Time-resolved functional brain networks reveal dynamics of human brain connectivity at rest

Supporting Information (SI) Appendix

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SI Movies

Cortical renderings of time-resolved regional efficiencies were compiled into AVI format movies for two representative individuals. Parameters: 1440 ms sampling period (2× repetition time); 15 frames per second; 1 second in movie time equals 21.6 seconds in real time.

- HCP105115 WMV movie (4 MB)
- HCP111312 WMV movie (4 MB)

Legend for SI Movie HCP105115: Movie of time-resolved regional network efficiencies rendered onto the cortical surface for individual HCP105115.

Legend for SI Movie HCP111312: Movie of time-resolved regional network efficiencies rendered onto the cortical surface for individual HCP111312.

SI Materials and Methods

Functional MRI Preprocessing

Minimally preprocessed rsfMRI data was obtained from the Human Connectome Project (HCP; 1). The minimal preprocessing included was completed according to HCP Functional Pipeline v2.0 (2, 3), which involved: 1) removal of spatial and gradient distortions; 2) correction for head movement; 3) intensity normalization and bias field removal; and, 4) transformation to MNI space (2 mm isotropic) using a single spline re-sampling from the original EPI frames.

Preprocessed EPI frames were bandpass filtered to suppress frequency components outside the range 0.01-0.1 Hz and spatially averaged with respect to established cortical and subcortical regional parcellations to yield representative regional time series (4–6). Regional time series were then subject to standard processing routines to reduce spurious variance unlikely to reflect neuronal activity (7, 8). In particular, the detrended regional time series were regressed against the following nuisance variables: 1) signal averaged from ventricular regions; 2) signal averaged from white matter regions; 3) six detrended head realignment parameters and corresponding derivatives (9); and, 4) physiological noise signals estimated with the CompCor procedure (10). The “broken-stick” method (11) identified between 4 to 6 significant noise components for each individual. All nuisance variables were bandpass filtered before regression (12), but CompCor was applied to the unfiltered data. It is the residuals from these multiple regressions that were
used in subsequent analysis and referred to as the \textit{regional time series} in our work. We use $\{x^i_t\}_{t=1}^T$ to denote the regional time series for the $i$th region, where $T$ is the total number of time points.

**Weighted Pearson Product-Moment Correlation**

For a window of length $N$ time points and a weighting vector $\{w_\tau\}_{\tau=1}^N$, the weighted Pearson product-moment correlation (13) between region $i$ and region $j$ at time $t \geq N$ was computed as $\rho^{ij}_t = \frac{\sigma^{ij}_t}{\sigma^i_t \sigma^j_t}$, where the weighted means, standard deviations and covariances were given by

$$\bar{x}^i_t = \sum_{\tau=1}^N w_\tau x^i_{t-N+\tau}, \quad \sigma^i_t = \sqrt{\sum_{\tau=1}^N w_\tau (x^i_{t-N+\tau} - \bar{x}^i_t)},$$

$$\sigma^{ij}_t = \sum_{\tau=1}^N w_\tau (x^i_{t-N+\tau} - \bar{x}^i_t)(x^j_{t-N+\tau} - \bar{x}^j_t).$$

**Null Models for Testing Synchrony in Transition Events**

A null model was developed to test whether transition events were uniformly distributed in time. Null data can be generated by randomly redistributing in time all transition events in the actual data. However, this approach does not account for inherent properties of correlation networks that can potentially yield coordinated behavior in the absence of any non-stationary connectivity dynamics. For example, non-stationary fluctuations in the \textit{activity} at a single region may result in coordinated fluctuations in the \textit{connectivity} between that region and many of its neighbors, due to the lack of degrees of freedom when using the correlation coefficient as a measure of connectivity in a network (14). As such, if many connections are found to transition at the same time point, it is possible that these transition events are related to non-stationary fluctuations in the activity at a single region. Transition events that are related in this way should therefore be reduced to a smaller set of unique (i.e. unrelated) transition events.

Related transition events are likely to be topologically clustered around a single node or group of nodes. We therefore defined \textit{related transition events} as any group of connections that: i) transitioned at the same time point; and, ii) formed a connected graph component. For example, transition events occurring at the same time on connections $(u, v)$ and $(u, w)$ were assumed to be related, since both events could have been due to the same behavior at region $u$. In this example, the connections associated with the two transition events form a connected graph component and are therefore reduced to a single transition event. Identifying related transitions in terms of connected graph components is conservative, since truly unrelated transitions—that is, transitions occurring due to specific dynamic aspects of connectivity (15)—can be neighbors as a matter of chance alone, and thus needlessly reduced to a single transition.
Null data sets were generated by randomly redistributing transition events in time, but preserving any groups of related transitions. For example, transition events occurring at the same time on connections \((u, v)\) and \((u, w)\) were related according to the above definition, and thus it was forbidden for \((u, v)\) to be redistributed to time \(t_i\), but \((u, w)\) to \(t_j\), \(i \neq j\). A total of 10,000 null data sets were generated as such. For each null data set, the total number of groups of related transition events at each time point was enumerated (i.e. total number of connected components). The greatest of these totals across all time points was then recorded for each null data set to yield the null distribution controlling for the familywise error rate (FWER) across all time points. The null hypothesis of uniformly distributed transition events was rejected if at least one time point was found in the actual data comprising more groups of related transition events than the 99th percentile of the empirical null distribution.

For brevity, we henceforth refer to a group of related transition events simply as a transition event.

Note that null models based on random correlation networks and randomization at the time series level were not appropriate here because the total number of transition events in the null data cannot be matched to the total number of transitions in the actual rsfMRI data.

**Simulation of Vector Autoregressive Null Model**

Vector autoregressive (VAR) model responses were simulated to generate surrogate regional time series satisfying the null hypothesis of a linearly correlated, stationary, multivariate stochastic process. This was repeated to generate 250 independent null data sets. The surrogate regional time series comprising each null data set were then processed identically as the actual data. This enabled empirical estimation of the null distribution of the test statistic and graph measures evaluated in this study. It was computationally infeasible to fit a single multidimensional VAR model with a covariance structure with dimensions equal to the number of regions. Two-dimensional VAR models were therefore independently fitted to each pair of regional time series, implying the model response for a given region was conditional on the pair of regions under consideration. The VAR model order was chosen to minimize the Bayesian information criterion (BIC). The BIC was evaluated for model orders between 1 and 50 in unity increments for 500 pairs of regions randomly sampled from the 10 individuals. The BIC was most consistently minimized for a model order of 11, corresponding to a maximum lag of approximately 8 seconds. Model order was not optimized for individual pairs of regions.

VAR model responses were simulated using an approach previously described in the literature (16, 17). In brief, simulations were initialized with a randomly sampled contiguous block of actual time series data. Innovations for the simulated processes were randomly sampled from the innovations (residuals) estimated for the actual data. As such, the innovation term for the simulated process at any given time step comprised a randomly-sampled residual of the VAR fit (16).
Fig. S1 shows the time-averaged cross-correlation, power spectral density, cross power spectral density and amplitude distribution for the actual rsfMRI time series and some sample null data.

To accurately estimate significance thresholds for connection-specific measures, the null distribution samples for each individual connection were pooled to yield a single, highly-resolved null distribution. This assumed the statistical properties among connections were homogeneous under the null hypothesis. Without this pooling, the individual null distributions for each pair of regions would not have comprised a sufficient number of samples to accurately estimate significance thresholds.

Consideration was given to generating null data by phase randomizing the regional time series. However, examples were found where the sliding window derived time series of correlation coefficients remained non-stationary even after the regional time series had been phase randomized. In other words, while phase randomization ensured stationarity of the regional time series, it did not necessarily ensure stationarity of the time series for which the null hypothesis was tested; namely, the time-resolved correlation coefficients.

**Graph Analysis**

To compute efficiency for a given region, shortest path lengths were determined between that region and all other regions in the network. That region’s efficiency was then given by the sum of the reciprocal of these shortest path lengths, normalized by one less the total number of regions comprising the network (19). Shortest path lengths were calculated for networks with a fixed connection density of 20%. Specifically, the top 20% largest connections according to correlation coefficient were identified and left untouched, while all other connections were set to zero. This calculation was repeated for each time-resolved connectivity matrix to yield a time series of regional efficiencies. Using a fixed connection density ensured efficiency fluctuations in time were not due to variability in this confound. The weight of a connection for shortest path calculation was taken as the reciprocal of its time-resolved correlation coefficient.

Newman’s spectral algorithm (20) was used to decompose the time-averaged connectivity matrices for each individual into modules. Modules defined non-overlapping groups of regions for which the connectivity between regions within the same module was stronger than the connectivity between regions residing in different modules. Two passes of the consensus algorithm (21) were used to determine a modular decomposition representing consensus among the 10 individuals. The first pass was performed separately for each individual and was used to find a stable partition among 100 independent decompositions. The second pass was used to find consensus among the 10 co-occurrence matrices generated by the first pass, yielding a single “median” decomposition that was most similar, on average, to the decomposition for each individual. Cortical renderings were visualized with BrainNet Viewer (22).
Simulated rsfMRI Data

Neuronal population dynamics were simulated for 47 neural masses representing visual, somatosensory and motor cortical regions comprising the macaque neocortex (23). Neural masses were interconnected according to an established binary connectivity matrix originally derived from the CoCoMac database (24). This connectivity matrix is available as part of the Brain Connectivity Toolbox (BCT; 25) and has been previously used to interconnect networks of neural masses (26). While anatomical connectivity matrices can be mapped for the whole human brain using diffusion imaging and tractography, these matrices are undirected and therefore do not preserve key network motifs (27). In contrast, axonal connectivity mapped in the CoCoMac database is directed.

We broadly followed the approach used by (28) to simulate rsfMRI data. In brief, each neural mass was modeled with a set of three coupled differential equations derived from the model of Morris and Lecar, but with several important adaptations (29). Neural masses were coupled according to the axonal connectivity matrix of the macaque neocortex described above. Axonal conduction delays were not modeled between coupled neural masses. The excitatory coupling coefficient was set to 0.04. The weight of each non-zero connection was randomly sampled from a Gaussian distribution with mean of 0.5 and a standard deviation of 0.1 (28).

The full system of coupled differential equations was simulated for a period of 16 minutes with a first-order method at a fixed resolution of 0.2 ms. The first 2 minutes were subsequently discarded to account for possible transient effects persisting from the initial conditions.

The Balloon-Windkessel hemodynamic model (30) was then applied to generate rsfMRI data matched in length and temporal resolution to the HCP data. The neuronal input to the hemodynamic model was the absolute value of the time derivative of the simulated mean excitatory membrane potential, which has been considered a proxy for glutamate turnover (28). The hemodynamic model was simulated independently for each neural mass using a Runge-Kutta method with a fixed step length of 1 ms. The hemodynamic response was then downsampled to a temporal resolution of 720 ms to match the HCP data.

After downsampling, the simulated rsfMRI data was analysed identically to the HCP rsfMRI data. Importantly, the simulated data was necessarily free of any head motion, scanner drift and physiological noise. Hence, replicating our findings in the simulated rsfMRI data excluded these noise confounds as a potential explanation of our results.
Fig. S1: The VAR null model generated surrogate time series that were well matched to the time-averaged cross-correlation, power spectral density, cross power spectral density and amplitude distribution of the actual rsfMRI time series. 
A) Time-averaged correlation matrix computed using rsfMRI data (lower triangular) and a sample VAR null data set (upper triangular). B) Power spectrum for two representative regions (left and right middle frontal gyrus) and their cross-spectrum computed using the actual rsfMRI data (blue lines) and a sample null data set (red lines). C) Regional time series amplitude distribution for the left middle frontal gyrus and 25 null data sets. Data for HCP105115.
Fig. S2: The variance in regional efficiency over time was computed for each region in the actual data and in 250 VAR null data sets. The cumulative distribution function of the variance in efficiency is shown for three healthy, young adults (blue lines) and 250 null data sets (black lines).
**Fig. S3**: Time-resolved regional efficiencies computed using different network connection densities for a healthy, young adult (HCP105115). Note that the color scale varies across connection densities to accommodate global efficiency increases with increasing connection density.
**Fig. S4**: *Upper:* Time-resolved regional efficiencies for two healthy, young adults and a sample null data set. *Middle Axes:* Regional efficiencies averaged across all regions to yield a measure of time-resolved global efficiency. *Lower Axes:* Time series of regional efficiency values for the region with the greatest variation in regional efficiency.
**Fig. S5**: The skewness in the forward difference of time-resolved global efficiency was computed in the actual data and in 250 VAR null data sets. Forward differences were significantly positively skewed for all individuals ($p < 0.01$; skewness range: 0.17–1.3). Histograms of forward differences are shown for three healthy, young adults and a sample null data set. The $p$-value for each individual was given by the proportion of null data sets with skewness of greater or equal value than the observed skewness. Positive skewness is consistent with the observation that transitions from low-to-high efficiencies are sudden, whereas high-to-low transitions are gradual.

**Fig. S6**: Time-averaged correlation coefficients were significantly correlated with the statistic developed to test for time-varying connectivity. Scatter plots characterizing this relation are shown for three healthy, young adults. Lines of best fit are also shown. Each data point (blue dot) represents a connection.
HCP 111312

(A) HCP 111312
HCP 105115

Noise Confound

Principal Component

(B) HCP 105115
Fig. S7: The principal component (thick black line) explaining the most temporal variation in the top-100 most dynamic connections was regressed against estimates of physiological noise derived using CompCor (10) as well as estimates of instantaneous head motion; namely, displacement and rotation in $x$, $y$ and $z$ directions and all associated first-order derivatives, denoted with $\Delta$. Each of these noise confounds was first smoothed with the exponential weight vector used for the sliding window analysis (see Materials and Methods). This ensured the smoothing extent and degrees-of-freedom of the noise confounds was matched to the principal component. None of the noise confounds (blue lines) were significant predictors of the principal component for any individual. Note that two principal components explaining at least 20% of the variation for HCP 118932 were found, but only one is shown.
Fig. S8: Replication of main results with simulated rsfMRI data. The Balloon-Windkessel hemodynamic model was applied to neuronal population dynamics generated by 47 neural masses interconnected according to the anatomical connectivity of the macaque neocortex.  

A) Anatomical connectivity matrix for the macaque neocortex (lower triangular; dark cells indicate a connection) and the time-averaged correlation matrix computed using simulated rsfMRI data (upper triangular).

B) Time-resolved regional network efficiencies. Matrix row/columns represent regions/time.

C) Simulated BOLD dynamics for a pair of strongly correlated regions (i.e. neural masses). Despite strong time-averaged correlation (Pearson correlation: 0.54), transient intervals with no correlation are evident.
Fig. S9: Replication of main results with an independent data set. Upper Axes: Time series of correlation coefficients pertaining to the top-100 most dynamic functional connections for three healthy, young adults comprising the replication data set. Percentages indicate the amount of variance explained by the principal component (thick black lines). Middle Axes: The transition count (blue lines) enumerates for each time point the number of connections that cross their median correlation value. The transition count for a sample null data set is also shown (black lines). The null hypothesis of uniformly distributed transitions across time was rejected at time points when the 0.01 FWER cutoff value (horizontal red lines) was exceeded. Lower: Time-resolved regional network efficiencies for the same three individuals. Matrix rows/columns represent regions/time.
Fig. S10: Replication of main results for a healthy, young adult (HCP105115) with scrubbing performed to alleviate head motion, in addition to the standard preprocessing steps used to control for noise confounds (31–33). Instantaneous head motion was indexed with a scalar quantity known as frame displacement (FD; 31). A) No scrubbing. B) Lenient scrubbing (FD > 0.5 mm). C) Stringent scrubbing (FD > 0.2 mm). Upper Axes: The transition count (blue lines) enumerates for each time point the number of connections that cross their median correlation value. The transition count for a sample null data set is also shown (black lines). The null hypothesis of uniformly distributed transitions across time was rejected at time points when the 0.01 FWER cutoff value (horizontal red lines) was exceeded. The null hypotheses was rejected with and without scrubbing. Middle: Time-resolved regional network efficiencies for the same three individuals. Matrix rows/columns represent regions/time. Lower Axes: Frame displacement (FD) as a function of time, with lenient and stringent scrubbing thresholds indicated.
\[ T_A \approx 0 \quad \quad T_B = |l_1h_1| + |l_2h_2| + |l_3h_1| \quad \quad T_C = |l_1h_1| + |l_2h_2| \quad \quad T_D = \sum |l_nh_n| \]

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**Fig. S11**: Test statistic exemplified for various stationary and non-stationary time series. Non-stationarity is quantified empirically by the existence of long and large excursions from the median value (red line). Consecutive crossing points of the median define a single excursion. The time between consecutive crossing points defines an excursion’s length, \( l_n \). The height, \( h_n \), of an excursion is the maximum separation reached between the time series and its median value. The test statistic is given by the sum over all excursions of the length-height product; that is, \( T = \sum |l_nh_n| \). Evidence against the null of a stationary time series increases in the four examples given from left to right; namely, \( T_A < T_B < T_C = T_D \). It can be argued that the center-right time series (C) shows greater evidence of non-stationarity than the rightmost time series (D) because it comprises excursions that are twice as long. To account for this, the statistic can be normalized by the total number of excursions. Under this normalization, \( T_C^* > T_D^* \).
Table S1: Basic demographics and preprocessing method for main and replication data sets.

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References


