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► To cite this version:

Pierpaolo Sorrentino, Caio Seguin, Rosaria Rucco, Marianna Liparoti, Emahnuel Troisi Lopez, et al.. The structural connectome constrains fast brain dynamics. eLife, 2021, 10, pp.e67400. 10.7554/eLife.67400 . hal-03552874

HAL Id: hal-03552874

<https://hal.science/hal-03552874>

Submitted on 2 Feb 2022

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The structural connectome constrains fast brain dynamics

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Abstract

Brain activity during rest displays complex, rapidly evolving patterns in space and time. Structural connections comprising the human connectome are hypothesized to impose constraints on the dynamics of this activity. Here, we use magnetoencephalography (MEG) to quantify the extent to which fast neural dynamics in the human brain are constrained by structural connections inferred from diffusion MRI tractography. We characterize the spatio-temporal unfolding of whole-brain activity at the millisecond scale from source-reconstructed MEG data, estimating the probability that any two brain regions will significantly deviate from baseline activity in consecutive time epochs. We find that the structural connectome relates to, and likely affects, the rapid spreading of neuronal avalanches, evidenced by a significant association between these transition probabilities and structural connectivity strengths ($r=0.37$, $p<0.0001$). This finding opens new avenues to study the relationship between brain structure and neural dynamics.

35 **Keywords:** brain dynamics, brain networks, magnetoencephalography, neuronal avalanches,
36 structural connectome

37 **Introduction**

38 The structural scaffolding of the human connectome (1) constrains the unfolding of large-scale
39 coordinated neural activity towards a restricted *functional repertoire* (2). While functional magnetic
40 resonance imaging (fMRI) can elucidate this phenomenon at relatively slow timescales (3–5), brain
41 activity shows rich dynamic behaviour across multiple timescales, with faster activity nested within
42 slower scales. Here, in healthy young adults, we exploit the high temporal resolution of resting-state
43 magnetoencephalography (MEG) data to study the spatial spread of perturbations of local
44 activations representative of neuronal avalanches. We aim to establish whether the structural
45 connectome constrains the spread of avalanches among regions (6, 7). We find that avalanche
46 spread is significantly more likely between pairs of grey matter regions that are structurally
47 connected, as inferred from diffusion MRI tractography. This result provides cross-modal empirical
48 evidence suggesting that connectome topology constrains fast-scale transmission of neural
49 information, linking brain structure to brain dynamics.

50 **Results**

51 Structural connectomes were mapped for 58 healthy adults (26 females, mean age \pm SD: 30.72 \pm
52 11.58) using diffusion MRI tractography and regions defined based on the Automated Anatomical
53 Labeling (AAL) and the Desikan-Killiany-Tourville (DKT) atlases. Interregional streamline counts
54 derived from whole-brain deterministic tractography quantified the strength of structural
55 connectivity between pairs of regions. Streamline counts were normalized by regional volume.
56 Group-level connectomes were computed by averaging connectivity matrices across participants.

57 MEG signals were pre-processed and source reconstructed for both the AAL and DKT atlases. All
58 analyses were conducted on source-reconstructed signal amplitudes. Each signal amplitude was z-
59 scored and binarized such that, at any time point, a z-score exceeding a given threshold was set to 1
60 (active); all other timepoints were set to 0 (inactive). An avalanche was defined as starting when
61 any region exceeded this threshold, and finished when no region was active. An avalanche-specific
62 transition matrix (TM) was calculated, where element (i, j) represented the probability that region j
63 was active at time $t+\delta$, given that region i was active at time t , where $\delta \sim 3$ ms. The TMs were
64 averaged per participant, and then per group, and finally symmetrized. Fig.1 provides an overview
65 of the pipeline.

66 We found striking evidence of an association between avalanche transition probabilities and
67 structural connectivity strengths (Fig. 2), suggesting that regional propagation of fast-scale neural
68 avalanches is partly shaped by the axonal fibers forming the structural connectome ($r=0.40$,
69 $p<0.0001$). Specifically, the association was evident for different activation thresholds and both the
70 AAL and DKT connectomes (AAL atlas: for threshold $z=2.5$, $r=0.41$; for threshold $z=3.0$, $r=0.40$;
71 for threshold $z=3.5$, $r=0.39$; DKT atlas: for threshold $z=2.5$, $r=0.38$; for threshold $z=3.0$, $r=0.37$; for
72 threshold $z=3.5$, $r=0.35$; in all cases, $p < 0.0001$), as well as for individual- and group-level
73 connectomes, although associations were stronger for group-level analyses (see Fig. 2, panel A).

74 We also investigated this phenomenon within specific frequency bands. Associations were evident
75 in all the classical frequency bands: delta (0.5 – 4 Hz; $r=0.39$), theta (4 – 8 Hz; $r=0.29$), alpha (8 –
76 13 Hz; $r=0.32$), beta (13 – 30 Hz; $r=0.32$), and gamma (30 – 48 Hz; $r=0.32$), with $p<0.0001$ for all
77 bands (see Supplementary File 1). Supplementary analyses suggested that these results could not be
78 attributable to volume conduction confounds (see Methods; Field spread analysis).

79

80 Next, we sought to test whether the associations were weaker for randomized transition matrices
81 computed after randomizing the times of each avalanche while keeping the spatial structure
82 unchanged. Randomized transition matrices resulted in markedly weaker associations with
83 structural connectivity, compared to the actual transition matrices (AAL atlas, $z\text{-score}=3$: mean $r =$
84 0.26 , observed $r= 0.40$, $p<0.001$). Note that the mean correlation coefficient was greater than zeros
85 for the randomized data because the randomization process preserved basic spatial attributes in the
86 data. We also found that the findings remained significant after excluding subcortical regions (with
87 lower signal-to-noise ratios). Finally, we replicated these findings for a group-level connectome
88 derived using diffusion MRI acquired from 200 healthy adults in the Human Connectome Project
89 ($r=0.11$, $p<0.001$, $z\text{-score}=3$; see Methods). Our results were thus robust to multiple connectome
90 mapping pipelines and parcellation atlases, significant for both group-averaged and individual
91 connectomes, and could not be explained by chance transitions and/or volume conduction effects.
92 Collectively, these results suggest that connectome organization significantly shapes the
93 propagation of neural activity.

94 Discussion

95 Our results provide new insight into the propagation of fast-evolving brain activity in the human
96 connectome. We show that the spatial unfolding of neural dynamics at the millisecond scale relates
97 to the network of large-scale axonal projections comprising the connectome, likely constraining the
98 exploration of the brain's putative functional repertoire. The short time scale of several milliseconds
99 biases the constraint to direct connections, which is the focus of this paper. Longer delays may
100 impose constraints upon larger-scale motifs of the network and further characterize the sub-spaces,
101 in which brain dynamics unfold.

102 Previous functional MRI studies provide evidence of coupling between structural connectivity and
103 slow activations (3, 8, 9). However, intrinsic neural dynamics evolve quickly and are nested within
104 slow activity (10). Our findings suggest that long-term structure-function coupling occurs against a
105 backdrop of faster fluctuations, which are also constrained by the connectome and may enable
106 individuals to rapidly respond to changing environments and new cognitive demands (11).

107 Consistent with our findings, two recent M/EEG studies showed that functional connectivity, as
108 estimated using amplitude-envelope coupling (AEC), relates to structural connectivity (12, 13).
109 However, in contrast to AEC, we conducted time-resolved analyses, characterizing avalanche
110 dynamics at high temporal resolution. Further work is needed to determine the extent to which
111 structure-function coupling is dynamic. To this regard, our results suggest that coupling is strongest
112 during avalanche events, consistent with established theories (14)). Finally, our results might
113 explain how the large-scale activity unfolding in time might lead to the previous observation that
114 average resting-state functional connectivity displays topological features that mirror those of the
115 structural connectome (15). Our proposed framework links the large-scale spreading of aperiodic,
116 locally generated perturbations to the structural connectome, and might be further exploited to
117 investigate polysynaptic models of network communication, which aim to describe patterns of
118 signalling between anatomically unconnected regions (16, 17). In fact, our results show that
119 transitions of activations are observed across regions that do not appear to be directly linked in the
120 structural connectome. This provides evidence for polysynaptic communication.

121 Neuronal avalanches have been previously observed in MEG data (7), and their statistical
122 properties, such as a size distribution that obeys a power-law with an exponent of $-3/2$, reported.
123 These features are compatible with those that would be predicted starting from a process operating
124 at criticality with a branching ratio equal to one. While beyond the scope of this paper, our
125 framework might contribute to elucidating the role of the structural scaffolding (and its topological
126 properties) to the emergence of the observed large-scale, scale-free critical dynamics. In turn, this

127 might be exploited to predict the effects of structural lesions on behaviour and/or clinical
128 phenotypes.

129 While our findings were replicated across multiple frequency bands, structural connectivity can
130 potentially impose frequency-dependent constraints on avalanche spread. Future work should
131 investigate frequency-specific data to understand what leads to the emergence of avalanches and,
132 most importantly, to the specific spatio-temporal patterns of recruited regions that defines
133 individual (or at least groups of) avalanches in each specific frequency-band.

134 For the present application, we reconstructed the structural connectome using a deterministic
135 tractography algorithm. While probabilistic algorithms can provide advantages in some
136 applications, they are prone to reconstruction of spurious connections (false positives), compared to
137 deterministic methods, reducing connectome specificity (18, 19). We used deterministic
138 tractography because previous functional MRI studies report that structure-functional coupling is
139 greater for connectivity matrices inferred from deterministic tractography, compared to probabilistic
140 methods (20). Nonetheless, additional studies are needed to clarify if and to what extent the present
141 results are influenced by the structural connectome reconstruction method. While we replicated our
142 findings using alternative datasets (i.e. HCP) and parcellations, further replication using alternative
143 connectome mapping pipelines is warranted.

144 In conclusion, using MEG to study fast neuronal dynamics and diffusion MRI tractography to map
145 connectomes, we found that the connectome significantly constrains the spatial spread of neuronal
146 avalanches to axonal connections. Our results suggest that large-scale structure-function coupling is
147 dynamic and peaks during avalanche events.

148 **Methods**

149 **Participants**

150 We recruited 58 young adults (male 32 / female 26, mean age \pm SD was 30.72 ± 11.58) from the
151 general community. All participants were right-handed and native Italian speakers. The inclusion
152 criteria were: 1) no major internal, neurological or psychiatric illnesses; 2) no use of drugs or
153 medication that could interfere with MEG/MRI signals. The study complied with the Declaration of
154 Helsinki and was approved by the local Ethics Committee. All participants gave written informed
155 consent.

156

157 **MRI acquisition**

158 3D T1-weighted brain volumes were acquired at 1.5 Tesla (Signa, GE Healthcare) using a 3D
159 Magnetization-Prepared Gradient-Echo BRAVO sequence (TR/TE/TI 8.2/3.1/450 ms, voxel $1 \times 1 \times$
160 1 mm^3 , 50% partition overlap, 324 sagittal slices covering the whole brain), and diffusion MRI data
161 for individual c connectome reconstruction were obtained using the following parameters: Echo-
162 Planar Imaging, TR/TE 12,000/95.5 ms, voxel $0.94 \times 0.94 \times 2.5 \text{ mm}^3$, 32 diffusion-
163 sensitizing directions, 5 B0 volumes). The MRI scan was performed after the MEG recording.
164 Preprocessing of the diffusion MRI data was carried out using the software modules provided in the
165 FMRIB Software Library (FSL, <http://fsl.fmrib.ox.ac.uk/fsl>). All diffusion MRI datasets were
166 corrected for head movements and eddy currents distortions using the "eddy_correct" routine,
167 rotating diffusion sensitizing gradient directions accordingly, and a brain mask was obtained from
168 the B0 images using the Brain Extraction Tool routine. A diffusion-tensor model was fitted at each
169 voxel, and streamlines were generated over the whole brain by deterministic tractography using
170 Diffusion Toolkit (FACT propagation algorithm, angle threshold 45° , spline-filtered, masking by
171 the FA maps thresholded at 0.2). For tractographic analysis, the ROIs of the AAL atlas and of a
172 MNI space-defined volumetric version of the Desikan-Killiany-Tourville (DKT) ROI atlas were
173 used, both masked by the GM tissue probability map available in SPM (thresholded at 0.2). To this
174 end, for each participant, FA volumes were normalized to the MNI space using the FA template
175 provided by FSL, using the spatial normalization routine available in SPM12, and the resulting
176 normalization matrices were inverted and applied to the ROIs, to apply them onto each subject. The
177 quality of the normalization was assessed visually. From each subject's whole brain tractography
178 and corresponding GM ROI set, the number of streamlines connecting each couple of GM ROIs and
179 the corresponding mean tract length was calculated using an in-house software written in Interactive
180 Data Language (IDL, Harris Geospatial Solutions, Inc., Broomfield, CO, USA).

181 Connectomes in the replication dataset were constructed using an alternative mapping pipeline and
182 diffusion MRI data from the Human Connectome Project (HCP). Deterministic tractography was
183 performed using MRtrix3 (21) under the following parameters: FACT algorithm, 5 million
184 streamlines, 0.5 mm propagation step size, 400 mm maximum propagation length, and 0.1 FA
185 threshold for the termination of streamlines (17). The number of streamlines connecting any couple
186 of regions was normalized by the combined volume of the two regions. Structural matrices were
187 constructed for 200 HCP participants using the AAL atlas and averaged to derive a group-level
188 connectome.

189

190 **MEG pre-processing**

191 MEG pre-processing and source reconstruction were performed as in (22). The MEG system was
192 equipped with 163 magnetometers, and was developed by the National Research Council of Italy at
193 the Institute of Applied Sciences and Intelligent Systems (ISASI). All technical details regarding the
194 MEG device are reported in (23). In short, the MEG registration was divided in two eyes-closed
195 segments of 3:30 minutes each. To identify the position of the head, four anatomical points and four
196 position coils were digitized. Electrocardiogram (ECG) and electro-oculogram (EOG) signals were
197 also recorded. The MEG signals, after an anti-aliasing filter, were acquired at 1024 Hz, then a
198 fourth order Butterworth IIR band-pass filter in the 0.5-48 Hz band was applied. To remove
199 environmental noise, measured by reference magnetometers, we used Principal Component
200 Analysis. We adopted supervised Independent Component Analysis to clean the data from
201 physiological artifacts, such as eye blinking (if present) and heart activity (generally one
202 component). Noisy channels were identified and removed manually by an expert rater (136 ± 4
203 sensors were kept). 47 subjects were selected for further analysis.

204 **Source reconstruction**

205 The time series of neuronal activity were reconstructed in 116 regions of interests (ROIs) based on
206 the Automated Anatomical Labeling (AAL) atlas (24, 25); and in 84 regions of interest based on the
207 Desikan-Killiany-Tourreville (DKT) atlas. To do this, we used the volume conduction model
208 proposed by Nolte (26) applying the Linearly Constrained Minimum Variance (LCMV)
209 beamformer algorithm (27) based on the native structural MRIs. Sources were reconstructed for the
210 centroids of each ROI. Finally, we considered a total of 90 ROIs for the AAL atlas, since we have
211 excluded 26 ROIs corresponding to the cerebellum because of their low reliability in MEG (28). All
212 the preprocessing steps and the source reconstruction were made using the Fieldtrip toolbox (29).

213 **Neuronal avalanches and branching parameter**

214 To study the dynamics of brain activity, we estimated “neuronal avalanches”. Firstly, the
215 time series of each ROI was discretized calculating the z-score, then positive and negative
216 excursions beyond a threshold were identified. The value of the threshold was set to 3 standard
217 deviations ($|z| = 3$), but we tested the robustness of the results changing this threshold from 2.5 to
218 3.5. A neuronal avalanche begins when, in a sequence of contiguous time bins, at least one ROI is
219 active ($|z| > 3$), and ends when all ROIs are inactive (30, 31). The total number of active ROIs in an
220 avalanche corresponds to its size.

221 These analyses require the time series to be binned. This is done to ensure that one is capturing
 222 critical dynamics, if present. To estimate the suitable time bin length, for each subject, for each
 223 neuronal avalanches and for each time bin duration, the branching parameter σ was estimated (32,
 224 33). In fact, system operating at criticality typically display a branching ratio ~ 1 . The branching
 225 ratio is calculated as the geometrically averaged (over all the time bins) ratio of the number of
 226 events (activations) between the subsequent time bin (descendants) and that in the current time bin
 227 (ancestors) and then averaging it over all the avalanches (34). More specifically:

228

$$229 \quad \sigma_i = \frac{1}{N_{bin}-1} \prod_{j=1}^{N_{bin}-1} \left(\frac{n_{events}(j+1)}{n_{events}(j)} \right)^{\frac{1}{N_{bin}-1}} \quad (1)$$

230

$$231 \quad \sigma = \frac{1}{N_{aval}} \prod_{i=1}^{N_{aval}} (\sigma_i)^{\frac{1}{N_{aval}}} \quad (2)$$

232

233 Where σ_i is the branching parameter of the i -th avalanche in the dataset, N_{bin} is the total amount of
 234 bins in the i -th avalanche, $n_{events}(j)$ is the total number of events active in the j -th bin, N_{aval} is the
 235 total number of avalanche in the dataset. We tested bins from 1 to 5, and picked 3 for further
 236 analyses, given that the branching ratio was 1 for bin =3. However, results are unchanged for other
 237 bin durations, and the branching ratio remains equal to 1 or differences were minimal (range: 0.999
 238 to 1.010 - data not shown). Bins of longer duration would violate the Nyquist criterion and were
 239 thus not considered. The results shown are derived when taking into accounts avalanches longer
 240 than 10 time bins. However, we repeated the analysis taking into account avalanches longer than 30
 241 time bins, as well as taking all avalanches into account, and the results were unchanged.

242

243

244 **Transition matrices**

245 The amplitude of each binned, z-scored source-reconstructed signal was binarized, such that, at any
 246 time bin, a z-score exceeding ± 3 was set to 1 (active); all other time bins were set to 0 (inactive).
 247 Alternative z-score thresholds (i.e. 2.5 and 3.5) were tested. An avalanche was defined as starting
 248 when any region is above threshold, and finishing when no region is active, as in (22). Avalanches
 249 shorter than 10 time bins (~ 30 msec) were excluded. However, the analyses were repeated including

only avalanches longer than 30 time bins (~90 msec), to focus on rarer events (sizes of the neuronal avalanches have a fat-tailed distribution) that are highly unlikely to be noise, and including all avalanches, and the results were unchanged. An avalanche-specific transition matrix (TM) was calculated, where element (i, j) represented the probability that region j was active at time $t + \delta$, given that region i was active at time t , where $\delta \sim 3$ ms. The TMs were averaged per participant, and then per group, and finally symmetrized. The introduction of a time-lag makes it unlikely that our results can be explained trivially by volume conduction (i.e. the fact that multiple sources are detected simultaneously by multiple sensors, generating spurious zero-lags correlations in the recorded signals). For instance, for a binning of 3, as the avalanches proceed in time, the successive regions that are recruited do so after roughly 3 msec (and 5 msec for the binning of 5). Hence, activations occurring simultaneously do not contribute to the estimate of the transition matrix. See below for further analyses addressing the volume conduction issue. Finally, we explored transition matrices estimated using frequency-specific signals. To this end, we filtered the source-reconstructed signal in the classical frequency bands (delta, 0.5 – 4 Hz; theta 4 – 8 Hz; alpha 8 – 13 Hz; beta 13 – 30 Hz; gamma 30 – 48 Hz), before computing neuronal avalanches and the transition matrix, by applying a fourth-order Butterworth pass-band filter to the source-reconstructed data, before proceeding to the further analysis as previously described. The results remained significant in all the explored frequency bands. This analysis was carried out for the DKT atlas, binning = 3, z-score threshold = ± 3 .

Field spread analysis

Volume conduction alone is an unlikely explanation of our results, given that simultaneous activations do not contribute to the transition matrix, due to the time lags introduced. To confirm that volume conduction effects were negligible, the transition matrices were re-computed using longer delays. In short, we identified the regions that were recruited in an avalanche after the first perturbation (i.e. the initial time-bin of an avalanche). Since we did not scroll through the avalanche in time, as previously described, we considered time delays as long as the avalanche itself, while minimizing the influence of short delays. This means that the avalanche-specific transition matrix is now binary, and the ij^{th} element is equal to 1 if region i started the avalanche (i.e. it was active at the first time-bin) and region j was recruited in the avalanche at any subsequent timepoint, and 0 otherwise. This alternative procedure for the estimation of the transition matrices was carried out for the AAL atlas, in the case of binning = 3, z-score threshold = ± 3 . In this case, a significant

282 association remained between transition probabilities and structural connectivity ($r=0.36$;
283 $p<0.0001$). Figure 2—figure supplement 1 provides further details.

284 To further rule out the possibility that field spread might introduce spurious correlations that might
285 drive the relationship between the Transition Matrix and the structural connectivity matrix, we
286 conducted further analyses involving surrogate data. We generated n white Gaussian processes,
287 with $n = 66$, i.e. the number of cortical regions, and we smoothed them using a zero-phase
288 polynomial filter. Then, we added 100 perturbations, where each perturbation was assigned to a
289 randomly chosen regions and random time point, subject to the following constraints. Perturbations
290 were separated by at least 200 samples (no overlap was allowed, i.e. the perturbations could only
291 occur in one region at a time), their length was randomly selected among 5, 10 or 100 samples, their
292 amplitude between 50 and 400. This procedure was carried out 47 times, to obtain an independent
293 surrogate dataset for each one of the 47 participants, that will be referred to as the “uncoupled”
294 dataset. The uncoupled dataset was then transformed using the subject-specific leadfield matrix,
295 yielding new surrogate sensor-level timeseries, where each sensor is a weighted sum of all the
296 sources, according to the same leadfield matrix that was used to reconstruct the real data. Noise,
297 correlated as $1/\text{distance among sensors}$, was then added to the sensor-level time series, with a $\text{SNR} = 4$.
298 Then, new source-reconstructed time series were computed for each subject. Based on these new
299 time series, we performed the same procedure to compute the transition matrix as described above.
300 Specifically, we z-scored the time series, thresholded them (threshold $z=\pm 3$), retrieved the
301 avalanche-specific transition matrices, averaged these within each subject and then across the
302 group, and finally symmetrized the matrix. We then investigated the extent of correlation between
303 the new transition matrix and the structural connectivity matrix. We repeated the entire procedure
304 reported above one hundred times, and show that is unlikely that linear mixing alone can explain
305 the significant association between transition probabilities and structural connectivity ($p < 0.001$).

306

307 **Statistical analysis**

308 The Spearman rank correlation coefficient was used to assess the association between transition
309 probabilities and structural connectivity. A correlation coefficient was computed separately for each
310 individual across all pairs of regions. Transition matrices were symmetrized before this
311 computation. Randomized transition matrices were generated to ensure that associations between
312 transition probabilities and structural connectivity could not be attributed to chance. Avalanches
313 were randomized across time, without changing the order of active regions at each time step. We
314 generated a total of 1000 randomized transition matrices and the Spearman rank correlation

315 coefficient was computed between each randomized matrix and structural connectivity. This yielded
316 a distribution of correlation coefficients under randomization. The proportion of correlation
317 coefficients that were greater than, or equal to, the observed correlation coefficient provided a p-
318 value for the null hypothesis that structure-function coupling was attributable to random transition
319 events.

320 Bibliography

- 321 1. O. Sporns, G. Tononi, R. Kötter, The Human Connectome: A Structural Description of the
322 Human Brain. *PLoS Comput. Biol.* **1**, e42 (2005).
- 323 2. G. Deco, V. K. Jirsa, A. R. McIntosh, Emerging concepts for the dynamical organization of
324 resting-state activity in the brain. *Nat. Rev. Neurosci.* **12**, 43–56 (2011).
- 325 3. C. J. Honey, R. Kötter, M. Breakspear, O. Sporns, Network structure of cerebral cortex shapes
326 functional connectivity on multiple time scales. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 10240–5
327 (2007).
- 328 4. J. Goni, *et al.*, Resting-brain functional connectivity predicted by analytic measures of network
329 communication. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 833–838 (2014).
- 330 5. A. Zalesky, A. Fornito, L. Cocchi, L. L. Gollo, M. Breakspear, Time-resolved resting-state
331 brain networks. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 10341–6 (2014).
- 332 6. J. M. Beggs, D. Plenz, Neuronal Avalanches Are Diverse and Precise Activity Patterns That
333 Are Stable for Many Hours in Cortical Slice Cultures. *J. Neurosci.* **24**, 5216–5229 (2004).
- 334 7. O. Shriki, *et al.*, Neuronal avalanches in the resting MEG of the human brain. *J. Neurosci.* **33**,
335 7079–7090 (2013).
- 336 8. C. J. Honey, J. P. Thivierge, O. Sporns, Can structure predict function in the human brain?
337 *NeuroImage* **52**, 766–776 (2010).
- 338 9. C. J. Honey, *et al.*, Predicting human resting-state functional connectivity from structural
339 connectivity. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 2035–2040 (2009).
- 340 10. M. L. Saggio, A. Spiegler, C. Bernard, V. K. Jirsa, Fast–Slow Bursters in the Unfolding of a
341 High Codimension Singularity and the Ultra-slow Transitions of Classes. *J. Math. Neurosci.* **7**,
342 1–47 (2017).
- 343 11. A. McIntosh, V. Jirsa, The hidden repertoire of brain dynamics and dysfunction. *Netw.*
344 *Neurosci.* **3** (2019).
- 345 12. K. Glomb, *et al.*, Using structural connectivity to augment community structure in EEG
346 functional connectivity. *Netw. Neurosci.* **4**, 761–787 (2020).
- 347 13. P. Tewarie, *et al.*, How do spatially distinct frequency specific MEG networks emerge from
348 one underlying structural connectome? The role of the structural eigenmodes. *NeuroImage*
349 **186**, 211–220 (2019).
- 350 14. S. Dehaene, M. Kerszberg, J.-P. Changeux, A neuronal model of a global workspace in
351 effortful cognitive tasks. *Proc. Natl. Acad. Sci.* **95**, 14529–14534 (1998).
- 352 15. E. Bullmore, O. Sporns, Complex brain networks: graph theoretical analysis of structural and
353 functional systems. *Nat. Rev. Neurosci.* **10**, 186–198 (2009).
- 354 16. C. Seguin, M. P. Van Den Heuvel, A. Zalesky, Navigation of brain networks. *Proc. Natl.*
355 *Acad. Sci. U. S. A.* **115**, 6297–6302 (2018).

- 356 17. C. Seguin, A. Razi, A. Zalesky, Inferring neural signalling directionality from undirected
357 structural connectomes. *Nat. Commun.* **10**, 1–13 (2019).
- 358 18. T. Sarwar, K. Ramamohanarao, A. Zalesky, Mapping connectomes with diffusion MRI:
359 deterministic or probabilistic tractography? *Magn. Reson. Med.* **81**, 1368–1384 (2019).
- 360 19. A. Zalesky, *et al.*, Connectome sensitivity or specificity: which is more important?
361 *NeuroImage* **142**, 407–420 (2016).
- 362 20. P. M. Abeyasinghe, M. Aiello, C. Cavaliere, A. M. Owen, A. Soddu, A comparison of
363 diffusion tractography techniques in simulating the generalized Ising model to predict the
364 intrinsic activity of the brain. *Brain Struct. Funct.* **226**, 817–832 (2021).
- 365 21. J. D. Tournier, *et al.*, MRtrix3: A fast, flexible and open software framework for medical
366 image processing and visualisation. *NeuroImage* **202**, 116137 (2019).
- 367 22. P. Sorrentino, *et al.*, Flexible brain dynamics underpins complex behaviours as observed in
368 Parkinson’s disease. *Sci. Rep.* **11**, 4051 (2021).
- 369 23. S. Rombetto, C. Granata, A. Vettoliere, M. Russo, Multichannel System Based on a High
370 Sensitivity Superconductive Sensor for Magnetoencephalography. *Sensors* **14**, 12114–12126
371 (2014).
- 372 24. N. Tzourio-Mazoyer, *et al.*, Automated anatomical labeling of activations in SPM using a
373 macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* **15**,
374 273–89 (2002).
- 375 25. A. Hillebrand, *et al.*, Direction of information flow in large-scale resting-state networks is
376 frequency-dependent. *Proc. Natl. Acad. Sci. U. S. A.* (2016)
377 <https://doi.org/10.1073/pnas.1515657113>.
- 378 26. G. Nolte, The magnetic lead field theorem in the quasi-static approximation and its use for
379 magnetoencephalography forward calculation in realistic volume conductors. *Phys. Med. Biol.*
380 **48**, 3637–3652 (2003).
- 381 27. B. D. Van Veen, W. Van Drongelen, M. Yuchtman, A. Suzuki, Localization of Brain
382 Electrical Activity via Linearly Constrained Minimum Variance Spatial Filtering. *IEEE Trans.*
383 *Biomed. Eng.* **44** (1997).
- 384 28. A. Lardone, *et al.*, Mindfulness meditation is related to long-lasting changes in hippocampal
385 functional topology during resting state: a magnetoencephalography study. *Neural Plast.* **2018**
386 (2018).
- 387 29. R. Oostenveld, *et al.*, FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG,
388 and Invasive Electrophysiological Data, FieldTrip: Open Source Software for Advanced
389 Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Comput. Intell. Neurosci.*
390 (2011) <https://doi.org/10.1155/2011/156869>, 10.1155/2011/156869.
- 391 30. J. M. Beggs, D. Plenz, Neuronal avalanches in neocortical circuits. *J. Neurosci. Off. J. Soc.*
392 *Neurosci.* **23**, 11167–77 (2003).
- 393 31. O. Shriki, *et al.*, Neuronal Avalanches in the Resting MEG of the Human Brain. *J. Neurosci.*
394 **33**, 7079–7090 (2013).

- 395 32. C. Haldeman, J. M. Beggs, Critical Branching Captures Activity in Living Neural Networks
396 and Maximizes the Number of Metastable States. *Phys. Rev. Lett.* **94**, 058101 (2005).
- 397 33. T. E. Harris, The Theory of Branching Process (1964).
- 398 34. P. Bak, C. Tang, K. Wiesenfeld, Self-organized criticality: An explanation of the 1/f noise.
399 *Phys. Rev. Lett.* **59**, 381 (1987).

400

401

402 **Figure 1.**

403

404

405 A. Rendering of streamlines reconstructed using diffusion MRI and tractography for an
406 individual. B. Structural connectivity matrix. Row/columns represent regions comprising a
407 brain atlas. Matrix entries store the number of streamlines interconnecting each pair of regions.
408 C. Source-reconstructed MEG series. Each blue line represents the z-scored activity of a
409 region, and the red lines denote the threshold ($z\text{-score} = \pm 3$). The inset represents a magnified
410 version of a time-series exceeding the threshold. D. Raster plot of an avalanche. For each
411 region, the moments in time when the activity is above threshold are represented in black,
412 while the other moments are indicated in white. The particular avalanche that is represented
413 involved three regions. E. Estimation of the transition matrix of a toy avalanche. Region i is
414 active three times during the avalanche. In two instances, denoted by the green arrows, region j
415 was active after region i . In one instance, denoted by the red arrow, region i is active but region
416 j does not activate at the following time step. This situation would result, in the transition
417 matrix, as a $2/3$ probability. F. Average structural matrix and average transition matrix (Log
418 scale).

419

420

421 **Figure 2.**

422

423

424 **A.** Distribution of the r 's of the Spearman's correlation between the subject-specific transition matrices
425 and structural connectomes. The black diamond represent the r 's of the group-averaged matrices. On the
426 left, the results for the AAL atlas, on the right, the results for the DKT atlas. Green, purple and orange dots
427 represent results obtained with a z-score threshold of 2.5, 3 and 3.5, respectively. **B and C.** Data referring to
428 the AAL atlas in B, to the DKT atlas in C. On the top-left, the average structural matrix, on the bottom left,
429 the average transition matrix. The scatterplot shows the correlation between the values of the structural
430 edges and the transition probabilities for the corresponding edge. The black line represents the best fit line in
431 the least-square sense. On the right, the distribution shows the r 's derived from the null distribution. The
432 dotted blue line represents the observed r . Please note that, for visualization purposes, the connectivity
433 weights and the transition probabilities were resampled to normal distributions. Figure 2-figure supplement
434 1 shows the comparison between the structural connectome and the transition matrix computed by taking
435 into account longer delays. In the Supplementary file 1, we report a table with an overview of the results of
436 the frequency-specific analysis.

437

438

439 **Figure 2-figure supplement 1.**

440 On the left, the average structural matrix. On the right, the average transition matrix.

441 **Supplementary File 1.**

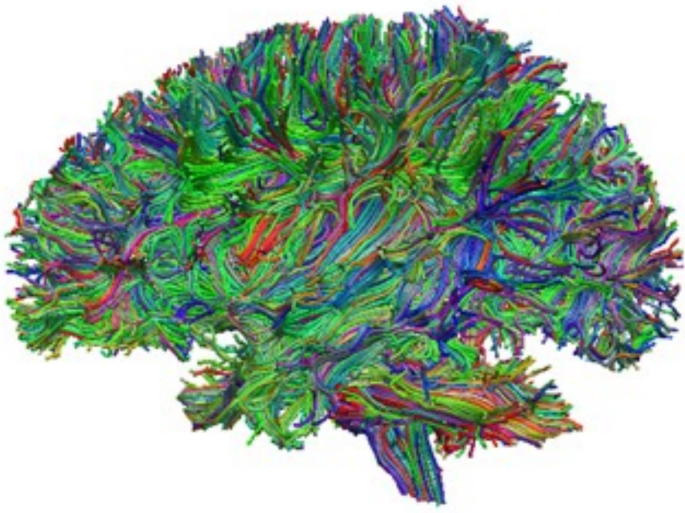
442 Correlations between the structural connectome and frequency-specific transition matrices.

443

444 **Source data File.**

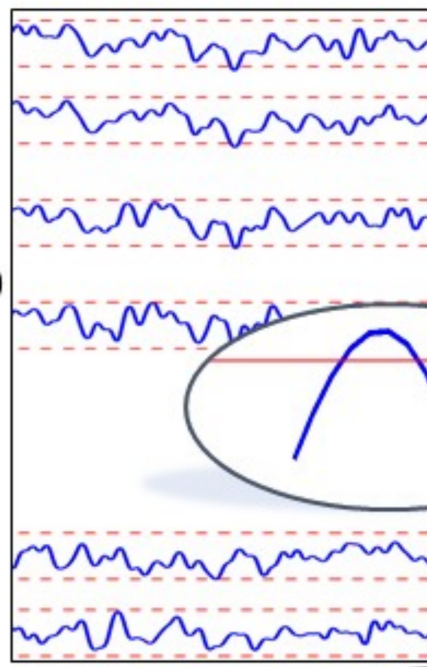
445 The source data file contains the code to generate the transition matrices starting from neuronal avalanches
446 and to compare them to null surrogates.

A.



C.

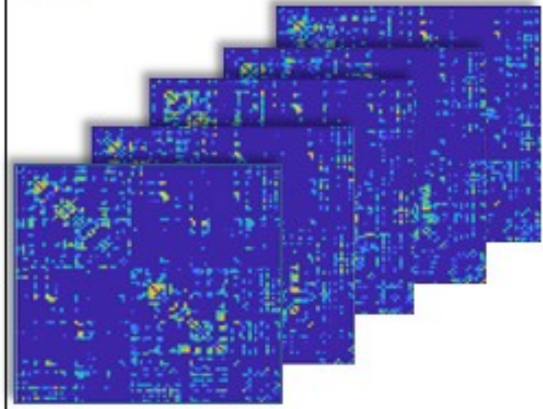
Brain Regions



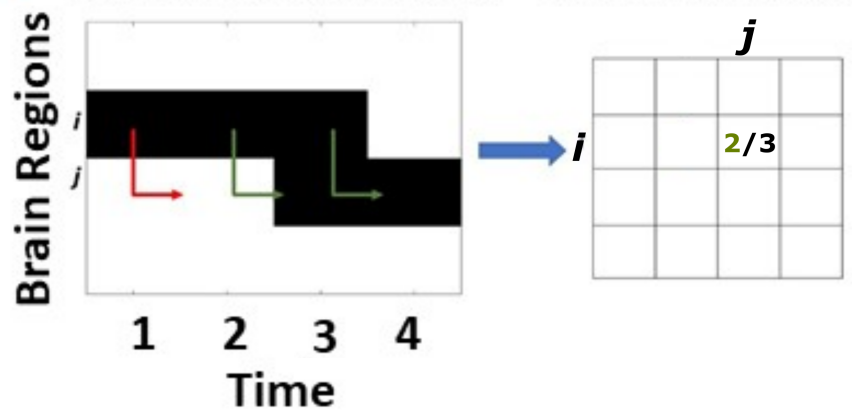
D.



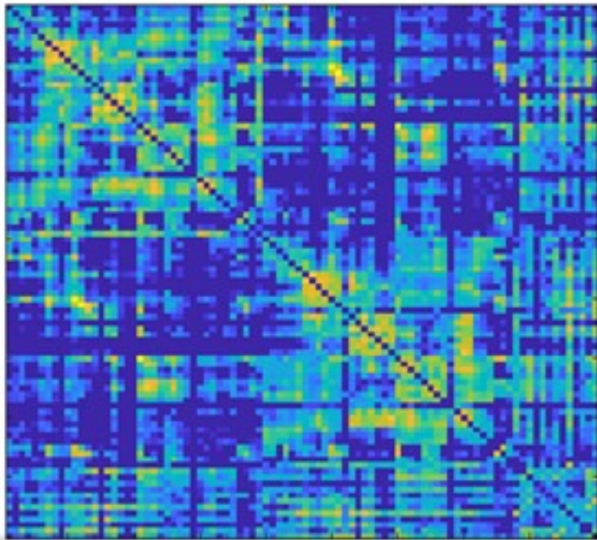
B. Structural matrices



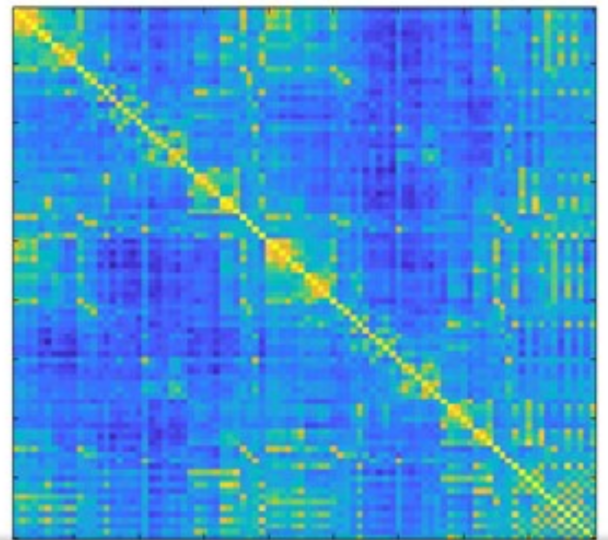
E. Neuronal avalanche Transition Matrix



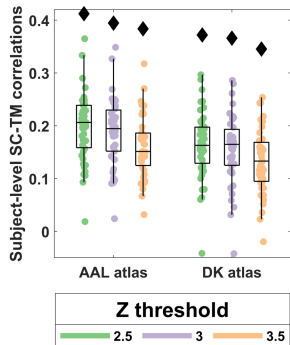
F. Structural matrix



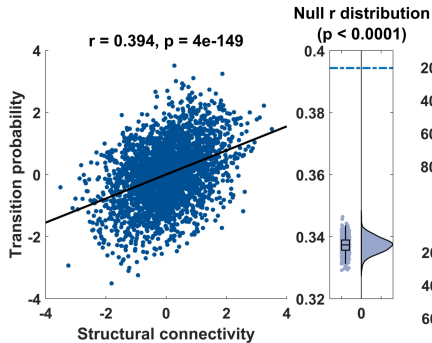
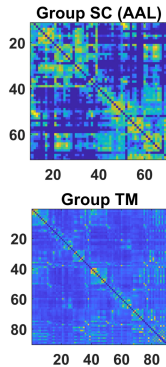
Transition matrix



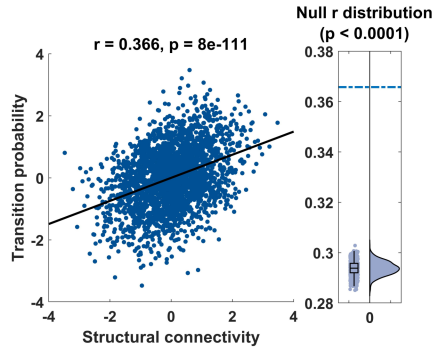
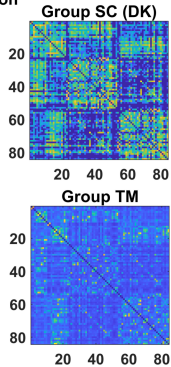
A.



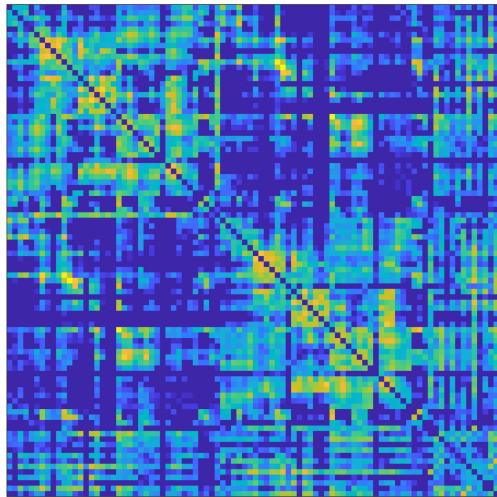
B.



C.

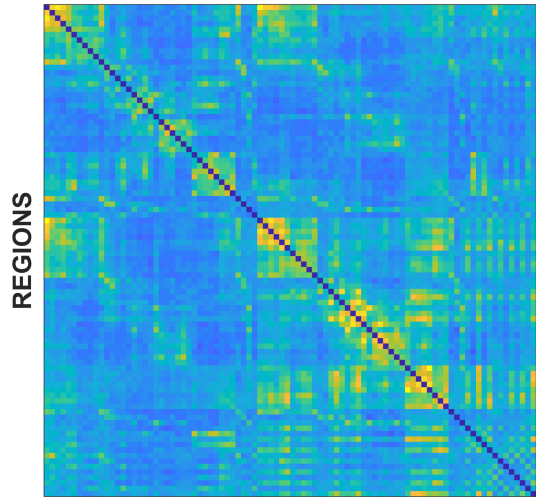


AVERAGE STRUCTURAL CONNECTOME



REGIONS

AVERAGE TRANSITION MATRIX



REGIONS

$p < 0.001$
 $r = 0.36$