

1 **High-level cognition is supported by at least second order**
2 **dynamic correlations in neural activity patterns**

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5 **Abstract**

6 Our thoughts arise from coordinated patterns of interactions between brain structures that change
7 with our ongoing experiences. High-order dynamic correlations in brain activity patterns reflect different
8 subgraphs of the brain’s connectome that display homologous lower-level dynamic correlations. We tested
9 the hypothesis that high-level cognition is supported by high-order dynamic correlations in brain activity
10 patterns. We developed an approach to estimating high-order dynamic correlations in timeseries data,
11 and we applied the approach to neuroimaging data collected as human participants either listened to a
12 ten-minute story or a temporally scrambled version of the story, or underwent a resting state scan. We
13 trained across-participants pattern classifiers to decode (in held-out data) when in the session each activity
14 snapshot was collected. We found that classifiers trained to decode from high-order dynamic correlations
15 yielded better performance on data collected as participants listened to the (unscrambled) story. By
16 contrast, classifiers trained to decode data from scrambled versions of the story or during the resting
17 state scan yielded the best performance when they were trained using first-order dynamic correlations
18 or raw activity patterns. We suggest that as our thoughts become more complex, they are supported by
19 higher-order patterns of dynamic network interactions throughout the brain.

20 **Introduction**

21 A central goal in cognitive neuroscience is to elucidate the *neural code*: the mapping between (a) mental
22 states or cognitive representations and (b) neural activity patterns. One means of testing models of the
23 neural code is to ask how accurately that model is able to “translate” neural activity patterns into known
24 (or hypothesized) mental states or cognitive representations (e.g., Haxby et al., 2001; Huth et al., 2016, 2012;
25 Kamitani & Tong, 2005; Mitchell et al., 2008; Nishimoto et al., 2011; Norman et al., 2006; Pereira et al., 2018;
26 Tong & Pratte, 2012). Training decoding models on different types of neural features can also help to elucidate
27 which specific aspects of neural activity patterns are informative about cognition– and, by extension, which
28 types of neural activity patterns might comprise the neural code. For example, prior work has used region
29 of interest analyses to estimate the anatomical locations of specific neural representations (e.g., Etzel et al.,
30 2009), or to compare the relative contributions to the neural code of multivariate activity patterns versus

31 patterns of dynamic correlations between neural activity patterns (e.g., Fong et al., 2019; Manning et al.,
32 2018). An emerging theme in this literature is that cognition is mediated by complex dynamic interactions
33 between brain structures (Bassett et al., 2006; Demertzi et al., 2019; Sporns & Honey, 2006; Turk-Browne,
34 2013).

35 Studies of the neural code to date have primarily focused on univariate or multivariate neural pat-
36 terns (for review see , NormEtal06) or (more recently) on patterns of dynamic first-order correlations (i.e.,
37 interactions between pairs of brain structures; Fong et al., 2019; Manning et al., 2018). We wondered what
38 the future of this line of work might hold. For example, is the neural code mediated by higher-order
39 interactions between brain structures? Second-order correlations reflect *homologous* patterns of correlation.
40 In other words, if the changing patterns of correlations between two regions, *A* and *B*, are similar to those
41 between two other regions, *C* and *D*, this would be reflected in the second-order correlations between (*A*-*B*)
42 and (*C*-*D*). In this way, second-order correlations identify similarities and differences between subgraphs
43 of the brain’s connectome. Analogously, third-order correlations reflect homologies between second-order
44 correlations– i.e., homologous patterns of homologous interactions between brain regions. More generally,
45 higher-order correlations reflect homologies between patterns of lower-order correlations. We can then ask:
46 which “orders” of interaction are most reflective of high-level cognitive processes?

47 Another central question pertains to the extent to which the neural code is carried by activity patterns
48 that directly reflect ongoing cognition (e.g., following Haxby et al., 2001; Norman et al., 2006), versus the
49 dynamic properties of the network structure itself, independent of specific activity patterns in any given set
50 of regions (e.g., following Bassett et al., 2006). For example, graph theoretic measures such as centrality and
51 degree (Bullmore & Sporns, 2009) may be used to estimate how a given brain structure is “communicating”
52 with other structures, independently of the specific neural representations carried by those structures. If
53 one considers a brain region’s graph theoretic position in the network (e.g., its eigenvector centrality) as a
54 dynamic property, one can compare how the positions of different regions are correlated, and/or how those
55 patterns of correlations change over time. We can also compute higher-order patterns in these correlations
56 to characterize homologous subgraphs in the connectome that display similar changes in their constituent
57 brain structures’ interactions with the rest of the brain.

58 To gain insights into the above aspects of the neural code, we developed a computational framework
59 for estimating dynamic high-order correlations in timeseries data. This framework provides an important
60 advance, in that it enables us to examine patterns in higher-order correlations that are computationally
61 intractable to estimate via conventional methods. Given a multivariate timeseries, our framework provides
62 timepoint-by-timepoint estimates of the first-order correlations, second-order correlations, and so on (up to
63 tenth-order correlations in this manuscript). Our approach combines a kernel-based method for computing

64 dynamic correlations in timeseries data with a dimensionality reduction step that projects the resulting dy-
65 namic correlations into a low-dimensional space. We explored two dimensionality reduction approaches:
66 principle components analysis (PCA; Pearson, 1901), which preserves an approximately invertable transfor-
67 mation back to the original data; and a second non-invertible algorithm that explored patterns in eigenvector
68 centrality (Landau, 1895). This latter approach characterizes correlations between each feature dimension's
69 relative *position* in the network in favor of the specific activity histories of different features.

70 We validated our approach using synthetic data where the underlying correlations were known. We
71 then applied our framework to a neuroimaging dataset collected as 125 participants listened to either an
72 audio recording of a ten-minute story or a temporally scrambled version of the story, or underwent a resting
73 state scan (Simony et al., 2016). We used a subset of the data to train across-participant classifiers to decode
74 listening times using a blend of neural features (comprising neural activity patterns, as well as different
75 orders of correlations between those patterns that were inferred using our computational framework).
76 We found that both the PCA-based and eigenvector centrality-based approaches yielded neural patterns
77 that could be used to decode accurately. Both approaches also yielded the best decoding accuracy for
78 data collected during (intact) story listening when high-order (PCA: second-order; eigenvector centrality:
79 fourth-order) dynamic correlation patterns were included as features. When we trained classifiers on the
80 scrambled stories or resting state data, only lower-order dynamic patterns were informative to the decoders.
81 Taken together, our results indicate that high-level cognition is supported by high-order dynamic patterns
82 of communication between brain structures.

83 Methods

84 Our general approach to comprises four general steps. First, we derive a kernel-based approach to com-
85 puting dynamic pairwise correlations in a T (timepoints) by K (features) multivariate timeseries, x_0 . This
86 yields a T by $O(K^2)$ matrix of dynamic correlations, y_1 , where each row comprises the upper triangle of the
87 correlation matrix at a single timepoint, reshaped into a row vector. Second, we apply a dimensionality
88 reduction step to project the matrix of dynamic correlations back onto a K -dimensional space. This yields a
89 T by K matrix, x_1 , that reflects an approximation of the dynamic correlations reflected in the original data.
90 Third, we use repeated applications of the kernel-based dynamic correlation step to x_n and the dimen-
91 sionality reduction step to the resulting y_{n+1} to estimate high-order dynamnic correlations. Each application
92 of these steps to a T by K time series x_n yields a T by K matrix, x_{n+1} , that reflects the dynamic correlations
93 between the columns of x_n . In this way, we refer to n as the *order* of the timeseries, where x_0 (order 0) denotes
94 the original data and x_n denotes n^{th} -order dynamic correlations between the columns of x_0 . Finally, we use

95 a cross-validation-based decoding approach to evaluate how well information contained in a given order
 96 (or weighted mixture of orders) may be used to decode relevant cognitive states. If including a given x_n in
 97 the feature set yields higher classification accuracy on held-out data, we interpret this as evidence that the
 98 given cognitive states are reflected in patterns of n^{th} -order correlations.

99 **JRM STOPPED HERE**

100 A major challenge to studying such patterns is that typically neither the correlations nor the hierarchical
 101 organizations of those correlations may be directly observed. Rather, these fundamental properties must
 102 be inferred indirectly by examining the observable parts of the system—e.g., the behaviors of the individual
 103 units of that system. Here we propose a series of mathematical operations that may be used to approximate
 104 dynamic correlations at a range of scales (i.e., orders of interaction).

105 There are two basic steps to our approach (Fig. 2). In the first step, we take a number-of-timepoints (T)
 106 by number-of-features (F) *matrix of observations* (\mathbf{X}) and we return a T by $\frac{F(F-1)}{2}$ *matrix of dynamic correlations*
 107 (\mathbf{Y}). Here \mathbf{Y}_0 describes, at each moment, how all of the features (columns of \mathbf{X}) are inferred to be interacting.
 108 (Since the interactions are assumed to be non-recurrent and symmetric, only the upper triangle of the full
 109 correlation matrix is computed.) In the second step, we project \mathbf{Y}_0 onto an F -dimensional space, resulting in
 110 a new T by F matrix \mathbf{Y}_1 . Note that \mathbf{Y}_1 contains information about the correlation dynamics present in \mathbf{X} , but
 111 represented in a compressed number of dimensions. By repeatedly applying these two steps in sequence,
 112 we can examine and explore higher order dynamic correlations in \mathbf{X} .

113 **Dynamic correlations**

Given a matrix of observations, we can compute the (static) correlations between any pair of observations,
 \mathbf{X}_i and \mathbf{X}_j using:

$$\text{corr}(\mathbf{X}_i, \mathbf{X}_j) = \frac{\sum_{t=1}^T (\mathbf{X}_i(t) - \bar{\mathbf{X}}_i)(\mathbf{X}_j(t) - \bar{\mathbf{X}}_j)}{\sqrt{\sum_{t=1}^T \sigma_{\mathbf{X}_i}^2 \sigma_{\mathbf{X}_j}^2}}, \text{ where} \quad (1)$$

$$\bar{\mathbf{X}}_k = \sum_{t=1}^T \mathbf{X}_k(t), \text{ and} \quad (2)$$

$$\sigma_{\mathbf{X}_k}^2 = \sum_{t=1}^T (\mathbf{X}_k(t) - \bar{\mathbf{X}}_k)^2 \quad (3)$$

114 We can generalize this formula to compute time-varying correlations by incorporating a *weight function*
 115 that takes a time t as input, and returns how much the observed data every timepoint (including t) contribute
 116 to the correlations at time t (Fig. 1).

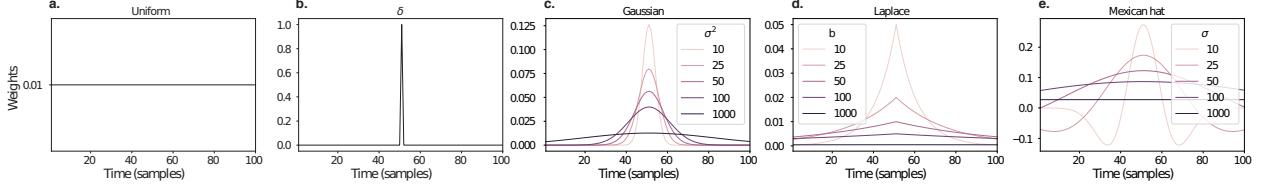


Figure 1: **Examples of time-varying weights.** Each panel displays per-timepoint weights at $t = 50$, evaluated for 100 timepoints (1, ..., 100). **a. Uniform weights.** The weights are timepoint-invariant; observations at all timepoints are weighted equally, and do not change as a function of t . This is a special case of weight function that reduces dynamic correlations to static correlations. **b. Dirac delta function.** Only the observation at timepoint t is given weight (of 1), and weights for observations at all other timepoints are set to 0. **c. Gaussian weights.** Each observation's weights fall off in time according to a Gaussian probability density function centered on $\mu = t$. Weights derived using several different example variance parameters (σ^2) are displayed. **d. Laplace weights.** Each observation's weights fall off in time according to a Laplace probability density function centered on $\mu = t$. Weights derived using several different example scale parameters (b) are displayed. **e. Mexican hat (Ricker wavelet) weights.** Each observation's weights fall off in time according to a Ricker wavelet centered on t . This function highlights the *contrasts* between local versus surrounding activity patterns in estimating dynamic correlations. Weights derived using several different example width parameters (σ) are displayed.

Given a weight function $w(t)$ for timepoint t , evaluated at timepoints in the interval $[1, \dots, T]$, we can extend the static correlation formula in Equation 2 to reflect an *instantaneous correlation* at timepoint t :

$$\text{timecorr}(\mathbf{X}_i, \mathbf{X}_j, t) = \frac{\sum_{t=1}^T (\mathbf{X}_i(t) - \tilde{\mathbf{X}}_i(t))(\mathbf{X}_j(t) - \tilde{\mathbf{X}}_j(t))}{\sqrt{\sum_{t=1}^T \tilde{\sigma}_{\mathbf{X}_i}^2(t) \tilde{\sigma}_{\mathbf{X}_j}^2(t)}}, \text{ where} \quad (4)$$

$$\tilde{\mathbf{X}}_k(t) = \sum_{i=1}^T w(t, i) \mathbf{X}_k(i), \quad (5)$$

$$\tilde{\sigma}_{\mathbf{X}_k}^2(t) = \sum_{i=1}^T (\mathbf{X}_k(i) - \tilde{\mathbf{X}}_k(t))^2, \quad (6)$$

¹¹⁷ and $w(t, i)$ is shorthand for $w(t)$ evaluated at timepoint i . Equation 5 may be used to estimate the instantaneous correlations between every pair of observations, at each timepoint (i.e., \mathbf{Y}).

¹¹⁹ Inter-subject dynamic correlations

Equation 5 provides a means of taking a single observation matrix, \mathbf{X} and estimating the dynamic correlations from moment to moment, \mathbf{Y} . Suppose that one has access to a set of multiple observation matrices that reflect the same phenomenon. For example, one might collect neuroimaging data from several experimental participants, as each participant performs the same task (or sequence of tasks). Let $\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_P$ reflect the T by F observation matrices for each of P participants in an experiment. We can use *inter-subject functional connectivity* (ISFC; Simony et al., 2016) to compute the degree of stimulus-driven correlations reflected in

the multi-participant dataset at a given timepoint t using:

$$\bar{\mathbf{C}}(t) = M \left(R \left(\frac{1}{2P} \sum_{i=1}^P Z(Y_i(t))^T + Z(Y_i, (t)) \right) \right), \quad (7)$$

where M extracts and vectorizes the diagonal and upper triangle of a symmetric matrix, Z is the Fisher z-transformation (Zar, 2010):

$$Z(r) = \frac{\log(1+r) - \log(1-r)}{2} \quad (8)$$

R is the inverse of Z :

$$R(z) = \frac{\exp(2z-1)}{\exp(2z+1)}, \quad (9)$$

and $\mathbf{Y}_i(t)$ denotes the correlation matrix (Eqn. 2) between each column of \mathbf{X}_i and each column of the average observations from all *other* participants, $\bar{\mathbf{X}}_{\setminus i}$:

$$\bar{\mathbf{X}}_i = R \left(\frac{1}{P-1} \sum_{i \in \setminus i} Z(\mathbf{X}_i) \right), \quad (10)$$

where $\setminus i$ denotes the set of all participants other than participant i . In this way, the T by $(\frac{F^2-F}{2} + F)$ matrix $\bar{\mathbf{C}}$ is the time-varying extension of the ISFC approach developed by Simony et al. (2016).

Higher-order correlations

Given a timeseries of dynamic correlations (e.g., obtained using Eqn. 5), higher-order correlations reflect the dynamic correlations between columns of \mathbf{Y} . Given unlimited computing resources, one could use repeated applications of Equation 5 to estimate these higher-order correlations (i.e., substituting in the previous output, \mathbf{Y} , for the input, \mathbf{X} in the equation). However, because each output \mathbf{Y} has $O(F^2)$ columns relative to F columns in the input \mathbf{X} , the output of Equation 5 grows with the square of the number of repeated applications (total cost of computing n^{th} order correlations is $O(F^{2n})$ for $n \in \mathcal{J}, n > 0$). When F or n is large, this approach quickly becomes intractable.

To make progress in computing \mathbf{Y}_{n+1} , we can approximate \mathbf{Y}_n by computing an $O(F)$ -dimensional embedding of \mathbf{Y}_n , termed $\hat{\mathbf{Y}}_n$, and then we can apply Equation 5 to $\hat{\mathbf{Y}}_n$ rather than directly to \mathbf{Y}_n . This enables us to maintain $O(n)$ scaling with respect to n , rather than exponential scaling via the direct approach.

There are many possible methods for computing $\hat{\mathbf{Y}}_n$ from \mathbf{Y}_n , including traditional dimensionality

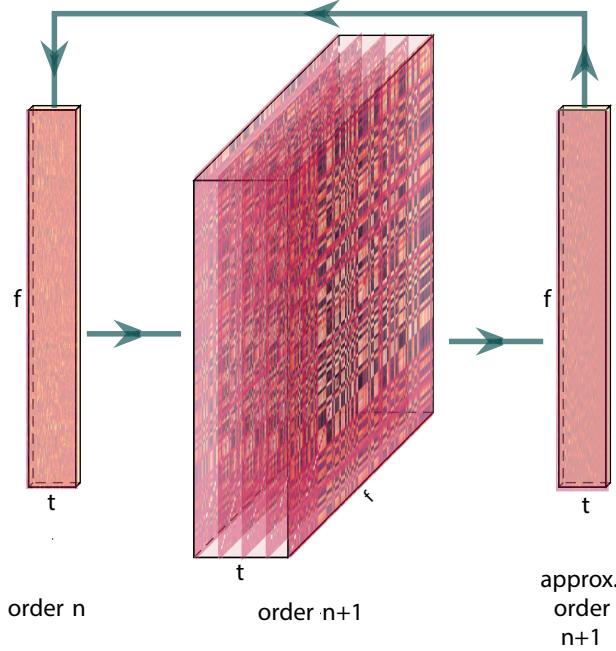


Figure 2: Computing higher order correlations. Dynamic correlations are computed then approximated to the same size as original data using dimensionality reduction. This process is repeated, and can be used to compute up to any arbitrary order with computations scaling linearly (as opposed to exponentially) with order.

134 reduction approaches and graph theory based approaches as described next. In the *Discussion* section we
 135 elaborate on other potential approaches.

136 **Dimensionality reduction-based approaches to computing $\hat{\mathbf{Y}}_n$**

137 Commonly used dimensionality reduction algorithms include Principal Components Analysis (PCA; Pear-
 138 son, 1901), Probabilistic PCA (PPCA; Tipping & Bishop, 1999), Exploratory Factor Analysis (EFA; Spearman,
 139 1904), Independent Components Analysis (ICA; Comon et al., 1991; Jutten & Herault, 1991), *t*-Stochastic
 140 Neighbor Embedding (*t*-SNE; van der Maaten & Hinton, 2008), Uniform Manifold Approximation and
 141 Projection (UMAP; McInnes & Healy, 2018), non-negative matrix factorization (NMF; Lee & Seung,
 142 1999), Topographic Factor Analysis (TFA) Manning et al. (2014), Hierarchical Topographic Factor analysis
 143 (HTFA) Manning et al. (2018), Topographic Latent Source Analysis (TLSA) Gershman et al. (2011), Dictio-
 144 nary learning (J. Mairal et al., 2009; J. B. Mairal et al., 2009), deep autoencoders (Hinton & Salakhutdinov,
 145 2006), among others. While complete characterizations of each of these algorithms is beyond the scope of
 146 the present manuscript, the general intuition driving these approaches is to compute the $\hat{\mathbf{Y}}$ with i columns
 147 that is closest to the original \mathbf{Y} with j columns, and where (typically) $i \ll j$. The different approaches place
 148 different constraints on what properties $\hat{\mathbf{Y}}$ must satisfy and which aspects of the data are compared (and

¹⁴⁹ how) to characterize the match between $\hat{\mathbf{Y}}$ and \mathbf{Y} .

¹⁵⁰ Applying dimensionality reduction algorithms to \mathbf{Y} yields a $\hat{\mathbf{Y}}$ whose columns reflect weighted combinations (or nonlinear transformations) of the original columns of \mathbf{Y} . This has two main consequences. First, ¹⁵¹ with each repeated dimensionality reduction, the resulting $\hat{\mathbf{Y}}_n$ has lower and lower fidelity (with respect to ¹⁵² what the “true” \mathbf{Y}_n might have looked like without using dimensionality reduction to maintain scalability). ¹⁵³ In other words, computing $\hat{\mathbf{Y}}_n$ is a lossy operation. Second, whereas the columns of \mathbf{Y}_n may be mapped ¹⁵⁴ directly onto pairs of columns of \mathbf{Y}_{n-1} , that mapping either becomes less cleanly defined in $\hat{\mathbf{Y}}_n$ due to the ¹⁵⁵ reweightings and/or nonlinear transformations.

¹⁵⁷ **Graph theory-based approaches to computing $\hat{\mathbf{Y}}_n$**

¹⁵⁸ Graph theoretic measures take as input a matrix of interactions (e.g., using the above notation, an $F \times F$ ¹⁵⁹ correlation matrix or binarized correlation matrix reconstituted from a single timepoint’s row of \mathbf{Y}) and ¹⁶⁰ return as output a set of F measures describing how each node (feature) sits within that interactions matrix ¹⁶¹ with respect to the rest of the population. Common measures include betweenness centrality (the proportion ¹⁶² of shortest paths between each pair of nodes in the population that involves the given node in question; e.g., ¹⁶³ Barthélémy, 2004; Freeman, 1977; Geisberger et al., 2008; Newman, 2005; Opsahl et al., 2010); diversity and ¹⁶⁴ dissimilarity (characterizations of how differently connected a given node is from others in the population; ¹⁶⁵ e.g., Lin, 2009; Rao, 1982; Ricotta & Szeidl, 2006); Eigenvector centrality and pagerank centrality (measures of ¹⁶⁶ how influential a given node is within the broader network; e.g., Bonacich, 2007; Halu et al., 2013; Lohmann ¹⁶⁷ et al., 2010; Newman, 2008); transfer entropy and flow coefficients (a measure of how much information is ¹⁶⁸ flowing from a given node to other nodes in the network; e.g., Honey et al., 2007; Schreiber, 2000); k -coreness ¹⁶⁹ centrality (a measure of the connectivity of a node within its local sub-graph; e.g., Alvarez-Hamelin et al., ¹⁷⁰ 2005; Christakis & Fowler, 2010); within-module degree (a measure of how many connections a node has to ¹⁷¹ its close neighbors in the network; e.g., Rubinov & Sporns, 2010); participation coefficient (a measure of the ¹⁷² diversity of a node’s connections to different sub-graphs in the network; e.g., Rubinov & Sporns, 2010); and ¹⁷³ sub-graph centrality (a measure of a node’s participation in all of the network’s sub-graphs; e.g., Estrada & ¹⁷⁴ Rodríguez-Velázquez, 2005).

¹⁷⁵ As an alternative to the above dimensionality reduction approach to embedding \mathbf{Y}_n in a lower-dimensional ¹⁷⁶ space, but still allowing for scalable explorations of higher-order structure in the data, we also explore using ¹⁷⁷ the above graph theoretic measures as a means of obtaining $\hat{\mathbf{Y}}_n$. In particular: for a given graph theoretic ¹⁷⁸ measure, $\eta : \mathcal{R}^{F \times F} \rightarrow \mathcal{R}^F$, we can use η to transform each row of \mathbf{Y}_n in a way that characterizes the ¹⁷⁹ corresponding graph-theoretic properties of each column. Whereas the dimensionality reduction approach

180 to computing $\hat{\mathbf{Y}}_n$ is lossy, the graph-theory approach is lossless. However, whereas the dimensionality
181 reduction approach maintains ties (direct or indirect) to the original activity patterns reflected in \mathbf{Y}_{n-1} , the
182 graph-theory approach does not. Instead, the graph-theory characterizes the nature and timecourse of each
183 feature's *participation* in the network.

184 Evaluation metrics

185 We evaluate our approach to extracting dynamic correlations and higher-order correlations using several
186 metrics detailed next. First, we generated synthetic data using known time-varying correlations, and then
187 we evaluated the fidelity with which Equation 5 could recover those correlations (for synthetic datasets
188 with different properties, and using different kernels to define the weights; Fig. 1). We then turned to a
189 series of analyses on a (real) neuroimaging dataset where the ground truth correlations were *not* known.
190 We evaluated whether the recovered correlations could be used to accurately label held-out neuroimaging
191 data with the time at which it was collected. We used this latter evaluations (using timepoint decoding)
192 as a proxy for gauging how much explanatory power the recovered correlations held with respect to the
193 observed data.

194 Generating synthetic data

195 To explore recovery of a constant covariance (Fig. 3, a.), we generated synthetic data sampled from a constant
196 covariance matrix. To do this, we created one random covariance matrix, K , with 50 features, and for each
197 of the 300 timepoints we sampled from a Gaussian distribution centered on K . Similarly, we generated
198 synthetic data sampled from a random covariance matrix (Fig. 3, b.) by creating a new random covariance
199 matrix $K(t)$, for each of the 300 timepoints and sampled from a Gaussian distribution centered on $K(t)$.

To generate synthetic data from a dynamically changing covariance matrix (Fig. 3, c.), we generated two
random covariance matrices, K_1 and K_2 . We then computed a weighted average covariance matrix for each
of the 300 timepoint, $K(t)$, by taking the linearly spaced weights (w) of the two random matrices,

$$K(t) = w(t) * K_1 + (1 - w(t)) * K_2, \quad (11)$$

$$(12)$$

200 and for each of the 300 timepoints sampled from a Gaussian distribution centered on $K(t)$.

201 Lastly, for the synthetic data containing block structure (Fig. 3, d.), we followed the same process of
202 creating synthetic data sampled from a constant covariance matrix (see above) but sampled from a new

203 random covariance matrix after 60 consecutive timepoints. We then pieced the blocks together to create a
204 synthetic dataset with 300 total timepoints but drawn from 5 separate covariance matrices.

205 **Recovery of ground truth parameters from synthetic data**

206 We applied timecorr, using delta and gaussian (width = 10) kernels Fig. 1) to each of these synthetic datasets,
207 then correlated each recovered correlation matrix with the ground truth. We repeated this process 10 times
208 and explored how recovery varies with the kernel and the specific structure of the data. For the ramping
209 synthetic dataset (Fig. 3, c.) and for the block synthetic dataset (Fig. 3, d.) we made further comparisons
210 of the timecorr recovered correlation matrices. We compared the ramping recovered correlation matrices to
211 only the first random covariance matrix K_1 (First, Fig. 3, c.) and to only the last random covariance matrix
212 K_2 (Last, Fig. 3, c.) from Equation 12. We also compared the block recovered correlation matrices in to the
213 block specific covariance matrix (Block 1-5, Fig. 3, d.).

214 **Timepoint decoding**

215 To explore how higher-order structure varies with stimulus structure and complexity, we used a previous
216 neuroimaging dataset Simony et al. (2016) in which participants listened to an audio recording of a story;
217 36 participants listen to an intact version of the story, 17 participants listen to time-scrambled recordings of
218 the same story where paragraphs were scrambled, 36 participants listen to word-scrambled version and 36
219 participants lay in rest condition.

220 Prior work has shown participants share similar neural responses to richly structured stimuli when
221 compared to stimuli with less structure. To assess whether the moment-by-moment higher order correlations
222 were reliably preserved across participants, we used inter-subject functional connectivity (ISFC) to isolate
223 the time-varying correlational structure (functional connectivity patterns that were specifically driven by
224 the story participants listened to. Following the analyses conducted by (HTFA) Manning et al. (2018), we
225 first applied *hierarchical topographic factor analysis* (HTFA) to the fMRI datasets to obtain a time series of
226 700 node activities for every participant. We then computed the dynamic weighted ISFC using a range of
227 kernels and widths. Specifically, we used Gaussian, Laplace, and mexican hat kernels, as well as widths of
228 5, 10, 20, and 50. We then approximated these dynamic correlation using two reduction measures, PCA and
229 eigenvector centrality, and computed the dynamic weighted ISFC on the approximations. We repeated this
230 process up to 10th order approximated correlations.

231 To assess decoding accuracy, we randomly divided participants for each stimulus into training and
232 testing groups. For the zeroth order, we computed the mean factor activity for each group. For all subsequent

233 orders up to the tenth order, we computed the mean approximated dynamic ISFC of factor activity for each
234 group. To assess how additional higher-order correlations contribute to decoding accuracy, for each order
235 we included a weighted-mixture (described below) of the activity patterns of all previous orders. For each
236 group of participants in turn, we compared these activity patterns (using Pearson correlations) to estimate
237 the story times each pattern corresponded to. Specifically, we asked, for each timepoint: what are the
238 correlations between the first group's and second group's activity patterns at each order. We note that the
239 decoding test we used is a conservative in which we count a timepoint label as incorrect if it is not an exact
240 match.

241 For each order we obtained the weighted-mixture of the correlation matrices for the current order and
242 all previous orders using mixing parameter, ϕ , where $0 < \phi < 1$ reflects a weighted mixture of order based
243 decoding Fig. 4 Panel c.). We calculated ϕ , by subdividing the training group and using the quasi-Newton
244 method of Broyden, Fletcher, Goldfarb, and Shanno (BFGS (Nocedal & Wright, 2006)) for optimization. We
245 repeated this cross-validation process 10 times for each parameter set.

246 Results

247 Synthetic data

248 To assess the performance of dynamic correlation recovery using timecorr, we varied width the kernel and
249 the specific structure of the data. We applied timecorr, using delta and gaussian kernels Fig. 1) to each of
250 the following synthetic datasets: constant, random, ramping, and block. We then correlated each recovered
251 correlation matrix with the ground truth.

252 For the constant synthetic dataset, a gaussian kernel (width=10) outperformed the delta kernel (Fig. 3,
253 a.). This is in contrast with the random synthetic dataset, for which the delta kernel best captures the rapidly
254 changing structure (Fig. 3, b.). For the ramping synthetic dataset, the slow changing strucutre within the
255 data is best captured by the gaussian kernel and the best recovery occurs in the middle (Ramping, Fig. 3,
256 c.). In addition to comparing the timecorr recovered correlation matrices to the ground truth, we further
257 compared the ramping recovered correlation matrices to only the first random covariance matrix K_1 (First,
258 Fig. 3, c.) and to only the last random covariance matrix K_2 (Last, Fig. 3, c.), both of which perform best at
259 the beginning and end respectively.

260 Similary for the block sythetic dataset, we compared the timecorr recovered correlation matrices to
261 the ground truth as well as to each block-specific covariance matrix (Block 1-5, Fig. 3, d.). Although the
262 structure is changing by block, the gaussian kernel once again outperforms the delta kernel. Performance

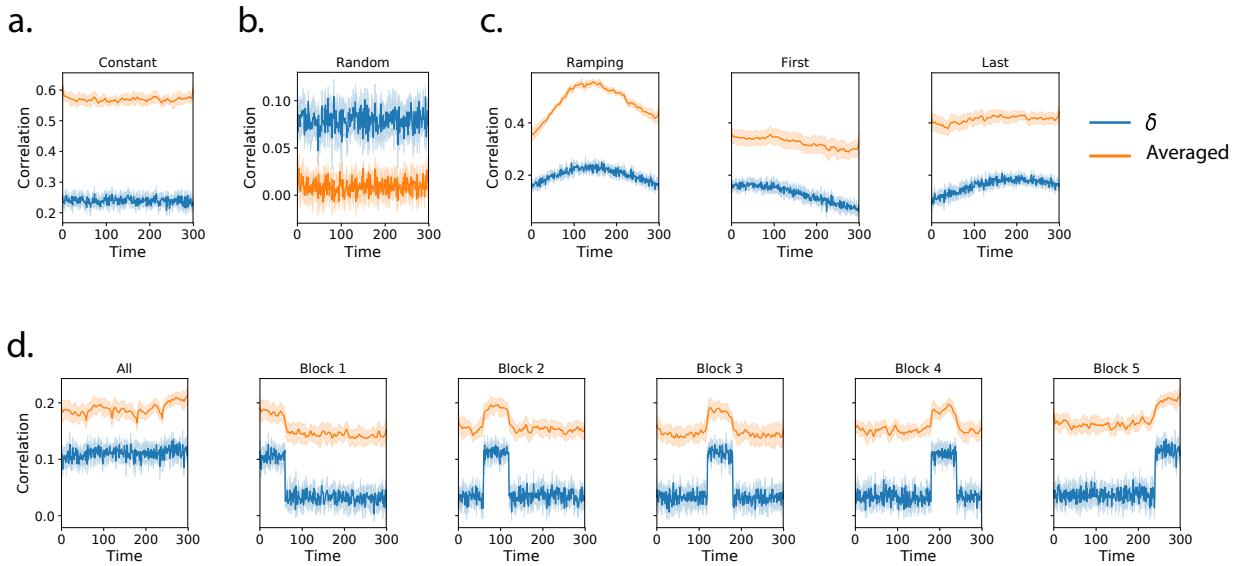


Figure 3: Dynamic correlation recovery with synthetic data. Using synthetic data containing different underlying correlational structure, we test how well we can recover dynamic correlation matrices using different kernels when compared to ground truth. We compare the results using a delta kernel with averaged results from several kernels (Gaussian, Laplace, and mexican hat) and several widths (5, 10, 20, and 50). We plot recovery using of datasets containing the following underlying structure: **a. Constant.** **b. Random.** **c. Ramping.** **d. Block.**

263 does however drop near even boundaries for when using the gaussian kernel.

264 Neuroimaging dataset (Simony et al., 2016)

265 For our decoding analysis, we used HTFA-derived node activities Manning et al. (2018) from fMRI data
 266 collected as participants listened to an audio recording of a story (intact condition; 36 participants), lis-
 267 tened to time scrambled recordings of the same story (17 participants in the paragraph-scrambled condition
 268 listened to the paragraphs in a randomized order and 36 in the word-scrambled condition listened to
 269 the words in a randomized order), or lay resting with their eyes open in the scanner (rest condition; 36
 270 participants). We sought to demonstrate how higher-order correlations may be used to examine dynamic
 271 interactions of brain patterns in (real) multi-subject fMRI datasets. This story listening dataset was col-
 272 lected as part of a separate study, where the full imaging parameters, image preprocessing methods, and
 273 experimental details may be found (Simony et al., 2016). The dataset is available at <http://arks.princeton.edu/ark:/88435/dsp015d86p269k>.

275 We next evaluated if our model of high-order correlations in brain activity can capture cognitively
 276 relevant brain patterns. We performed a decoding analysis, using cross validation to estimate (using other
 277 participants' data) which parts of the story each weighted-mixture of higher-order brain activity pattern

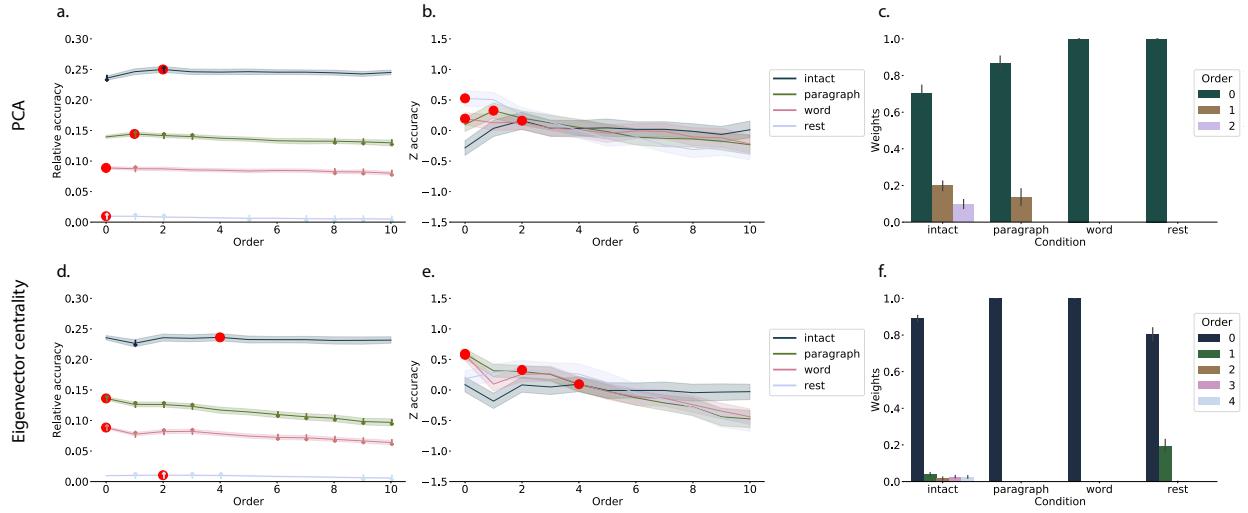


Figure 4: **Decoding by order.** **a.&d. Relative decoding accuracy by order.** Ribbons of each color display cross-validated decoding performance averaged over all parameters for each condition (intact, paragraph, word, and rest) using PCA (a.) or eigenvector centrality (d.) to approximate correlations. Decoders were trained using increasingly more higher-order information and this ribbon are displayed relative to chance at 0. The red dots indicates maximum decoding accuracy for each condition. **b.&e. Z-transformed decoding accuracy by order.** We Z-transformed the decoding accuracy by order to better visualize the order with the maximum decoding accuracy for each condition using PCA (b.) or eigenvector centrality (e.) to approximate correlations. **c.&f. Optimized weights.** Bar heights indicate the optimized mixing parameter ϕ of each contributing order up to and including the order with the maximum decoding accuracy for each contributing order using PCA (c.) or eigenvector centrality (f.) to approximate correlations. For the order with maximum decoding accuracy by condition, we show barplots of the optimized weights ϕ for each contributing order.

278 corresponded to (see *Materials and methods*). We note that our primary goal was not to achieve perfect
279 decoding accuracy, but rather to use decoding accuracy as a benchmark for assessing whether different
280 neural features specifically capture cognitively relevant brain patterns.

281 Separately for each experimental condition, we divided participants into two groups. For the zeroth
282 order, we computed the mean factor activity for each group. For all subsequent orders up to the tenth
283 order, we computed the mean approximated dynamic ISFC of factor activity for each group (see *Materials*
284 and *methods*), and combined in a weighted mixutre with all previous orders (i.e. cross-validation for the
285 second order contained a weighted-mixture of zeroth, first, and second order (Fig. 4, c.&f.). For each
286 order, we correlated the group 1 activity patterns with group 2 activity patterns. We then subdivided
287 the group 1 to obtain an optimal weighting parameter for each order's correlation matrix using the same
288 cross validation method. We used the optimal weighting parameters to obtain a weighted-mixture (see
289 *Materials and methods*) of each order's correlation matrix. Using these correlations, we labeled the group 1
290 timepoints using the group 2 timepoints with which they were most highly correlated; we then computed
291 the proportion of correctly labeled group 1 timepoints. (We also performed the symmetric analysis whereby
292 we labeled the group 2 timepoints using the group 1 timepoints as a template.) We repeated this procedure
293 100 times (randomly re-assigning participants to the two groups each time) to obtain a distribution of
294 decoding accuracies for each experimental condition. There were 272 timepoints for paragraph condition,
295 300 timepoints for intact and word conditions, and 400 timepoints for rest condition, so chance performance
296 on this decoding test is was $\frac{1}{272}$, $\frac{1}{300}$, and $\frac{1}{400}$ respectively.

297 We repeated this process for each set of parameters, varying kernel type and width, and averaged over the
298 reduction technique used to approximate the higher-order correlations (PCA Fig. 4, a.-c. and eigenvector
299 centrality Fig. 4, d.-f.). Since there is no ground truth in these analyses, and we did not know which
300 parameters best capture the data, we instead report a robustness search by averaging over the parameters
301 and reporting which results consistently showed up across all parameters.

302 The two methods used to approximate the higher-order correlations (PCA Fig. 4, a.-c. and eigenvector
303 centrality Fig. 4, d.-f.) capture different facets of the activity patterns. Using PCA, the higher-order
304 correlations are all linked to the original activity patterns, whereas eigenvectory centrality breaks the
305 immediate link with specific brain areas and instead characterizes the position of the nodes in the network
306 that are similar over time.

307 We found for both PCA and eigenvector centrality, during the intact condition in the experiment,
308 classifiers that incorporated higher-order correlations yielded consistently higher accuracy than classifiers
309 trained only on lower-order patterns (Fig. 4, a.&d.). We plot the average correlations for up to the fourth
310 order for the intact condition (Fig. 5) representing the degree of agreement by location pair over time. By

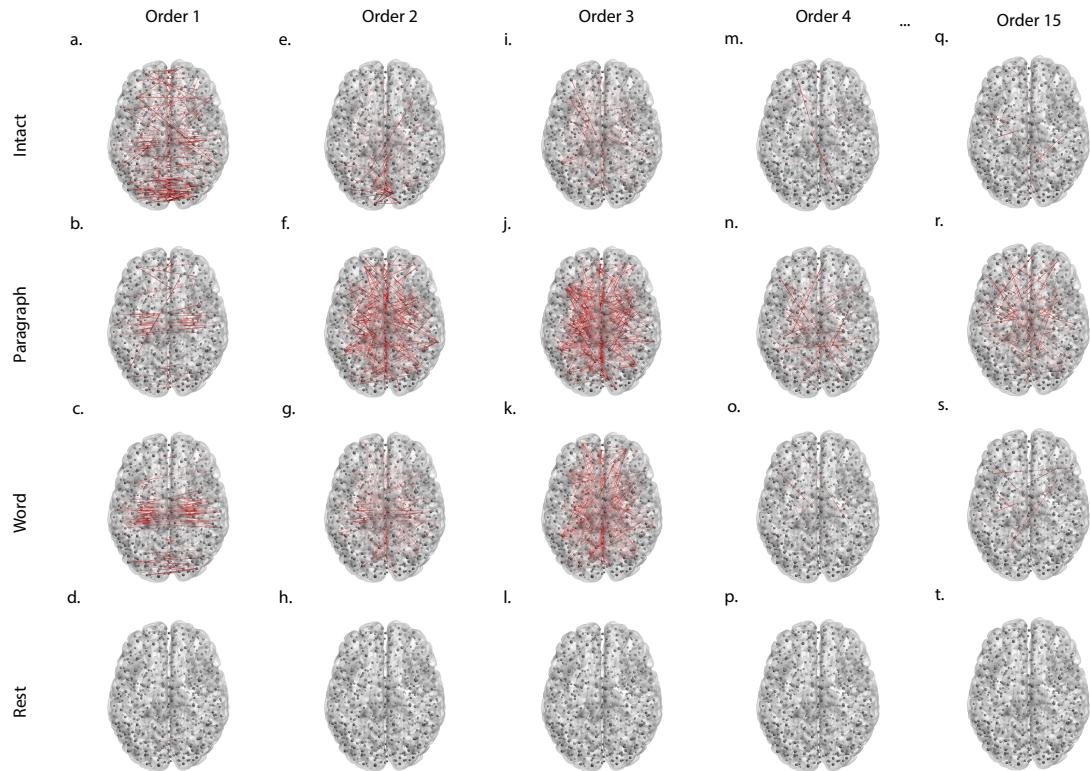


Figure 5: Average correlations by order for the intact listening condition. Using eigenvector centrality to approximate higher-order correlations for the intact, paragraph scrambled, word scrambled, and rest condition. We plot the strongest 50% absolute value mean correlation for **a.-d. first order, e.-h. second order, i.-l. third order, and m.-p. fourth order**, representing the degree of agreement by location pair over time. To demonstrate how this method is computationally scalable, we also approximated **a.-d. fifteenth order** dynamic correlation, which would be possible to compute using conventional methods since it would require more bits to represent the solution than there are molecules in the universe.

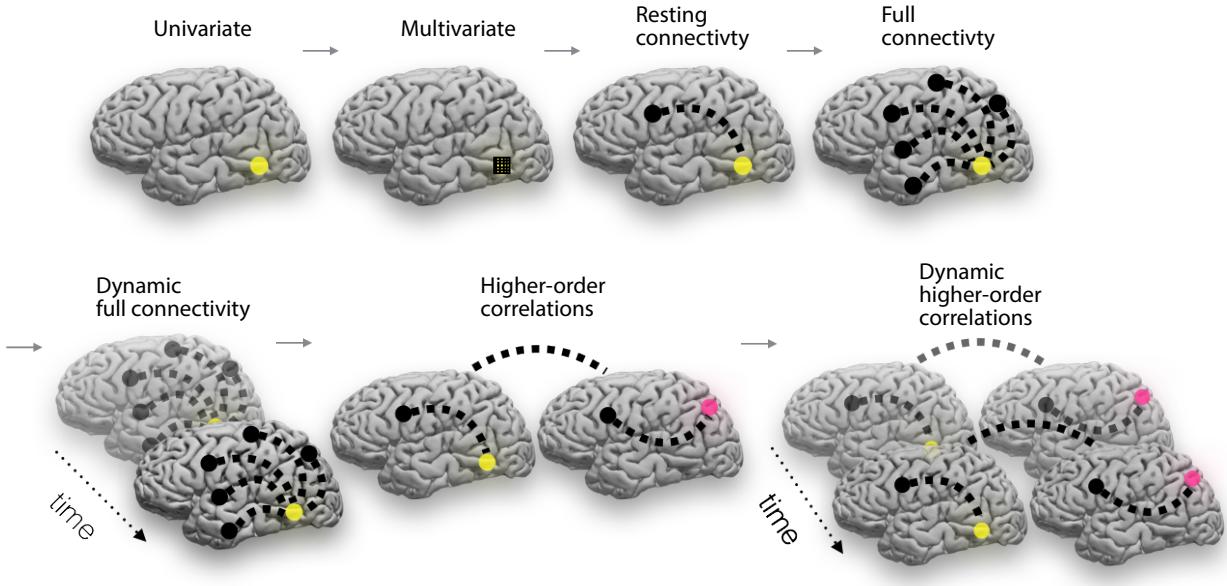


Figure 6: Direction of the field (adapted from (Turk-Browne, 2013)). The evolution of fMRI analyses started with univariate activation, which refers to the average amplitude of BOLD activity evoked by events of an experimental condition. Next, multivariate classifiers are trained on patterns of activation across voxels to decode distributed representations for specific events. The next, resting connectivity, is the temporal correlation of one or more seed regions with the remainder of the brain during rest. Additionally, task-based connectivity examines how these correlations differ by cognitive state. Following this increasing trajectory of increasing complexity, full connectivity considers all pairwise correlations in the brain, most commonly at rest. Next, dynamic full connectivity considers how full connectivity changes over time. Continuing this line of reasoning, we expect higher-order network dynamics might provide even richer insights into the neural basis of cognition.

311 contrast, we found that incorporating higher-order (greater than first order) correlations did not further
 312 improve decoding accuracy for the other listening conditions or rest condition. This suggests that the
 313 cognitive processing that supported the most cognitively rich condition involved higher-order network
 314 dynamics.

315 Discussion

316 Based on prior work (Demertzis et al., 2019) and following the direction of the field (Turk-Browne, 2013)
 317 we think our thoughts might be encoded in dynamic network patterns, and possibly higher order network
 318 patterns (Fig. 6). We sought to test this hypothesis by developing an approach to inferring high-order
 319 network dynamics from timeseries data.

320 One challenge in studying dynamic interactions is the computational resources required to calculate
 321 higher-order correlations. We developed a computationally tractable model of network dynamics (Fig. 2)
 322 that takes in a feature timeseries and outputs approximated first-order dynamics (i.e., dynamic functional

323 correlations), second-order dynamics (reflecting homologous networks that dynamically form and disperse),
324 and higher-order network dynamics (up to tenth-order dynamic correlations).

325 We first validated our model using synthetic data, and explored how recovery varied with different
326 underlying data structures and kernels. We then applied the approach to an fMRI dataset (Simony et al.,
327 2016) in which participants listened to an audio recording of a story, as well as scrambled versions of the
328 same story (where the scrambling was applied at different temporal scales). We trained classifiers to take
329 the output of the model and decode the timepoint in the story (or scrambled story) that the participants
330 were listening to. We found that, during the intact listening condition in the experiment, classifiers that
331 incorporated higher-order correlations yielded consistently higher accuracy than classifiers trained only
332 on lower-order patterns (Fig. 4, a.&d.). By contrast, these higher-order correlations were not necessary
333 to support decoding the other listening conditions and (minimally above chance) during a control rest
334 condition. This suggests that the cognitive processing that supported the most cognitively rich listening
335 conditions involved second-order (or higher) network dynamics.

336 Although we found decoding accuracy was best when incorporating higher-order network dynamics
337 for all but rest condition, it is unclear if this is a product of the brain or the data collection technique. It could
338 be that the brain is second-order or it could be that fMRI can only reliably give second-order interactions.
339 Exploring this method with other data collection technique will be important to disentangle this question.

340 Concluding remarks

341 How can we better understand how brain patterns change over time? How can we quantify the potential
342 network dynamics that might be driving these changes? One way to judge the techniques of the future is
343 to look at the trajectory of the fMRI field so far has taken so far (Fig. 2). The field started with univariate
344 activation, measuring the average activity for each voxel. Analyses of multivariate activation followed,
345 looking at spatial patterns of activity over voxels. Next, correlations of activity were explored, first with
346 measures like resting connectivity that take temporal correlation between a seed voxel and all other voxels
347 then with full connectivity that measure all pairwise correlations. Additionally, this path of increasing
348 complexity also moved from static to dynamic measurements. One logical next step in this trajectory would
349 be dynamic higher-order correlations. We have created a method to support these calculations by scalably
350 approximating dynamic higher-order correlations.

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358 **Author contributions**

359 Concept: J.R.M. Implementation: T.H.C., L.L.W.O., and J.R.M. Analyses: L.L.W.O and J.R.M.

360 **References**

- 361 Alvarez-Hamelin, I., Dall'Asta, L., Barrat, A., & Vespignani, A. (2005). *k*-corr decomposition: a tool for the
362 visualization of large scale networks. *arXiv*, cs/0504107v2.
- 363 Barthélémy, M. (2004). Betweenness centrality in large complex networks. *European Physical Journal B*, 38,
364 163–168.
- 365 Bassett, D., Meyer-Lindenberg, A., Achard, S., Duke, T., & Bullmore, E. (2006, December). Adaptive
366 reconfiguration of fractal small-world human brain functional networks. *Proceedings of the National
367 Academy of Sciences, USA*, 103(51), 19518-23.
- 368 Bonacich, P. (2007). Some unique properties of eigenvector centrality. *Social Networks*, 29(4), 555–564.
- 369 Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and
370 functional systems. *Nature Reviews Neuroscience*, 10(3), 186–198.
- 371 Christakis, N. A., & Fowler, J. H. (2010). Social network sensors for early detection of contagious outbreaks.
372 *PLoS One*, 5(9), e12948.
- 373 Comon, P., Jutten, C., & Herault, J. (1991). Blind separation of sources, part II: Problems statement. *Signal
374 Processing*, 24(1), 11 - 20.

- 375 Demertzi, A., Tagliazucchi, E., Dehaene, S., Deco, G., Barttfeld, P., Raimondo, F., ... Sitt, J. D. (2019). Human
376 consciousness is supported by dynamic complex patterns of brain signal coordination. *Science Advances*,
377 5(2), eaat7603.
- 378 Estrada, E., & Rodríguez-Velázquez, J. A. (2005). Subgraph centrality in complex networks. *Physical Review
379 E*, 71(5), 056103.
- 380 Etzel, J. A., Gazzola, V., & Keysers, C. (2009). An introduction to anatomical ROI-based fMRI classification.
381 *Brain Research*, 1282, 114–125.
- 382 Fong, A. H. C., Yoo, K., Rosenberg, M. D., Zhang, S., Li, C.-S. R., Scheinost, D., ... Chun, M. M. (2019).
383 Dynamic functional connectivity during task performance and rest predicts individual differences in
384 attention across studies. *NeuroImage*, 188, 14–25.
- 385 Freeman, L. C. (1977). A set of measures of centrality based on betweenness. *Sociometry*, 40(1), 35–41.
- 386 Geisberger, R., Sanders, P., & Schultes, D. (2008). Better approximation of betweenness centrality. *Proceedings
387 of the meeting on Algorithm Engineering and Experiments*, 90–100.
- 388 Gershman, S., Blei, D., Pereira, F., & Norman, K. (2011). A topographic latent source model for fMRI data.
389 *NeuroImage*, 57, 89–100.
- 390 Halu, A., Mondragón, R. J., Panzarasa, P., & Bianconi, G. (2013). Multiplex PageRank. *PLoS One*, 8(10),
391 e78293.
- 392 Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and
393 overlapping representations of faces and objects in ventral temporal cortex. *Science*, 293, 2425–2430.
- 394 Hinton, G. E., & Salakhutdinov, R. R. (2006). Reducing the dimensionality of data with neural networks.
395 *Science*, 313(5786), 504–507.
- 396 Honey, C. J., Kotter, R., Breakspear, M., & Sporns, O. (2007). Network structure of cerebral cortex shapes
397 functional connectivity on multiple time scales. *Proceedings of the National Academy of Science USA*, 104(24),
398 10240–10245.
- 399 Huth, A. G., de Heer, W. A., Griffiths, T. L., Theunissen, F. E., & Gallant, J. L. (2016). Natural speech reveals
400 the semantic maps that tile human cerebral cortex. *Nature*, 532, 453–458.
- 401 Huth, A. G., Nisimoto, S., Vu, A. T., & Gallant, J. L. (2012). A continuous semantic space describes
402 the representation of thousands of object and action categories across the human brain. *Neuron*, 76(6),
403 1210–1224.

- 404 Jutten, C., & Herault, J. (1991). Blind separation of sources, part I: An adaptive algorithm based on
405 neuromimetic architecture. *Signal Processing*, 24(1), 1–10.
- 406 Kamitani, Y., & Tong, F. (2005). Decoding the visual and subjective contents of the human brain. *Nature*
407 *Neuroscience*, 8, 679–685.
- 408 Landau, E. (1895). Zur relativen Wertbemessung der Turnierresultate. *Deutsches Wochenschach*, 11, 366–369.
- 409 Lee, D. D., & Seung, H. S. (1999). Learning the parts of objects by non-negative matrix factorization. *Nature*,
410 401, 788–791.
- 411 Lin, J. (2009). Divergence measures based on the Shannon entropy. *IEEE Transactions on Information Theory*,
412 37(1), 145–151.
- 413 Lohmann, G., Margulies, D. S., Horstmann, A., Pleger, B., Lepsién, J., Goldhahn, D., … Turner, R. (2010).
414 Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain.
415 *PLoS One*, 5(4), e10232.
- 416 Mairal, J., Ponce, J., Sapiro, G., Zisserman, A., & Bach, F. R. (2009). Supervised dictionary learning. *Advances*
417 *in Neural Information Processing Systems*, 1033–1040.
- 418 Mairal, J. B., Bach, F., Ponce, J., & Sapiro, G. (2009). Online dictionary learning for sparse coding. *Proceedings*
419 *of the 26th annual international conference on machine learning*, 689–696.
- 420 Manning, J. R., Ranganath, R., Norman, K. A., & Blei, D. M. (2014). Topographic factor analysis: a Bayesian
421 model for inferring brain networks from neural data. *PLoS One*, 9(5), e94914.
- 422 Manning, J. R., Zhu, X., Willke, T. L., Ranganath, R., Stachenfeld, K., Hasson, U., … Norman, K. A. (2018).
423 A probabilistic approach to discovering dynamic full-brain functional connectivity patterns. *NeuroImage*,
424 180, 243–252.
- 425 McInnes, L., & Healy, J. (2018). t-SNE: Uniform manifold approximation and projection for dimension
426 reduction. *arXiv*, 1802(03426).
- 427 Mitchell, T., Shinkareva, S., Carlson, A., Chang, K., Malave, V., Mason, R., & Just, M. (2008). Predicting
428 human brain activity associated with the meanings of nouns. *Science*, 320(5880), 1191.
- 429 Newman, M. E. J. (2005). A measure of betweenness centrality based on random walks. *Social Networks*, 27,
430 39–54.
- 431 Newman, M. E. J. (2008). The mathematics of networks. *The New Palgrave Encyclopedia of Economics*, 2, 1–12.

- 432 Nishimoto, S., Vu, A., Naselaris, T., Benjamini, Y., Yu, B., & Gallant, J. (2011). Reconstructing visual
433 experience from brain activity evoked by natural movies. *Current Biology*, 21, 1 - 6.
- 434 Nocedal, J., & Wright, S. J. (2006). *Numerical optimization*. New York: Springer.
- 435 Norman, K. A., Newman, E., Detre, G., & Polyn, S. M. (2006). How inhibitory oscillations can train neural
436 networks and punish competitors. *Neural Computation*, 18, 1577–1610.
- 437 Opsahl, T., Agneessens, F., & Skvoretz, J. (2010). Node centrality in weighted networks: generalizing degree
438 and shortest paths. *Social Networks*, 32, 245–251.
- 439 Pearson, K. (1901). On lines and planes of closest fit to systems of points in space. *The London, Edinburgh,
440 and Dublin Philosophical Magazine and Journal of Science*, 2, 559-572.
- 441 Pereira, F., Lou, B., Pritchett, B., Ritter, S., Gershman, S. J., Kanwisher, N., ... Fedorenko, E. (2018). Toward
442 a universal decoder of linguistic meaning from brain activation. *Nature Communications*, 9(963), 1–13.
- 443 Rao, C. R. (1982). Diversity and dissimilarity coefficients: a unified approach. *Theoretical Population Biology*,
444 21(1), 24–43.
- 445 Ricotta, C., & Szeidl, L. (2006). Towards a unifying approach to diversity measures: Bridging the gap
446 between the Shannon entropy and Rao's quadratic index. *Theoretical Population Biology*, 70(3), 237–243.
- 447 Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpreta-
448 tions. *NeuroImage*, 52, 1059–1069.
- 449 Schreiber, T. (2000). Measuring information transfer. *Physical Review Letters*, 85(2), 461–464.
- 450 Simony, E., Honey, C. J., Chen, J., & Hasson, U. (2016). Uncovering stimulus-locked network dynamics
451 during narrative comprehension. *Nature Communications*, 7(12141), 1–13.
- 452 Spearman, C. (1904). General intelligence, objectively determined and measured. *American Journal of
453 Psychology*, 15, 201–292.
- 454 Sporns, O., & Honey, C. J. (2006). Small worlds inside big brains. *Proceedings of the National Academy of
455 Science USA*, 103(51), 19219–19220.
- 456 Tipping, M. E., & Bishop, C. M. (1999). Probabilistic principal component analysis. *Journal of Royal Statistical
457 Society, Series B*, 61(3), 611–622.
- 458 Tong, F., & Pratte, M. S. (2012). Decoding patterns of human brain activity. *Annual Review of Psychology*, 63,
459 483–509.

- 460 Turk-Browne, N. B. (2013). Functional interactions as big data in the human brain. *Science*, 342, 580–584.
- 461 van der Maaten, L. J. P., & Hinton, G. E. (2008). Visualizing high-dimensional data using t-SNE. *Journal of
462 Machine Learning Research*, 9, 2579-2605.
- 463 Zar, J. H. (2010). *Biostatistical analysis*. Prentice-Hall/Pearson.