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 profoundly shapes 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.

Keywords: brain dynamics, brain networks, magnetoencephalography, neuronal avalanches, structural connectome

Introduction

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

Results

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

MEG signals were pre-processed and source reconstructed for both the AAL and DKT atlases. All analyses were conducted on source-reconstructed signal amplitudes. Each signal amplitude was z-scored and binarized such that, at any time point, a z-score exceeding a given threshold was set to 1 (active); all other timepoints were set to 0 (inactive). An avalanche was defined as starting when any region exceeded this threshold, and finished when no region was active. 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 δ~3ms. The TMs were averaged per participant, and then per group, and finally symmetrized. Fig.1 provides an overview of the pipeline.

We found striking evidence of an association between avalanche transition probabilities and structural connectivity strengths (Fig. 2), suggesting that regional propagation of fast-scale neural avalanches is partly shaped by the axonal fibers forming the structural connectome (r=0.37,

$p<0.0001$). Specifically, the association was evident for different activation thresholds and both the AAL and DKT connectomes (AAL atlas: for threshold $z=2.5$, $r=0.38$; for threshold $z=3.0$, $r=0.37$; for threshold $z=3.5$, $r=0.34$; DKT atlas: for threshold $z=2.5$, $r=0.32$; for threshold $z=3.0$, $r=0.31$; for threshold $z=3.5$, $r=0.30$; in all cases, $p<0.0001$), as well as for individual- and group-level connectomes, although associations were stronger for group-level analyses (see Fig. 2, panel A).

We also investigated this phenomenon within specific frequency bands. Associations were evident in all the classical frequency bands: delta (0.5 – 4 Hz; $r=0.39$), theta (4 – 8 Hz; $r=0.29$), alpha (8 – 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 bands (see Supplementary File 1).

The introduction of a time-lag makes it unlikely that volume conduction alone could explain the association, given that simultaneous activations do not contribute to the transition matrix. To confirm that volume conduction effects were negligible, the transition matrices were re-computed using longer delays. In short, we computed the probability of any region activating at any time point (during 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 took into account time delays as long as the avalanche itself, while minimizing the influence of short delays. In this case, a significant association remained between transition probabilities and structural connectivity ($r=0.34$; $p<0.0001$). Supplement 1 of Fig. 2 provides further details.

Next, we sought to test whether the associations were weaker for randomized transition matrices computed after randomizing the times of each avalanche while keeping the spatial structure unchanged. Randomized transition matrices resulted in markedly weaker associations with structural connectivity, compared to the actual transition matrices (AAL atlas, z-score=3: mean $r = 0.25$, observed $r= 0.38$, $p<0.001$). This suggests that the empirical organization of the connectome significantly shapes the temporally resolved propagation of neural activity.

Finally, we replicated these findings for a group-level connectome derived using diffusion MRI acquired from 200 healthy adults in the Human Connectome Project ($r=0.11$, $p<0.001$, z-score=3; see methods). Our results were thus robust to multiple connectome mapping pipelines and parcellation atlases, significant for both group-averaged and individual connectomes, and could not be explained by chance transitions and/or volume conduction effects.

Discussion

Our results provide new insight into the propagation of fast-evolving brain activity in the human connectome. We show that the spatial unfolding of neural dynamics at the millisecond scale is shaped by the network of large-scale axonal projections comprising the connectome, thereby constraining exploration of the brain's putative functional repertoire. While previous studies provide evidence of coupling between structural connectivity and functional MRI activity (3, 8, 9), the neural signals measured with MEG in the present study are orders of magnitude faster, enabling investigation of intrinsic neural dynamics nested in slow activity (10). Our findings suggest that long-term structure-function coupling previously uncovered with functional MRI occurs against a backdrop of faster fluctuations, which are also constrained by the connectome and may enable individuals to rapidly respond to changing environments and new cognitive demands (11). Finally, our results explain how the large-scale activity unfolding in time might lead to the previous observation that average resting-state functional connectivity displays topological features that mirror those of the structural connectome (12). The proposed framework links the large-scale spreading of aperiodic, locally generated perturbations to the structural connectome, and might be further exploited to investigate polysynaptic models of network communication, which aim to describe patterns of signalling between anatomically unconnected regions (13, 14). Therefore, our work provides a foundational step towards elucidating the mechanisms governing communication in the human connectome. In turn, this can be exploited to predict the effects of structural lesions on behaviour and/or clinical phenotypes, under the above-mentioned hypothesis that structure influences behavioural outcomes by constraining global dynamics. In conclusion, using MEG to study neuronal avalanches, we provide a new framework to link fast neural dynamics to the structural connectome.

Methods

Participants

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

MRI acquisition

3D T1-weighted brain volumes were acquired at 1.5 Tesla (Signa, GE Healthcare) using a 3D Magnetization-Prepared Gradient-Echo BRAVO sequence (TR/TE/TI 8.2/3.1/450 ms, voxel 1 × 1 × 1 mm3, 50% partition overlap, 324 sagittal slices covering the whole brain). The MRI scan was performed after the MEG recording. A subject-specific connectome was obtained in all subjects on the same MRI scanner (1.5 Tesla, Signa, GE Healthcare). Preprocessing of the diffusion MRI data was carried out using the software modules provided in the FMRIB Software Library (FSL, http://fsl.fmrib.ox.ac.uk/fsl). All diffusion MRI datasets were corrected for head movements and eddy currents distortions using the "eddy_correct" routine, rotating diffusion sensitizing gradient directions accordingly, and a brain mask was obtained from the B0 images using the Brain Extraction Tool routine. A diffusion-tensor model was fitted at each voxel, and fiber tracks were generated over the whole brain by deterministic tractography using the Diffusion Toolkit (FACT propagation algorithm, angle threshold 45°, spline-filtered, masking by the FA maps thresholded at 0.2). For tractographic analysis, the ROIs of the AAL atlas and of a MNI space-defined volumetric version of the Desikan-Killiany-Tourville (DKT) ROI atlas were used, both masked by the GM tissue probability map available in SPM (thresholded at 0.2). To this end, for each participant, FA volumes were normalized to the MNI space using the FA template provided by FSL, using the spatial normalization routine available in SPM12, and the resulting normalization matrices were inverted and applied to the ROIs, to apply them onto each subject. The quality of the normalization was assessed visually. From each subject's whole brain tractography and corresponding GM ROI set, the number of streamlines connecting each couple of GM ROIs and the corresponding mean tract length was calculated using an in-house software written in Interactive Data Language (IDL, Harris Geospatial Solutions, Inc., Broomfield, CO, USA).

Connectomes in the replication dataset were constructed using an alternative mapping pipeline and diffusion MRI data from the Human Connectome Project (HCP). Deterministic tractography was performed using MRtrix3 (15) under the following parameters: FACT algorithm, 5 million streamlines, 0.5 mm propagation step size, 400 mm maximum propagation length, and 0.1 FA threshold for the termination of streamlines (14). Structural matrices were constructed for 200 HCP participants using the AAL atlas and averaged to derive a group-level connectome.

MEG pre-processing

MEG pre-processing and source reconstruction were performed as in (16). In short, the MEG registration was divided in two eyes-closed segments of 3:30 minutes each. To identify the position of the head, four anatomical points and four position coils were digitized. Electrocardiogram (ECG) and electro-oculogram (EOG) signals were also recorded. The MEG signals, after an anti-aliasing filter, were acquired at 1024 Hz, then a fourth order Butterworth IIR band-pass filter in the 0.5-48 Hz band was applied. To remove environmental noise, measured by reference magnetometers, we used Principal Component Analysis. We adopted Independent Component Analysis to clean the data from physiological artifacts, such as eye blinking (if present) and heart activity (generally one component). Noisy channels were identified and removed manually by an expert rater. 47 subjects were selected for further analysis.

Source reconstruction

The time series of neuronal activity were reconstructed in 116 regions of interests (ROIs) based on the Automated Anatomical Labeling (AAL) atlas (17, 18); and in 84 regions of interest based on the Desikan-Killiany-Tourreville (DKT) atlas. To do this, we used the volume conduction model proposed by Nolte (19) applying the Linearly Constrained Minimum Variance (LCMV) beamformer algorithm (20) based on the native structural MRIs. Sources were reconstructed for the centroids of the each ROI. Finally, we considered a total of 90 ROIs for the AAL atlas, since we have excluded 26 ROIs corresponding to the cerebellum because of their low reliability in MEG (21). All the preprocessing steps and the source reconstruction were made using the Fieldtrip toolbox (22).

Neuronal avalanches and branching parameter

To study the dynamics of brain activity, we estimated "neuronal avalanches". Firstly, the time series of each ROI was discretized calculating the z-score, then positive and negative excursions beyond a threshold were identified. The value of the threshold was set to 3 standard deviations ($|z| = 3$), but we tested the robustness of the results changing this threshold from 2.5 to 3.5. A neuronal avalanche begins when, in a sequence of contiguous time bins, at least one ROI is active ($|z| > 3$), and ends when all ROIs are inactive (23, 24). The total number of active ROIs in an avalanche corresponds to its size.

These analyses require the time series to be binned. This is done to ensure that one is capturing critical dynamics, if present. To estimate the suitable time bin length, for each subject, for each neuronal avalanches and for each time bin duration, the branching parameter σ was estimated (25,

26). In fact, system operating at criticality typically display a branching ratio ~1. The branching ratio is calculated as the geometrically averaged (over all the time bins) ratio of the number of events (activations) between the subsequent time bin (descendants) and that in the current time bin (ancestors) and then averaging it over all the avalanches (27). More specifically:

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

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

Where σ_i is the branching parameter of the i-th avalanche in the dataset, N_{bin} is the total amount of 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 total number of avalanche in the dataset. We tested bins from 1 to 5, and picked 3 for further analyses, given that the branching ratio was 1 for bin =3. However, results are unchanged for other bin durations (data not shown). The results shown are derived when taking into accounts avalanches longer than 10 time bins. However, we repeated the analysis taking into account avalanches longer than 30 time bins, as well as taking all avalanches into account, and the results were unchanged.

Transition matrices

The amplitude of each binned, z-scored source-reconstructed signal was binarized, such that, at any time bin, a z-score exceeding ± 3 was set to 1 (active); all other time bins were set to 0 (inactive). Alternative z-score thresholds (i.e. 2.5 and 3.5) were tested. An avalanche was defined as starting when any region is above threshold, and finishing when no region is active, as in (16). Avalanches 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 (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 δ~3ms. 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 msecs (and 5 msecs for the binning of 5). Hence, activations occurring simultaneously do not contribute to the estimate of the transition matrix. To further rule out this possibility, we have computed the transition matrices in a different way, to include even longer delays. After the initial time-bin of an avalanche, we kept track of what other regions were recruited after the first perturbation. Importantly, we did not scroll through the avalanche in time, as previously described, so as to include time delays as long as the avalanche itself. 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. 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. Further studies are warranted to investigate frequency-specific behaviour of large-scale avalanche spreading.

Statistical analysis

The Spearman rank correlation coefficient was used to assess the association between transition probabilities and structural connectivity. A correlation coefficient was computed separately for each individual across all pairs of regions. Transition matrices were symmetrized before this computation. Randomized transition matrices were generated to ensure that associations between transition probabilities and structural connectivity could not be attributed to chance. Avalanches were randomized across time, without changing the order of active regions at each time step. We generated a total of 1000 randomized transition matrices and the Spearman rank correlation coefficient was computed between each randomized matrix and structural connectivity. This yielded a distribution of correlation coefficients under randomization. The proportion of correlation coefficients that were greater than, or equal to, the observed correlation coefficient provided a p-

value for the null hypothesis that structure-function coupling was attributable to random transition events.

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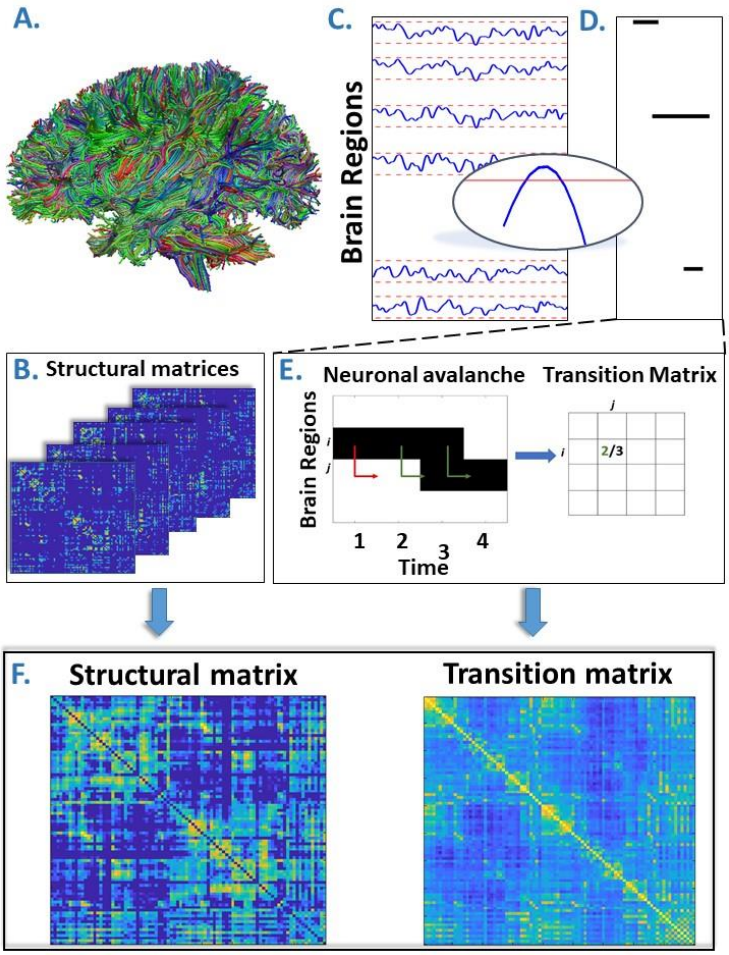
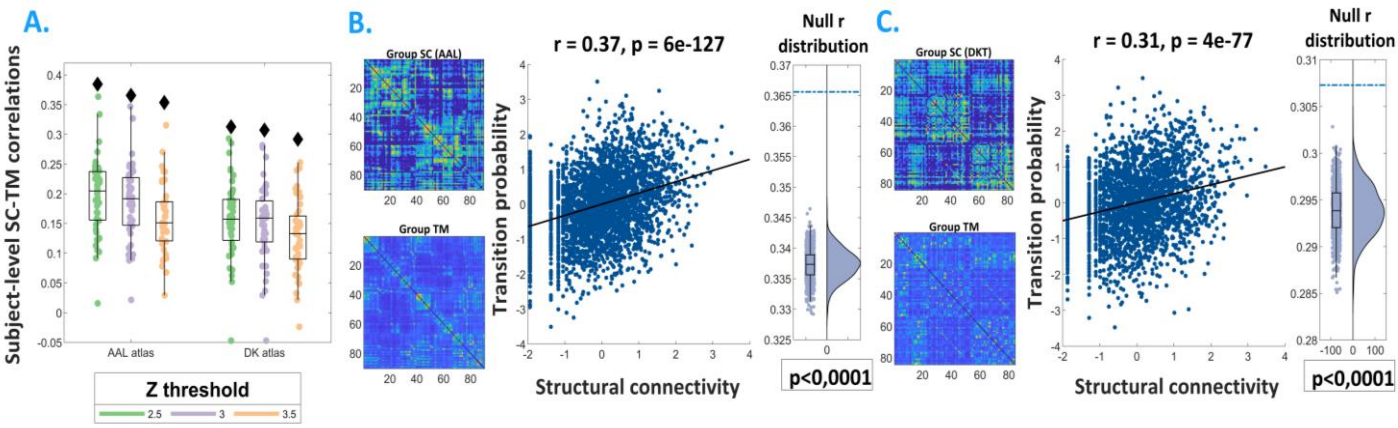
Figure 1.



A. Rendering of streamlines reconstructed using diffusion MRI and tractography for an individual. B. Structural connectivity matrix. Row/columns represent regions comprising a brain atlas. Matrix entries store the number of streamlines interconnecting each pair of regions. C. Source-reconstructed MEG series. Each blue line represents the z-scored activity of a region, and the red lines denote the threshold (z-score= ± 3). The inset represents a magnified version of a time-series exceeding the threshold. D. Raster plot of an avalanche. For each region, the moments in time when the activity is above threshold are represented in black, while the other moments are indicated in white. The particular avalanche that is represented involved three regions. E. Estimation of the transition matrix of a toy avalanche. Region *i* is active three times during the avalanche. In two instances, denoted by the green arrows, region *j* was active after region *i*. In one instance, denoted by the red arrow, region *i* is active but region *j* does not activate at the following time step. This situation would result, in the transition

matrix, as a 2/3 probability. F. Average structural matrix and average transition matrix (Log scale).

Figure 2.



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