portions of them, changed over time in terms of the number of white-matter fibers. We found significant global changes (averaging across all nodes) from 3 to 12 months both in the number of fibers and their topology. We also found significant increases in the number of fibers at the level of many brain networks. In contrast, no significant differences from $t_1$ to $t_2$ were detected in healthy controls.

Next, we investigate which connections were more strongly related to the alteration and recovery of criticality. To this end, we used a multivariate machine learning approach, based on a cross-validated Ridge Regression\textsuperscript{65}, to relate the model’s neural activity variables to the structural connectivity matrix. This approach allows to identify edges (and sub-networks) across the whole
brain that are most strongly related to the variable of interest (see Methods for details).

First, we investigate the relationship between structural connectivity and criticality, both in healthy participants and in stroke patients. We employ the threshold independent dynamical variable $I_2$, defined as: $I_2 = S_2 dt$. The rationale behind the choice of this variable is twofold. First, $I_2$ is positively correlated to $S_2$ evaluated at the critical point ($\rho \approx 0.9$ and $p$-value $< 10^{-16}$), but it is much more stable. Indeed, the integration of $S_2$ over the entire range of excitation smoothes out the fluctuations due to the intrinsic variability in brain topologies and associated dynamics. Second, this variable predicts a large amount of behavioral performance at each time point separately (see next section). Figure 5 shows that the structural connectivity accounts for a large proportion of variance in $I_2$ (controls: $R^2 = 0.68$; patients at $t_1$: $R^2 = 0.57$; patients at $t_2$: $R^2 = 0.69$). The map of predictive edges, $W_{ij}$ (see Eq. (14)), plays a key role in understanding the alterations of neural dynamics criticality ($I_2$) vis-a-vis white-matter remodeling. We provide two distinct complementary visualizations of $W_{ij}$. First, we display the top 200 edges embedded in an anatomical space (top, Fig. 5). Small values of $I_2$ correspond to neural patterns compatible with critical dynamics. Thus, positive edges (colored orange) contributes to criticality loss ($W_{ij} > 0$), while negative edges (colored green, $W_{ij} < 0$) reinforce the emergence of critical dynamics. In healthy participants predictive edges concentrate in auditory, cingulo-opercular, default mode, fronto-parietal and somato-motor mouth networks; interestingly, the visual network contributes with few regions with weak edges. Healthy participants show a predominance of negative edges (positively associated with the emergence of criticality). In contrast, predictive maps of structural connections in stroke patients show a different organization. The connectivity weights are not as balanced as controls (see width of the edges). The visual network is more prominent in patients, especially at $t_2$.

The second analysis considers the network topology involving different functional networks (bottom, Fig. 5). Specifically, we analyze the average link between pairs of functional networks, $\langle W \rangle_{XY} = \sum_{x \in X} \sum_{y \in Y} \langle W_{xy} \rangle / N_{XY}$, where $X$ and $Y$ designate ROIs belonging to a given functional network (visual, default mode etc) and $N_{XY} = N_X N_Y$ is the total number of connections. We use the same sign convention described above for edge colors and show the quartile 50% for ease visualization. The network topology of controls is quite balanced, but few connections are stronger, such as AUD-SMM, SAL-CPA, VAT-CAP, etc. The network topology is dramatically different for patients at $t_1$. Many pairs of RSNs are associated with criticality loss (orange edges, $\langle W \rangle > 0$), such as DMN-SAL, DMN-SMM, SAL-VAT, to name a few. There are also more and stronger negative edges between networks than in healthy participants (e.g., VIS-SMM/AUD/CAP/VAT). The pattern normalizes on $t_2$, with more balanced connections compared to $t_1$, although relatively stronger compared to controls. We used Pearson’s correlation to estimate the similarity between healthy and stroke networks in predicting criticality, as described by the average connectivity across RSNs, $\langle W \rangle_{XY}$. The correlation between healthy and stroke network at $t_2$ was moderately high ($\rho_{(W)} = 0.72$), but much smaller at $t_1$ ($\rho_{(W)} = 0.36$). Both $p$-values were statistically significant. In summary these findings show that structural connectivity at 12 months post-stroke predictive of criticality becomes more like that of healthy participants.

To examine whether structural connectivity changes predicting criticality truly reflect remodeling of structural connections, we compared, at the level of networks, the ridge regression maps of the edges predicting criticality at 3 or 12 months with the maps of the structural connectivity changes in the same interval. The correlation was moderate at 3 months ($\rho = 0.52$), but high at 12 months ($\rho = 0.80$). This result implies that connections predicting criticality values were remodeled over time.

Finally to test if criticality predictive edges were part of the normal functional architecture or reflect random connections, we correlated the number of predictive edges for each node (ROI) with the corresponding node’s strength in the healthy controls’ average functional connectivity. The high correlation seen at both time-points ($\rho = 0.98$ for positive/negative edges vs. node functional connectivity) indicates that the predictive edges are not random, but consistent with the normal variability of the brain functional architecture.
Relationship between recovery of criticality, functional connectivity, and behavior. Up to this point, our results strongly suggest that stroke recovery induces a normalization of the neural activity patterns that can be quantified by criticality. One important question is whether these dynamical signatures reflect the patients’ recovery as typically seen in behavioral measures and in the functional connectivity. We used the framework described in to simulate the functional connectivity from the structural one for each individual patient. Briefly, the time-series of node’s activity, \( s(t) \), is convolved with a canonical hemodynamic response function (HRF). We further applied a band-pass filter in the range of 0.01 – 0.1 Hz. Next, we obtain the functional connectivity matrix, FC, through the Pearson correlation, Eq. (6), between each pair of ROIs in the network. We use the averaged correlation across ROIs FC to characterize the strength of the functional connections in patients and controls (see Eq. (7)). We also compute the entropy, \( H \), of the functional matrices following the framework of Saenger et al. (see Methods section, Eq. (13)). The entropy measures the repertoire diversity and the complexity of the functional connections, and may serve as a biomarker of stroke recovery as well. The behavioral performance of patients and controls was inferred from a neuropsychological battery measuring performance in 8 behavioral domains (motor left / right, language, verbal and spatial memory, attention visual field, attention average performance, attention shifting). The Supplementary Note 2 report a full description of the tests used. We used principal component analysis (PCA), a common data reduction strategy that identifies hidden variables or factors, to capture the possible correlation of behavioral scores across participants. In each domain one component explained the majority of variance across participants (57–77% depending on the domain). The component scores were normalized with respect to healthy controls (mean = 0 and SD = 1). This normalization allows to express the patients’ scores in units of standard deviations below average — i.e. \( B(Lang) = -4 \) is equivalent to language function 4 SD below the control average. Here, to characterize each patient’s overall performance, we use the average component score obtained from averaging the normalized factor scores across domains,

\[
\langle B \rangle = \frac{\sum_i B_i}{8}.
\]

The composite behavioral score \( \langle B \rangle \) is well behaved as it accurately tracks individual behavioral deficit variability across time points \( (R^2 = 0.81 \text{ and } p = 0.9) \) (Supplementary Fig. 2). To quantify the relationship between dynamical and behavioral deficits we used the integral of the first, \( I_1 = \int S_1 dT \), and second,
Removing this outlier from the analysis we obtain
\( p \) reproduces the positive correlation with behavior observed empirically (black dots) with a corresponding peak in the statistical significance for all the tests. The (two-tailed) \( p \)-values reported in panels (d, h) were not corrected for multiple comparisons. Source data are provided as a Source Data file.

\[ I_2 = \int S_2 dT, \] cluster sizes over the entire range of excitability \( T \), respectively. Notably, both variables were strongly correlated with \( B \) (Fig. 6a, b, e, f). The correlation is positive for \( I_1 \) (\( t_1; p = 0.4; t_2; p = 0.5 \)) while it is negative for \( I_2 \) (\( t_1; p = -0.25; t_2; p = -0.51 \)). This relationship indicates that a larger \( S_1 \) cluster and a smaller \( S_2 \) cluster are associated with better performance. Note the improvement in correlation of both variables from \( t_1 \) to \( t_2 \) (compare \( t_1 \) Fig. 6a, e with \( t_2 \) b, f). This suggests normalization of the structure-function (behavior) relationship, well captured by the stochastic model over the course of the stroke recovery. Supplementary Table 2 shows the relevant statistical tests corrected for multiple comparisons (FDR). All correlation with behavior were significant except \( I_2 \) at \( t_1 \) (Fig. 6b). These findings are consistent with the second prediction that variations in neural dynamics are behaviorally relevant.

Variations in neural dynamics estimated from the structural model may be reflected in the patterns of functional connectivity (FC). In Fig. 1 we already showed that the model FC derived from applying an hemodynamics response model to the neural activity, as described by \( I_1 \) and \( I_2 \), were signficantly correlated with the empirical average homo-FC\(_m\) (Fig. 7a–d). The correlation was positive for \( I_1 \) (\( t_1; p = 0.43; t_2; p = 0.46; p\text{-values} < 0.05 \), corrected), i.e., large values of \( S_1 \)—hence more integrated networks, correlated with the average homotopic connectivity at both time points. On the other side, the correlation was negative for \( I_2 \) (\( t_1; p = -0.27; t_2; p = -0.44 \); only the latter \( p \)-value remained significant). Interestingly, the relationship with the average empirical FC (FC\(_e\)) was in the same direction, but weaker in correlation strength (Supplementary Table 2): \( I_1 \) (\( t_1; p = 0.23; t_2; p = 0.29 \)) and \( I_2 \) (\( t_1; p = -0.11; t_2; p = -0.37 \)). In contrast, we did not find any overall significant correlation between average homo-FC\(_m\) and average homo-FC\(_e\) at the critical point \( T_c \) (Supplementary Fig. 17). Furthermore, the relationship between FC\(_m\) and FC\(_e\) not only was maximal at the critical point, but it
reached statistical significance at criticality at \( t_1 \) \((p < 0.05)\), not at \( t_3 \) (Supplementary Fig. 4). These findings therefore suggest that both model and empirical FC normalize and become more similar consistently with a normalization of structure-function relationships. These results are very encouraging since we did not use any optimization of the model inputs to reproduce the empirical FC as done for example in ref. 49.

Overall this section shows that neural dynamics from the model correlate with behavioral performance and that this relationship becomes stronger at 12 months. Moreover, the model can reproduce the patterns of homotopic FC that behave similarly to empirical FC in the correlation with behavior. While it is not surprising given the lack of any optimization that overall empirical FC does not correlate across participants with model FC, the model shows that interestingly empirical and model FC become more similar at criticality, especially when the lesioned model approximates normality in the course of recovery (from 3 to 12 months).

Fig. 7 Statistical correlates between model dynamical patterns and empirical homotopic functional connectivity. In the legend we show the (linear) correlation, \( \rho \) and the \( R^2 \). a, c Relationship between \( h_i \) and empirical homo-FC at \( t_1 \) and \( t_2 \), respectively. b, d The same as before, but for \( l_2 \). Both dynamical variables predicted a significant amount of functional variance, but panel b did not remain significant after correcting at level of \( \alpha = 0.05 \). Sample size \((n = 50)\). Source data are provided as a Source Data file.

**Discussion**

We set out to examine whether criticality is affected by lesions, and whether alterations of criticality are behaviorally relevant. We use lesions as a causal manipulation to test the theory that criticality is a fundamental property of healthy brains that provides optimal functional and behavioral capabilities. Several interesting results are worth of discussion.

First, our stochastic model is personalized since it used as input direct estimates of structural connectivity at the individual level. The model provides measures of activity, functional connectivity, and criticality that tracked individual variability in healthy and stroke participants. Importantly, alterations in stroke patients were evident both at the group and individual level, and easily separated stroke from healthy participants. Second, these criticality alterations normalized over time. This normalization reflects changes of the underlying structural connectivity, with associated changes in the average degree, connectivity disorder, modularity and global efficiency. We describe which connections are most predictive of the final level of criticality, and which predict improvements in criticality. The distribution of predictive connections was not random but matched the normal functional architecture of the healthy brain. Third, we show that alterations of criticality were behaviorally relevant as they correlate with improvements in performance. Finally, we show that the model can reproduce the relationship between functional connections and behavioral deficits/recovery that have been established empirically in many studies 34–36,50,55,66,67.

Methodological considerations. The whole-brain mesoscopic model, a variant of the Greenberg-Hastings cellular automata, was proposed by Haimovici et al. 21. When poised at the critical point, the model captures, at the group level, the emergence of experimental spatiotemporal patterns, the temporal correlation between regions (functional connectivity, FC), the organization of brain wide patterns in so-called resting-state networks (RSNs), and the scaling law of the correlation length, among others.

We improved the Haimovici model by adding a normalization to each node’s excitatory input, a mechanism of homeostatic plasticity 69–71. This simple adjustment balanced the macroscopic dynamics increasing the strength of critical transitions. The clusters of activity became more heterogeneous spreading along the whole network and not mainly in the hubs, as in the un-normalized model. In the normalized model, the cluster size distribution in proximity to the critical point follows a truncated power-law with a critical exponent \( \alpha \) close to the hallmark exponent of avalanches sizes, \( \alpha = 3/2 \). Finally, the homeostatic normalization mechanism significantly improves the correspondence between simulated and empirical functional networks based on fMRI.

An important feature of the normalized model is that it minimizes the variability of the critical points and neuronal activity patterns among healthy participants. The normalization collapses the model state variables of healthy participants into universal curves, which allows to compare critical points between patients and stroke, and stroke patients at different time points.
Whether similar results could be obtained without the inclusion of the homeostatic mechanism is an interesting question that we shall investigate in future work.

Another important innovation is that the input to the model were individually measured structural connectomes, both in healthy participants and stroke patients at two time points. The repeated measures allowed the estimation of the stability of the criticality values that were quite narrow in healthy participants, thus supporting the inference that changes of criticality in stroke were related to the effect of the lesions, and not to the inter-individual variability. The availability of individual structural connectomes is not common, and most whole-brain studies have used population atlases of white-matter connections78,79. The group of patients studied here is partially in overlap with Lin et al.52 who, however, only studied a subgroup of patients with motor deficits. Also Lin et al. used fractional anisotropy, a measure of white-matter microstructure in an anatomically defined ROI. Here, for the first time, we use direct tractography creating a structural connectome of each control and stroke patient. This approach is also different from the recent Salvador et al.13 in which we used an indirect approach to estimate structural disconnections by embedding the lesion in a normative atlas of white-matter connections. Another innovative methodological aspect of this work is that we use the structural connectomes without additional optimization - fMRI connectivity is often used to enhance the accuracy of structural connectivity due to its low sensitivity or incomplete coverage49,50.

However, the model can be certainly improved. The DWI data were not state-of-the-art. The sequence was 10-year old with 60 directions and a single b-value of 1000 s/mm². This group of healthy and stroke participants began enrollment in a prospective stroke study at Washington University in 2010 with completion in 2015 (WU Stroke cohort I). The tractography used in this study has been produced following the standards of analyses that lead to the publication of classical atlases of the white matter74,75 that match post-mortem dissections76 and axonal tracing77. Tractography reconstructions were checked by an expert neuroanatomist (MTS). The controls were tested 3 months apart while the stroke patients were tested at 2 weeks, 3 months and 12 months with the last two time points being the object of this study. We did not acquire diffusion imaging data at 2 weeks given the rapid changes of diffusion signals in the first 1–2 weeks post-stroke. Since most behavioral changes in stroke occur in the first 3 months post-injury, it is likely that the changes in structural connectivity in relation to criticality were actually underestimated. In healthy participants we did not expect significant changes 3 months apart in their structural connectomes based on the literature78,79. This was empirically confirmed in our healthy control analyses. We have completed the acquisition of a second cohort (WU Stroke cohort II 2016–2020) from which we will have access to multi-shell, multi-directional and multi-weighted diffusion-weighted images80 at 2 weeks, 3 and 12 months. This will allow us to track structural connectivity changes from 2 weeks to 3 months when the rate of behavioral recovery is the strongest.

We simulated fMRI functional connectivity by augmenting the stochastic whole brain personalized model with a standard hemodynamic model. We used the average (across ROIs) and inter-hemispheric homotopic functional connectivity (homo-FC) and entropy (H, which measures the functional weight diversity) to characterize stroke-related changes. The model reproduced changes of functional connectivity observed empirically in stroke, such as a decrease of inter-hemispheric FC35–37,66,67 and entropy80, subsequent normalization34, and correlation with behavioral performance35. However, the model’s fit with the empirically measured FC was low (see Supplementary Fig. 4a, c), but approached significance at t2. We elected not to optimize the input through functional connectivity because it would have hidden the role of structural connectivity in supporting critical phase transitions in stroke patients and longitudinal changes. Fitting the model with free parameters has its own issues including variable parameter sensitivities81, identifiability problem82 and overfitting issues83. More importantly, this work aims at unveiling robust and universal features of brain criticality in relation to the anatomical brain connectivity structure and foci lesions, and therefore it is crucial that the model dynamics has the smallest possible degrees of freedom84.

The whole-brain modeling is invariably based on arbitrary choices of the density of structural connectivity and the brain parcellation as well85. The latter has been often employed without scrutiny to accommodate the hypotheses of the study in question (e.g., functional versus structural); while the former is subject of intense research and ongoing debates in the literature86. A recent study by Jung et al.87 shed light on the effect of these two variables on the performance of a whole-brain model represented by a system of interacting oscillators. They reported that the parcellation with different atlases showed similar changes of the architecture of the structural networks, but distinct trends of the goodness-of-fit of the model to the empirical data across tractography densities (i.e., number of streamlines). On the one hand, high densities are desirable to guarantee the reproducibility of the graph-theoretical properties of the structural network; on the other hand, high densities are not always the best condition for whole-brain modeling. These nonlinear effects reflect the inter-individual variability of the brain topologies, thus making it difficult to have a closed set of tractography parameters that reliably capture the brain architecture. One possible middle ground approach would be based on personalized data processing and modeling85.

Along these lines, in the supplementary information (Supplementary Figs. 5–9 and Supplementary Note 5) we investigate the sensitivity of the results with respect to the brain parcellation. We test the robustness of our results by replicating our analyses in a uniform parcellation87. Specifically, we characterized each brain voxel uniquely based on its anatomical location, in terms of x, y, and z coordinates. The matrix of anatomical coordinates of the brain was then fed into the k-means clustering in python. We asked the algorithm to parcellate the brain in 400 clusters, to enable the comparison with the Gordon parcellation. In this uniform parcellation all ROIs have equal size, but their functional or anatomical macroscopic relationship have been disorganized, i.e., neighboring voxels can be randomly assigned to other neighboring voxels that can be either correlated or not. However, replication indicates that global neural dynamics parameters like $S_1$ and $S_2$ seem to be more dependent on maintenance of local connectivity rather than large-scale functional systems.

**Stroke lesions cause changes in activity, entropy, and criticality.** Whole-brain models of healthy controls showed stable patterns of neural activity, both across time-points and individuals. It is important to understand the model dynamics in healthy participants before considering changes in stroke. For low thresholds of activation, the system is super-critical with high levels of activity, low entropy, low levels of functional connectivity, and a single giant first cluster (S1). This is akin to a brain in status epilepticus with very high level of activity but low entropy, hence no efficient processing of information and lack of consciousness. For very high thresholds of activation, the system is sub-critical with low levels of activity, low functional connectivity, and entropy. Activity is mostly local with small clusters (S1). For intermediate thresholds, the neural patterns followed the
expected behavior, with a phase transition peaking around the maximum of $S_2$ (Fig. 3). In contrast, simulations of the patients’ brains at 3 months post-stroke show striking attenuation in the signatures of brain criticality for many individuals, as revealed by the patients $S_1$ monotonic behavior (Fig. 6a, e/b, f). Patients with higher-IQ have neural dynamics closer to criticality than participants with lower-IQ.

Our findings show that focal lesions from stroke, a causal manipulation of brain activity, modify criticality in a significant behavioral manner. We used an aggregate measure of behavioral impairment across multiple domains (motor, vision, attention, behavioral manner) to assess criticality. We used an aggregate measure of behavioral abnormalities post-stroke based on the literature (see Supplementary Figs. 10–16). The curves of overall activity ($A$), variability of activity ($\sigma_A$), clusters sizes ($S_1$ and $S_2$), functional connectivity (FC), and entropy ($H$) are significantly decreased. The first cluster is significantly decreased in size, while the second cluster is significantly larger as compared to controls at multiple thresholds of activation. All these patterns are consistent with lack of criticality. Crucially, the same criticality signatures reveal the recovery at 1 year post-stroke for many individuals and on average for the group. The neural patterns at $t_2$ approach the corresponding controls’ average (see probability distributions of Euclidean distances Fig. 3 and Supplementary Fig. 3). Longitudinal changes of the neural variables from $t_1$ to $t_2$ were confirmed for $\sigma_A$, $S_1$, and $I_t$.

**Correlation between criticality and behavior.** The role of criticality in behavior has been discussed in prior studies. For instance, Palva et al. reported a correlation between scale-free neuronal avalanches and behavioral time-series in MEG/EEG data. The connection between human cognitive performance and criticality has also been investigated. Ezaki et al. provided empirical support that participants with higher-IQ have neural dynamics closer to criticality than participants with lower-IQ.

Our findings show that focal lesions from stroke, a causal manipulation of brain activity, modify criticality in a significant behavioral manner. We used an aggregate measure of behavioral impairment across multiple domains (motor, vision, attention, memory, language) by averaging factor scores of impairments across domains as in (see Supplementary Fig. 3). This aggregate index captured global motor and cognitive disability, as we did not have a specific hypothesis about a link between one behavioral domain and criticality. This performance index manifested known properties such as a strong relationship between different time points, with 3-month scores predicting 12-month scores. It also showed a robust relationship with homotopic inter-hemispheric FC as in previous work. Importantly, modularity in neural networks as indexed by the integral of $S_1$ and $S_2$ ($I_1$, $I_2$) correlated with behavioral performances at both time points (Fig. 6a, e/b, f). Patients with higher normal performance showed larger $S_1$ and smaller $S_2$ clusters. Interestingly, the integral of the cluster sizes, $I_1$ and $I_2$, proved a better predictor of behavioral performance than variations in model FCm (Supplementary Fig. 4b, d) or homo-FCm (Fig. 6d, h).

We find a weak relationship between lesion size and loss of criticality. We did not investigate the effect of lesion size on behavioral dysfunction, a topic that we shall investigate in future work. However, we did not expect a significant influence of lesion size on behavioral deficits and functional/structural connectivity abnormalities post-stroke based on the literature. The use of the integrated variables ($I_1$, $I_2$) instead of the original ones ($S_1$, $S_2$) is motivated by the relevance of the former for clinical applications. First, these integrated variables are highly correlated with the corresponding original variables ($S_1$, $S_2$), however, they are more stable. Second, the aberrant behavior of the patients’ neural dynamics is more easily quantified when considering the profile of the curves for all excitation regimes, and not just the value of the cluster’s sizes at the critical point; this latter is more subject to fluctuations from different sources, such as noise in data acquisition, the neural dynamics itself, etc. The integrated variables capture relevant biological information as they consider the neural dynamics response to different excitation regimes; this makes it possible to access the response of a brain (from its connectivity matrix) to intrinsic changes in (self) regulatory mechanisms (caused by stroke, for example) that are responsible for the degree of activation and inhibition. In other words, in general we may have different excitation’s thresholds over the trials (during fMRI acquisition, for instance) and therefore it is a way to conditioning out this degree of freedom that is not accessible from the data.

**Anatomical connections supporting criticality and prediction of recovery.** The available theory predicts that criticality deviations are closely related to alterations of the brain’s network topology. We find statistically significant changes in stroke patients’ average degree, connectivity disorder, modularity and global efficiency as compared to healthy controls (see Supplementary Table 3). All these measures exhibited a normalization pattern, with associated probability distributions shifting toward the healthy control distributions (Fig. 4a, b). Patients at $t_1$ showed significantly lower average degree, connectivity disorder and global efficiency, but significantly higher modularity. These results are in line with a recent study performed in a smaller stroke cohort ($n = 17$; patients with >6 months since stroke onset) where the authors reported significantly lower global efficiency with significantly higher values of global clustering and modularity as compared to healthy controls. The evolution of these measures over time points was not investigated. In this study, we find notable recovery of these global graph measures across time points. Indeed, patients at $t_2$ tend to normalize the integration-segregation balance exhibiting statistically significant increase in average degree, connectivity disorder, global efficiency and a less robust decrease in modularity. In the Supplementary Information we provide an additional compelling evidence of the intricate relationship between brain criticality, the underlying network topology and behavior (see Supplementary Table 4 and Supplementary Note 3).

Few studies have addressed the relationship between the structural and functional network topology in recovering stroke patients. This same cohort was investigated by Siegel et al. who analyzed the functional network organization based on fMRI. It is worth noting that the functional modularity presents the opposite trend as reported here; modularity increases over time-points towards the controls; this same study did not find significant differences in global efficiency between controls and patients or over recovery. However, an important difference is that Siegel et al. measured modularity in a priori selected functional networks while we measured modularity using a data-driven Louvain community detection to optimize the modular organization of the structural network. There are many potential differences that can explain such opposite trend. Functional networks are bilaterally organized, and the breakdown of inter-hemispheric connectivity post-stroke decreases their modularity. Moreover, some networks become abnormally linked with other networks, which further decreases network modularity, proportionally to the decrement of inter-hemispheric interaction. In contrast, in a data-driven approach communities will be detected in each hemisphere, early on post-stroke, but their number will decrease in the course of recovery as inter-hemisphere interactions improve.

A notable result is the remodeling of the structural connectivity in the white matter supporting the normalization of criticality from 3 to 12 months post-stroke. Indeed, we find that specific connections in the brain predicted with high accuracy, in a ridge regression model, criticality values (e.g., $I_2$) at both time points, but with higher accuracy at 12 months. Notably the maps of predictive edges differ from healthy controls at 3 months, normalize at 12 months, but are even more like the map of
structural connection changes occurring in the same time interval. In other words, the brain normalizes criticality post-stroke using a different set of connections than a healthy brain. Importantly, these new connections are not randomly located but are part of the normal functional architecture as shown by the strong correlation with the intrinsic pattern of functional connectivity.

The structural connections that predict criticality are best illustrated by the circle plots in Fig. 5. Healthy controls show a balanced set of structural connections predicting criticality (e.g., auditory-ventral attention, ventral attention-cinguloparietal) while others become negatively related to criticality, i.e., their strength predicts low criticality value. Interestingly, some of these latter connections involve the default mode network and other networks (motor, salience). It is speculative to think that this effect may be related functionally to the loss of segregation between regions of the default mode and sensory-motor-attention networks, previously reported. At 12 months many of the edges that were negatively predicting criticality (including DMN edges) become positively correlated to criticality. In a recent review, Gollo et al. hypothesized that hub regions within the DMN represent a structural signature of near-critical dynamics. Our findings provide some support for this idea. Edges to/from DMN regions as well as networks sub-serving visual, attention and executive control (cingulo-opercular and dorsal attention networks) predicted higher criticality values at $t_2$.

An increase in critical signatures from $t_1$ to $t_2$ must correspond to the recovery of structural (anatomical) connections, which is captured by diffusion-weighted imaging (DWI) and tractography (Supplementary Table 1). Changes in DWI and tractography may reflect a number of different homeostatic plasticity mechanisms, including structural plasticity in gray and white-matter tracts, recovery of neural cells, remyelination, and rewiring. Whether long-range anatomical connections changes support the recovery of function in stroke is not a well-explored issue. Longitudinal changes in micro- and macro-scale structural anatomy and physiology following experimentally induced strokes have been tracked in animals, mostly in the perilesional area. However, there are also observations of long-range plasticity. In humans, structural plasticity can be measured at the macro-scale level with diffusion MRI. There is now convincing evidence in both humans and animals that learning through activity-dependent plasticity can modify white matter in healthy adults, and possibly in stroke patients.

In summary, our theoretical framework to model individual brain dynamics based on real structural connectivity networks suggests that patients affected by stroke present decreased levels of neural activity, decreased entropy, and decreased strength of the functional connections. All these factors contribute to an overall loss of criticality at 3 months post-stroke that recovers at 12 months, driven by white matter connections remodeling. Notably, our model contains only three parameters ($r_1, r_2$, and $T$), all set apriori without any fitting procedures. In conclusion, personalized whole-brain dynamical models poised at criticality track and predict stroke recovery at the level of the single patient, thereby opening promising paths for computational and translational neuroscience.

**Methods**

This research complies with all relevant ethical regulations. All studies with human participants were approved by the Washington University Institutional Review Board. Stroke patients and healthy controls provided informed consent according to procedures approved by the Washington University Institutional Review Board.

**Stroke dataset.** All data came from a large prospective longitudinal stroke study described in previous publications. We provide here a brief description of the dataset and refer the reader to those articles for a more comprehensive description.

**Clinical sample.** The dataset includes 132 stroke patients (mean age 54, standard deviation 11, range 19–83; 71 males; 68 left side lesions) at the sub-acute stage (2 weeks post-stroke). The inclusion/exclusion criteria were as follows: first symptomatic stroke, ischemic or hemorrhagic, and clinical evidence of any neurological deficit. We used data from the subset of 103 patients who returned for clinical and imaging assessments at 3 months post-stroke, as well as the data from the 88 patients who returned for 1 year post-stroke assessment (for details see Corbetta et al. The control group, formed by 28 individuals, was matched with the stroke sample for age, gender, and years of education. Data was collected twice in healthy controls, 3 months apart.

The neuropsychological battery included 44 behavioral scores across five behavioral domains: language, memory, motor, attention, and visual function. These domains were chosen to represent a wide range of the most commonly identified deficits in people after a stroke.

**MRI Acquisition.** Patients were studied 2 weeks (mean = 13.4 days, SD = 4.8 days), 3 months (mean = 112.5 days, SD = 18.4 days), and 1 year (mean = 393.5 days, SD = 51.1 days) post-stroke. Diffusion data were obtained only at 3 months and 1 year. Controls were studied twice with an interval of 3 months. All imaging was performed using a Siemens 3T Tim-TRio scanner at WUSM and the standard 12-channel head coil. The MRI protocol included structural, functional, pulsed arterial spin labeling (PASL) and diffusion tensor scans. Structural scans included: (i) a sagittal T1-weighted MPRAGE (TR = 1950 ms, TE = 2.26 ms, flip angle = 90°, voxel size = 1.0 × 1.0 × 1.0 mm); (ii) a transverse T2-weighted echo (TR = 2500 ms, TE = 435 ms, voxel size = 1.0 × 1.0 × 1.0 mm); and (iii) sagittal fluid attenuated inversion recovery (FLAIR) (TR = 7500 ms, TE = 326 ms, voxel size = 1.5 × 1.5 × 1.5 mm). PASL acquisition parameters were: TR = 2600 ms, TE = 13 ms, flip angle = 90°, bandwidth 2232 kHz/Px, and FOV 220 mm; 120 volumes were acquired (332 ± 2 total), each containing 15 slices with slice thickness 6- and 23.7-mm gap. Resting state functional scans were acquired with a gradient echo EPI sequence (TR = 2000 ms, TE = 27 ms, 32 contiguous 4-mm slices, 4 × 4 mm in-plane resolution) during which participants were instructed to fixate on a small cross in a low luminance environment. Six to eight resting-state fMRI runs (including 182 volumes (30 min total), were acquired). Pre-processing of fMRI data included: (i) compensation for asynchronous slice acquisition using sinc interpolation; (ii) elimination of odd/even slice intensity differences resulting from interleaved acquisition; (iii) whole-brain intensity normalization to achieve a mode value of 1000; (iv) removal of distortion using field map estimation and partial realignment within and across fMRI runs; and (v) resampling to 3-mm cubic voxels in atlas space including realignment and atlas transformation in one resampling step. Cross-modal (e.g., T2 weighted to T1 weighted) image registration was accomplished by aligning image gradients. Cross-modal image registration in patients was checked by comparing the optimized voxel similarity measure to the 97.5 percentile obtained in the control group. In some cases, structural images were substituted across sessions to improve the quality of registration.

Diffusion-weighted imaging (DWI) included a total of 64 near-axial slices. We used a fully optimized acquisition sequence for tractography that provided isotropic (2 × 2 × 2 mm) resolution and coverage of the whole head with a posterior-anterior phase of acquisition. We set the echo time (TE) and the repetition time (TR) to 9.2 ms and 9200 ms, respectively. At each slice location, diffusion-weighted images were acquired using a 6- and 23.7-mm gap. Resting state functional scans were acquired with a gradient echo EPI sequence (TR = 2000 ms, TE = 27 ms, 32 contiguous 4-mm slices, 4 × 4 mm in-plane resolution) during which participants were instructed to fixate on a small cross in a low luminance environment. Six to eight resting-state fMRI runs (including 182 volumes (30 min total), were acquired). Pre-processing of fMRI data included: (i) compensation for asynchronous slice acquisition using sinc interpolation; (ii) elimination of odd/even slice intensity differences resulting from interleaved acquisition; (iii) whole-brain intensity normalization to achieve a mode value of 1000; (iv) removal of distortion using field map estimation and partial realignment within and across fMRI runs; and (v) resampling to 3-mm cubic voxels in atlas space including realignment and atlas transformation in one resampling step. Cross-modal (e.g., T2 weighted to T1 weighted) image registration was accomplished by aligning image gradients. Cross-modal image registration in patients was checked by comparing the optimized voxel similarity measure to the 97.5 percentile obtained in the control group. In some cases, structural images were substituted across sessions to improve the quality of registration.

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**MRI and lesion analysis.** Individual T1 MRI images were registered to the Montreal Neurological Institute brain using FSL (FMRI Software Library) FNIRT (FMRIb nonlinear imaging registration tool). Lesions were manually segmented on individual structural MRI images (T1-weighted MPRAGE, T2-weighted spin echo images, and FLAIR images obtained at 3-4 week post-stroke) using the Analyze biomedical imaging software system (http://www.mayoclinic.org). Two board-certified neurologists (M.C. and Alexandre Carter) reviewed all segmentations. Special attention was given to distinguish lesion from cerebral spinal fluid (CSF), hemorrhage from surrounding edema, and to identify the degree of periventricular white matter damage present. In hemorrhagic strokes, edema was included in the lesion. A neurologist (M.C.) reviewed all segmentations a second time, paying special attention to the borders of the lesions and degree of white-matter disease. The staff that was involved in segmenting or in reviewing the lesions was blind to the individual behavioral data. Atlas-registered segmented lesions ranged from 0.02 to 82.97 cm³ with a mean of 10.15 cm³ (SD = 13.94 cm³). Lesions were summed to display the number of patients with structural damage for each voxel.

**Functional connectivity (FC) processing.** FC processing followed previous work from the laboratory (see ref. 14), with the addition of surface projection and processing steps developed by the Human Connectome Project. First, data were passed...
through several additional preprocessing steps: (i) regressors were computed based on Freesurfer segmentation; (ii) removal by regression of the following sources of spurious variance: (a) drift parameters obtained from rigid body correction of head motion, (b) the signal averaged over the whole brain, signal from ventricles and CSF, and (d) signal from white matter; (ii) temporal filtering retaining frequencies in the 0.009-0.08 Hz band; and (iii) frame censoring. The first four frames of each BOLD run were excluded. Frame censoring was computed using framewise displacement with a threshold of 0.5 mm. This frame-censoring criterion was uniformly applied to all R-fMRI data (patients and controls) before functional connectivity computations. Participants with <120 usable BOLD frames were excluded from volume to surface mapping\(^{103}\). Time courses were then smoothed similar to Glasser et al.\(^{103}\), with additional consideration for cortical segmentation excluded (13 patients, three controls).

Surrogate generation and processing of functional data followed procedures similar to Glasser et al.\(^{103}\), with additional consideration for cortical segmentation in stroke patients. First, anatomical surfaces were generated for each participant’s T1 MRI using FreeSurfer automated segmentation\(^{104}\). This included brain extraction, segmentation, generation of white matter and pial surface, inflation of the surfaces to a sphere, and surface shape-based spherical registration to the participants (native) surface to the IHS average surface. Segmentations were manually checked for accuracy. For patients in whom the stroke disrupted automated segmentation, or registration, values within lesioned voxels were filled with normal atlas values before segmentation, and then masked immediately after (seven patients). The left and right hemispheres were then resampled to 164,000 vertices and registered to each other, and finally downsampled to 10,242 vertices each for projection of functional data. Following preprocessing of BOLD data, volumes were sampled to each participant’s individual surface (between white matter and pial surface) using a ribbon-constrained sampling available in Connectome Workbench. Voxels with a high coefficient of variation (0.5 SDs above the mean coefficient of variation of all voxels in a 5-mm radius Gaussian neighborhood) were excluded from volume to surface mapping\(^{103}\). Time courses were then smoothed along the 10,242 vertex surface using a 6-mm FWHM Gaussian kernel. Finally, time courses of all vertices within a parcel are averaged to make a parcelwise time course.

Characterization of simulated brain activity

We have considered the following standard quantities to characterize the simulated brain activity:

- the mean network activity,

\[
(A) = \frac{1}{N} \sum_{i=1}^{N} A(t),
\]

where \(A(t) = \sum_{i=1}^{N} s(t)\) is the instantaneous activity and \(t_i\) is the simulated total time;

- the standard deviation of \(A(t)\),

\[
\sigma = \left( \frac{1}{L} \sum_{t=1}^{L} (A(t) - \langle A \rangle)^2 \right)^{1/2},
\]

- the sizes of the averaged clusters, the largest \(S_h\) and the second largest \(S_{h+1}\), as ensembles of clusters that are structurally connected to each other and simultaneously active. We use numerical derivative (forward finite difference method) to determine the monotonic behavior of \(S_h\). In theory, the monotonic behavior occurs when the sign of the derivative remains constant. We relaxed this criterion due to the noisy behavior of the derivative / model data (mainly for small values of \(T\)). Therefore, for a few cases where the change of sign happened before \(T \leq 0.07\) we attribute it as noise or artifact, and classified it as monotonic behavior.

Following our previous work\(^{28}\), we set the model parameters to the following values, \(r_i = 2/N\) (with \(N = 324\), \(r_1 = r_2\)), and we vary the activation threshold \(T \in [0, 0.2]\). We updated the network states, starting from random configurations of \(A, I\) and \(R\) states, for a total of \(t_i = 2000\) time-steps. For each value of the threshold \(T\) we computed the state variables, \(S_h\), \(S_{h+1}\), \(\langle A \rangle\), and \(\langle \sigma \rangle\). Throughout this study, unless stated otherwise, the final numerical results presented were averages over 10 initial random configurations. For computation of model data, we discarded the initial transient dynamics (first 100 time-steps).

From the model output to BOLD signal. We have employed a standard procedure to transform model output to BOLD functional signals\(^{22,28}\). Accordingly, the model’s activity, \(s(t)\), is convolved with a canonical double-gamma hemodynamic response function (HRF),

\[
x(t) = \int_0^\infty h(t-\tau) s(\tau) d\tau,
\]

with

\[
h(t) = \left( \frac{\tau}{\tau_d} \right)^{5/6} e^{-\frac{\tau}{\tau_d}} - \frac{\tau}{\tau_d} \left( \frac{\tau}{\tau_d} \right)^{5/6} e^{-\frac{\tau}{\tau_d}},
\]

where \(x(t)\) is the BOLD signal of the \(i\)-th node. The free parameters in (4) were fixed according to values found in\(^{111}\), i.e., \(\tau_i = 4/18/C_19\). Finally, the BOLD time-series, \(x(t)\), were filtered with a zero lag finite impulse response band-pass filter in the frequency range of 0.01 – 0.1 Hz.

From the generated BOLD signal we can finally extract the following quantities:

- the functional connectivity network (FC). In fact, the FC matrix \(FC_{ij}\) is defined through Pearson correlation:

\[
FC_{ij} = \frac{x_i \cdot x_j}{\sigma_i \sigma_j},
\]

where \(\sigma_i = \sqrt{\langle x_i^2 \rangle - \langle x_i \rangle^2}\) is the standard deviation and \(\langle \cdot \rangle\) is the mean of the corresponding BOLD data set. The average of the functional connectivity:

\[
\langle FC \rangle = \frac{2}{N(N-1)} \sum_{i,j} \text{FC}_{ij}.
\]

From the above expression we observe that only the upper triangular elements of \(\text{FC}\) are considered in the average.
the Shannon entropy:
\[ H = -\sum_{i=1}^{m} p_i \log p_i / \log m, \]
where \( m \) is the number of bins used to construct the probability distribution function of the upper triangular elements of [FC]. The normalization factor in the denominator, i.e., \( \log m \), is the entropy of a uniform distribution, and it ensures that \( H \) is normalized between 0 and 1. The distributions were partitioned with \( m = 20 \) bins. The higher the diversity of the functional connectivity matrix, the higher the entropy of that functional connectivity matrix.

Finally, we characterize the distance between any given simulated neural variable with the corresponding controls average through the Euclidean distance:
\[ d(t) = \sqrt{\sum_{i}(X_i(t) - X_i(T))^2}, \]
where \( X(T) \) is a given neural pattern at time-point \( t \) and threshold \( T \), while \( (X) \) is the corresponding controls average.

Network measures of brain connectivity. We have applied the following measures from graph theory to quantify the topology of the corresponding structural brain networks:

- Newman’s modularity was calculated from the binary (undirected) adjacency matrix \((A_{uv})\):
\[ Q = \frac{1}{2m} \sum_{i,j} A_{ij} \left( A_{ii} + A_{jj} - 1 \right) \frac{d_{ij}}{d_i d_j}, \]
where the network is fully subdivided into a set of nonoverlapping communities such that node \( v \) belongs to community \( c_v = 1 \) if \( \sum A_{iv} \) is the number of edges and \( k_v = \sum A_{iv} \) is the degree of node \( v \). We employed the Louvain community detection as implemented in R (igraph package).
- The global efficiency:
\[ E_{global}(G) = \frac{1}{N(N-1)} \sum_{i < j} \frac{d_{ij}}{d_i d_j}, \]
where \( d_{ij} \) is the shortest path length between nodes \( i \) and \( j \). We used the (binary) adjacency matrix to compute the shortest path lengths.
- The average degree:
\[ K = \frac{\sum k_i}{N}, \]
where \( N \) is the number of nodes and \( k_i \) is the degree of node \( i \) as defined above.
- The connectivity disorder (i.e., structural entropy):
\[ H_{SC} = -\sum_{i=1}^{m} p_i \log p_i / \log m, \]
where \( m = 100 \) is the number of bins used to construct the probability distribution function of all the elements of \( W_{SC} \).

Mapping criticality to structural connectivity. The main aim of these analyses was to identify topographical patterns of the structural connectivity matrix (SC) that are related to criticality indexes through multivariate (machine learning) analyses. In our multivariate approach (also see Siegel et al.\(^1\) and Salavaggion et al.\(^2\)), features of the individual SC matrices extracted by Principal Component Analysis (PCA) were used as multivariate predictors for a Ridge Regression (RR) model trained to predict patients’ criticality values. RR differs from multiple linear regression because it uses L2-normalization to regularize model coefficients, so that unimportant features are automatically down-weighted or eliminated, thereby preventing overfitting and improving generalization on test data\(^3,4\). The model weights \( W \) are computed as:
\[ W = (X^T X + \lambda I)^{-1} X^T Y \]
where \( X \) is the set of predictors and \( Y \) is the outcome variable. The regularization term provides a constraint on the size of weights and it is controlled by parameter \( \lambda \). A tuning procedure is necessary to find the appropriate value of \( \lambda \). Importantly, this approach also allows to project predictive weights back to brain data in a very simple way\(^5,6\). Before applying RR, principal component analysis (PCA) was performed on the SC matrix to reduce the input dimensionality. The latter included 52, 326 edges, corresponding to all non-diagonal elements of one half of the symmetric SC matrix of 324 nodes/parcels. Principal Components (PCs) that explained 95% of the variance were retained and used as input for the RR model. All predictors (PC scores) and the outcome variable (criticality value) were z-normalized before applying RR. All RR models were trained and tested using a leave-one-(patient)-out cross validation (LOOCV) loop\(^7\). In each loop, the regularization coefficient \( \lambda \) was optimized by identifying a value between \( 10^{-5} \) and \( 10^5 \) (logarithmic steps) that minimized leave-one-out prediction error over the training set. Optimal weights were solved across the entire training set using gradient descent to minimize error for the ridge regression equation by varying \( \lambda \). These model weights were then applied to the left-out patient to predict the criticality value. A prediction was generated for all patients in this way. Model accuracy was assessed using the coefficient of determination
\[ R^2 = 1 - \frac{\sum(Y - \hat{Y})^2}{\sum(Y - \bar{Y})^2}, \]
where \( Y \) are the measured criticality values, \( \hat{Y} \) are the predicted criticality values and \( \bar{Y} \) is the mean of predicted criticality indexes. The statistical significance of all LOOCV results was assessed using permutation test. For each regression model, criticality scores were randomly permuted across participants 10,000 times, and the entire regression was carried out with each set of randomized labels. A P-value was calculated as the probability of observing the reported \( R^2 \) values by chance (number of permutation \( R^2 > \) observed \( R^2 \))/(number of permutation). Finally, the RR weight matrix was averaged across all LOOCV loops to generate a single set of consensus weights. Statistical reliability of each consensus weight was assessed by comparing its distribution of values (throughout the LOOCV loops) to a null distribution (obtained from the null models generated for permutation testing) using a FDR corrected \( t \)-test. The final set of (statistically reliable) consensus weights was back projected to the brain to display a map of the most predictive structural connections.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability. Data to replicate all the figures and tables are provided as Source data with this paper and are also deposited in Github (https://github.com/CorbettaLab/Rodrigo2022NatComm) and Zenodo\(^2\) (https://doi.org/10.5281/zenodo.6459955). Individual structural connectivity matrices for controls and patients have been deposited in the Github and Zenodo repositories. Raw neuroimaging and neuropsychological data from\(^3,4\) are publicly available at cnda.wustl.edu and require controlled access as they contain sensitive patients’ data. The person requesting the data must sign a confidentiality agreement provided by Washington University stipulating that they will make no attempt to identify the patients and to use data only for research purposes. Correspondence and requests for materials should be addressed to R.P.R. (rodrigo.rocha@ufsc.br) Source data are provided with this paper.

Code availability. The custom code for criticality modeling is freely available at https://github.com/CorbettaLab/Rodrigo2022NatComm and https://doi.org/10.5281/zenodo.6459955.

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Competing interests
The authors declare no competing interests.

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