Fundamental Units of Inter-Individual Variation in Resting State Connectomes

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Abstract

Resting state functional connectomics holds the promise of illuminating and predicting individual differences in behavioral and clinical phenotypes. To realize this goal, however, it is critical to gain greater understanding of the nature, kind, and extent of population-wide inter-individual connectomic variation. We examined whole-brain resting state functional connectomes from healthy young adults from the Human Connectome Project 1200 release. We found clear evidence of low rank structure in which a modest number of connectomic components, around 50-150, account for a sizable portion of cross-individual connectomic variation. This number was convergently arrived at with multiple methods including estimation of intrinsic dimensionality and assessment of reconstruction of out-of-sample data. In addition, we show that these connectomic components enable prediction of a broad array of neurocognitive and clinical symptom variables at levels comparable to a leading method that is trained on the whole connectome. Qualitative observation reveals that these connectomic components exhibit extensive community structure reflecting interrelationships between intrinsic connectivity networks. We provide quantitative validation of this observation using novel stochastic block model-based methods. We propose that the fundamental connectivity units identified in this study form an effective basis set for quantifying and interpreting inter-individual connectomic differences, and for predicting behavioral and clinical phenotypes.

1 Introduction

Resting state functional connectomics has emerged as a leading method for mapping the organization of human brain networks [1, 2, 3]. In addition, it presents a major opportunity for elucidation of the brain basis of individual differences [4]: functional networks are thought to be critical substrates for major neurocognitive and behavioral phenotypes [5], so across-individual differences in network organizations may predict differences in these phenotypes [4]. The

eventual goal is to refine phenotypic prediction sufficiently that functional connectomes can serve as reliable, objective "biomarkers" of clinically meaningful traits and dimensions [6, 7].

Notably, while attempts to utilize functional connectomes for prediction of individual differences are numerous [6, 8], attempts to descriptively assess the nature, kind, and extent of population-wide inter-individual functional connectomic variation remain scarce [9, 10]. One important open question concerns the dimensionality of inter-individual variation.

In high-dimensional data, there is often substantial dependency in the feature set, and it is often useful for a wide of variety of purposes—computation, interpretation, explanation, and prediction—to identify low rank structure in the data, i.e., major units that explain a substantial portion of the variation. Over the last 15 years, there has been extensive work in detecting low rank structure in *intra-individual* across-time variation in the connectome, i.e., the tendency of distributed brain regions to exhibit coherent fluctuations in their BOLD time series [11, 12, 13]. This work has culminated in the identification of a small number of intrinsic connectivity networks (ICNs)—e.g., default mode network (DMN) and fronto-parietal network (FPN)—as "fundamental units" of intra-individual cross-time variation [2, 3, 14]. These units, in turn, have played central roles in recent models and explanations of cognitive capacities and behavioral phenotypes [15, 16, 17].

Importantly, however, there have not been corresponding systematic attempts to identify low rank structure in patterns of *inter-individual* variation (but see [18, 19] for limited attempts). This is the question we address in this study. That is, analogous to the intra-individual case, are there major units of inter-individual variation that explain a sizable portion of cross-individual connectomic differences, and that can be effectively harnessed for the purposes of understanding and predicting phenotypes of interest?

In this study, we provide evidence that the answer to this question is yes. Using convergent methods, we show that a modest number of connectivity components, around 50-150, do indeed capture a sizable share of inter-individual differences, and they together constitute a highly effective basis set for phenotypic prediction. Thus, while the resting state connectome is a massive and complex object encompassing tens to hundreds of thousands of connections (depending on the parcellation), differences in a fairly small set of fundamental units explain a sizable portion of how any two individuals meaningfully differ.

2 Methods

2.1 Data Acquisition

All data were from the HCP-1200 release [20]. Four runs of resting state fMRI data (14.5 minutes each; two runs per day over two days) were acquired on a modified Siemans Skyra 3T scanner using multiband gradient-echo EPI (TR=720ms, TE=33ms, flip angle=52, multiband acceleration factor=8, 2mm

isotropic voxels, FOV=208x180mm, 72 slices, alternating RL/LR phase encode direction). T1 weighted scans were acquired with 3D MPRAGE sequence (TR=2400ms, TE=2.14ms, TI=1000ms, flip angle=8, 0.7mm isotropic voxels, FOV=224mm, 256 sagittal slices). T2 weighted scans were acquired with a Siemens SPACE sequence (TR=3200ms, TE=565ms, 0.7mm isotropic voxels, FOV=224mm, 256 sagittal slices).

Subjects were eligible to be included if they had structural T1 and T2 data and had 4 complete resting state fMRI runs (1206 subjects total in release files, 1003 with full resting state and structural).

2.2 Data Preprocessing

Processed volumetric data from the HCP minimal preprocessing pipeline including ICA-FIX denoising were used. Full details of these steps can be found in [21] and [22]. Briefly, T1w and T2w data were corrected for gradient-nonlinearity and readout distortions, inhomogeneity corrected, and registered linearly and non-linearly to MNI space using FSL's FLIRT and FNIRT. blood oxygen level dependent (BOLD) resting state fMRI data were also gradient-nonlinearity distortion corrected, rigidly realigned to adjust for motion, fieldmap corrected, aligned to the structural images, and then registered to MNI space with the nonlinear warping calculated from the structural images. Then FIX was applied on the data to identify and remove motion and other artifacts in the time series. These files were used as a baseline for further processing and analysis (e.g. `MNINonLinear/Results/rfMRI_REST1_RL/rfMRI_REST1_RL_hp2000_clean.nii.gz` from released HCP data).

Images were smoothed with a 6mm FWHM Gaussian kernel, and then resampled to 3mm isotropic resolution. This step as well as the use of the volumetric data, rather than the surface data, were done to allow comparability with other large datasets in ongoing and planned analyses that are not amenable to surface-based processing.

The smoothed images then went through a number of resting state processing steps, including motion artifact removal steps comparable to the type B (i.e., recommended) stream of Siegel *et al.* [23]. These steps include linear detrending, CompCor to extract and regress out the top 5 principal components of white matter and CSF [24], bandpass filtering from 0.1-0.01Hz, and motion scrubbing of frames that exceed a framewise displacement of 0.5mm. Subjects with more than 10% of frames censored were excluded from further analysis, leaving 966 subjects. A resting state quality control plot [25] relating motion effects by edge length showed a near zero mean (0.006), low dispersion around the mean (sd 0.06) and absence of a meaningful distance-dependent relationship.

2.3 Connectome Generation

We next calculated spatially-averaged time series for each of 264 4.24mm radius ROIs from the parcellation of Power *et al.* [14]. We then calculated Pearson's

correlation coefficients between each ROI. These were then were transformed using Fisher's r to z-transformation.

2.4 Train/Test/Retest Split

The 966 subjects after exclusions were divided into three groups. First, 38 subjects who had two separate completed scans were pulled aside for later test-retest reliability analysis. Of the remaining subjects, 18 did not have complete behavioral data for our analyses so were excluded. Next, 100 unrelated subjects were randomly selected from all unrelated subjects to serve as our held-out test set, with the other 810 serving as our training set.

2.5 Estimation of Intrinsic Dimensionality

In the training dataset, each subject's connectome was vectorized and concatenated yielding an 810 subjects x 34,716 connections matrix. We estimated the number of intrinsic dimensions of this matrix using two methods.

First, we used a maximum likelihood estimation method based on distance between close neighbors [26], appropriate for low-dimensional data that is embedded in a high-dimensional space in a complicated, potentially non-linear, fashion. Levina and Bickel [26] provides a full derivation of the estimator using a Poisson approximation and demonstrates improved performance relative to alternatives in simulated and real data. The method averages over a range of values of k, the number of nearest neighbors, from k_1 to k_2. We used the default values $k_1 = 10$ to $k_2 = 20$ suggested by the original analysis.

Second, we used the method of Choi *et al.* [27], which attempts to calculate an upper bound on the on the number of dimensions with exact type 1 error control. This is a distribution-based method that leverages a post-selection inference framework, and extends the work of Taylor, Loftus, and Tibshirani [28] to the PCA setting.

To visualize the presence of low rank structure, we ordered the components by eigenvalue (i.e., percent variance explained), and plotted these eigenvalues. Next, we constructed a null distribution of eigenvalues by permutation methods. Specifically, we permuted columns of the data matrix separately for each subject. We plotted the permutation mean and 95% confidence interval for the null distribution.

2.6 Principal Component Analysis

The subjects x connections matrix from the training dataset was next submitted to principal components analysis using the pca function in MATLAB, yielding 809 components ordered by descending eigenvalues.

2.7 Assessing Out-of-Sample Reconstruction

We examined the ability of an n-sized basis set (consisting of the first n PCA components ordered by descending eigenvalues), to reconstruct out-of-sample data, systematically varying the size of n. First, a full set of 809 PCA components were learned on the training dataset. Next, for each value of n from 1 to 809, we did the following: Using multiple regression, each subject in the test dataset was reconstructed as linear combination of the components of a n-sized basis set. Goodness of reconstruction was measured by calculating the Pearson's correlation across edges between actual versus reconstructed connectomes for each subject and averaging across subjects.

2.8 Assessing Phenotypic Prediction

2.8.1 HCP Phenotypic Measures

We used a total of 11 phenotypes from the HCP data. Factor analysis, implemented in SPSS 23, was used to produce two neuropsychological factors. First, a general executive factor was created based on overall accuracy for three tasks: n-back working memory task, relational processing task, and Penn Progressive Matrices task. Factor loadings were 0.81, 0.80, and 0.76 respectively, and the factor accounted for 62.2% of the variance in the variables. A speed of processing variable was created based on three NIH toolbox tasks: processing speed, flanker task, and card sort task (all age-adjusted performance), similar to Carlozzi *et al.* [29]. Of note, for subjects with accuracy above 80% (which is nearly everyone in this sample), performance scoring on the latter two tasks is based exclusively on reaction time. This variable had loadings of 0.75, 0.81, and 0.82 respectively, and the factor accounted for 63.0% of the variance in the variables. From the Adult Self Report (ASR) instrument [30], we used three scale-derived summary scores for psychopathology: overall internalizing, overall externalizing, and attention. In addition, from the Neuroticism/Extroversion/Openness Five Factor Inventory instrument [31], we used the five personality factors: openness to experience, conscientiousness, extroversion, agreeableness, and neuroticism. Finally, we used the Penn Progressive Matrices task by itself as it has been featured in other connectome-based prediction studies of HCP data [32, 33].

In an additional analysis, we used multiple regression to remove a number of potential confounds from each of the 11 phenotypic variables. Variables regressed from the phenotypes were: age, age^2, mean FD, mean FD^2, gender, brain size (S_BrainSeg_Vol), brain size^2, and multiband reconstruction algorithm version number (fMRI_3T_ReconVrs). Analyses involving phenotypic prediction (2.8.3 and 2.8.4) were then repeated with the confound-cleansed phenotypes. Results were broadly similar to the original analyses, and are presented in the Supplement.

2.8.2 Brain Basis Set Modeling

To generate predictions of phenotypes from a basis set consisting of n components, we used Brain Basis Set (BBS) modeling, similar to the approach introduced in [18]. In a training dataset, we calculate the expression scores for each of the n components for each subject. We then fit a linear regression model with these expression scores as predictors and the phenotype of interest as the outcome, saving $\mathbf{B}$, the n x 1 vector of fitted coefficients for later use. In a test dataset, we again calculate the expression scores for each of the n components for each subject. Our predicted phenotype for each test subject is the dot product of $\mathbf{B}$ learned from the training dataset with the vector of component expression scores for that subject.

2.8.3 10-fold cross-validation procedure

We assessed prediction of HCP phenotypes as a function of number of components in the predictive basis set, in order to identify the presence of plateaus where adding components does not enhance predictive accuracy. This analysis was performed using a 10-fold cross-validation procedure within the training dataset split described above (to preserve the test dataset for additional analyses described below). On each of the ten folds, we used the training partition to learn new PCA components and then fit beta coefficients for BBS modeling. We then made predictions for the phenotypes in the held-out test partition. The correlations between actual phenotype and predicted phenotype were then averaged across the ten folds.

2.8.4 Comparison with CPM

To further assess the effectiveness of a low rank basis set for capturing phenotypic differences in the HCP dataset, we compared the accuracy of phenotypic predictions derived from the 100 component basis set (coupled with BBS modeling) with predictions derived from an alternative leading method: connectome predictive modeling (CPM) [4], which has achieved excellent results in a number of studies using diverse phenotypes [34, 32, 35]. In brief, CPM is first trained with every edge of the connectome to identify edges that are predictive of the phenotype of interest above some prespecified level (e.g., Pearson's correlation with significance of $p < 0.01$). The sum of weights for these specified edges is then calculated for each test subject, and these sums serve as "predicted scores" that are correlated with the actual phenotypic scores. CPM treats positively and negatively predictive edges differently, and we focus on the positive edges in the main article, and present results for negative edges in the Supplement.

2.9 Density of Parcellation Analysis

To assess the robustness of the analysis to parcellations of systematically varying densities, we used the set of parcellations created by Craddock *et al.* [36]. These parcellations (available here) were produced with a spatially constrained

spectral clustering approach that, for preset values of K, produces approximately K functionally and spatially coherent regions. We utilized parcellations with K ranging from 100-900 in intervals of 100. For each parcellation, we repeated steps 3 through 8 of the above analysis in order to assess whether our three methods for identifying low rank structure (assessment of: intrinsic dimensionality, out-of-sample reconstruction, and phenotypic prediction) differed according to parcellation density. Of note, our implementation of the method of Choi *et al.* did not converge for larger parcellations ($K > 500$) and so we focus on the the method of Levina and Bickel for this analysis.

2.10 Assessing Community Structure

2.11 Stochastic Block Model

For all 809 components, we assessed the presence of community structure corresponding to ICNs from the parcellation of Power *et al.* [14] using a non-parametric testing procedure based on random permutations of the data. For each of the 809 components, we first fix node community assignments according to the Power parcellation [14], and then estimate the parameters of a stochastic block model (SBM [37]) with these fixed community assignments. We replace the Bernoulli distribution assumption on binary edges made by the classical SBM with a normal distribution assumption on edge weights, since we work with Fisher-transformed correlations as edge weights. Once these parameters are estimated, we summarize the fit with the profile log-likelihood statistic. Then we permute node labels many times, keeping the total number of nodes in each of the communities fixed, and obtain a profile likelihood value from each of these fits corresponding to permuted node labels. We then obtained a p-value by comparing the profile likelihood for the Power parcellation to the empirical null distribution of profile likelihoods. Finally, the p-values for the 809 components were adjusted for multiple comparisons using Bonferroni's correction, to control the Family-Wise Error Rate at $\alpha = 0.05$. A more detailed description of this procedure is provided in Appendix A.

2.12 Test/Retest Reliability

Test-retest reliability was assessed in 38 subjects in the HCP test-retest dataset. Reliability was assessed with intra-class correlation (ICC) statistic, specifically type (2,1) according to the scheme of Shrout and Fleiss [38]. For each subject, ICC's were calculated for each individual edge as well as for expression scores for each component in the 100-member basis set. Since aggregating edges can itself improve ICC, we also examined ICC's for "random" aggregations of edges created by permuting the edges of each of the 100 components. For each component, 1000 randomly permuted components were created in this way, and ICC's for the expressions of these components were calculated.

3 Results

3.1 There is convergent evidence for substantial low rank structure in cross-individual connectomic variation based on three different methods.

3.1.1 Method 1: Assessing Intrinsic dimensionality

Figure 1 shows the percent variance explained (i.e., eigenvalues) for all 809 components (in blue). Also plotted is mean eigenvalues for 1000 realizations of random data created through permutation methods (in red). This plot provides initial suggestive evidence of significant low rank stricture in the data, indicated by the substantially elevated variance explained by early components derived from observed connectomes relative to what components derived from random data.

We next turned to quantitative dimensionality estimation procedures. Applying the maximum likelihood method from Levina and Bickel [26] yielded an estimated dimensionality of 62. Applying the dimensionality estimation method of Choi *et al.* [27] found an upper bound of 147 components with α set at 0.05. Importantly, these two results should be seen as complementary and not necessarily in tension, as the Levina and Bickel method attempts to arrive at the number of components that is *most likely* given the data, while the Choi *et al.* method attempts to provide an *upper bound* on the number of components, with statistical control over type 1 errors. Taken together, these methods provide strong initial evidence for substantial low rank structure in cross-individual connectomic variation. In addition, they suggest a plausible range for the number of true dimensions in the data as being somewhere between 50 and 150.

3.1.2 Method 2: Assessing out of sample reconstruction

A second method for detecting and quantifying low rank structure relies on examining the ability of the PCA components to accurately reconstruct connectomes from an independent test sample, i.e., a sample that was not used to generate the components. Figure 2 shows the Pearson's correlations between actual test sample connectomes and connectomes reconstructed with a PCA-derived basis set, as a function of the number of components in the basis set. Using all 809 components in the basis set, this correlation was 0.68, and this represents the ceiling correlation that is achievable. With 50, 100, and 150 components, the correlation is 0.47, 0.53, 0.57, respectively. This represents, respectively, 69%, 78%, and 84% of ceiling, and it provides additional evidence that a low rank representation captures a sizable portion of the generalizable variance in the data.

3.1.3 Method 3: Assessing predictive accuracy with respect to a broad range of HCP phenotypes

An additional means to assess low rank structure consists in examining prediction of criterion variables: If a modest sized basis set captures a large portion of cross-individual variation, then it ought to predict a broad range of behavioral and clinical phenotypes (that are plausibly linked to functional connectomic variation) similarly to the full unreduced dataset.

For each of 11 phenotypes, we used the BBS modeling method to make predictions of phenotype values for each subject based on connectomic component expression scores. We applied BBS to the 810 subjects in the train dataset in a 10-fold cross validation procedure (see Methods 2.8.3).

As shown in Figure 3, there is a noticeable plateau at around 50-100 components for most of the phenotypes: Adding further components to the basis set beyond this number does not appreciably increase accuracy of phenotypic prediction. Table 1 shows the correlations between predicted and actual phenotypes across three basis set sizes: 50, 100, and 150 components. All three basis sets perform similarly, though there is a slight advantage for the 100-component basis set, especially with regard to the processing speed factor.

To further assess the performance of a modest sized basis set in predicting phenotypes of interest, we compared performance with CPM, a leading alternative method for phenotypic prediction that is trained on the whole connectome [4]. Since the 100-component basis set performed slightly better than the others in cross-validation within the training dataset, we focused on this basis set for comparison with CPM in the held out test set.

For each of the 11 phenotypes, we trained both methods in the training dataset and tested accuracy of phenotypic prediction in the held out test dataset. Results showed that performance of BBS was comparable to or better than CPM on all 11 phenotypes (comparable to CPM on 8 phenotypes and better than CPM on the other 3 phenotypes; Table 1).

3.1.4 Role of parcellation density

We next examined the robustness of the preceding three analyses to parcellations of varying densities. We used Craddock and colleagues' parcellations [36] derived from a spectral clustering algorithm with K, the prespecified number of parcels, set from 100 to 900 in increments of 100. While there were some differences observed with the most sparse parcellation (K=100), for all analyses in which K exceeded 200, the results were highly stable and broadly similar to what we observed with the Power parcellation with 264 ROIs (Figure 4).

3.2 Network structure of the fundamental units of cross-individual differences

We next turn to characterizing connectivity patterns in the components themselves. Figure 5, panels A through C, shows the first three components with

Phenotype	BBS	CPM
General Executive	0.44	0.42
Processing Speed	0.39*	0.23
Penn Progressive Matrices	0.30	0.32
ASR Externalizing	0.24*	0.03
ASR Internalizing	0.20	0.04
ASR Attention	0.15*	0.00
NEO Openness	0.18	0.11
NEO-Conscientiousness	0.19	0.15
NEO-Extroversion	0.13	0.04
NEO-Agreeableness	0.19	0.10
NEO-Neuroticism	0.00	0.05

Table 1: Pearson's correlations between actual and predicted phenotypes for two different predictive modeling approaches. BBS = Brain Basis Set modeling (with 100 component basis set); CPM = Connectome Predictive Modeling [4]. * = statistically significant difference at $p < 0.05$.

nodes organized by membership in ICN communities (e.g., DMN, FPN, etc.) according the node assignments of Power *et al.* [14]. Qualitatively, these components appear to exhibit prominent ICN structure: the lines on these figures, which represent boundaries of ICN-ICN interrelationships, appear to be highly informative for characterizing connectivity patterns in the components.

To quantitatively assess the presence of ICN-based community structure in these components, we utilized an SBM-based method as described in Methods (see 2.10) coupled with permutation tests for statistical significance. We found that for all 809 components, the observed components' connectivity patterns are highly statistically significantly more likely under Power ICN community assignments than alternative randomly shuffled assignments (permutation-based p-values for all components survive Bonferroni correction for 809 tests with $\alpha = 0.05$). Additionally, as a descriptive follow up to quantify the extent of network structure in the components, we investigated how, for each component, the profile log-likelihood corresponding to the Power *et al.* parcellation [14] differed from the median profile log-likelihood across the permutations (see Figure 6. This analysis suggests that while ICN structure is significantly present in all components, such structure is most prominent in early components and plateaus substantially around component 100 to 200.

Given evidence of prominent network structure in the components, especially of earlier components, we sought to further characterize their patterns of network interrelationships. Figure 7 shows network-to-network relationships for the first 100 components. Visual network, DMN, and FPN are especially prominent.

3.3 Test-retest reliability

The preceding analyses suggest that a modest sized basis set is sufficient to quantify cross-individual variation across the entire connectome, especially the meaningful (i.e., phenotypically predictive) aspects of this variation. A further question concerns the stability of the basis set—or more specifically, each subject's component expression scores—across scanning sessions.

To address this question, we examined the intra-class correlation (ICC) of component expression scores in the 38 HCP test-retest subjects. Components were generated in the full train dataset and assessed across the two scanning sessions of the test-retest dataset, which was not used to generate the components. The mean ICC for individual edges is 0.54, similar to values seen in previous studies [39]. In contrast, the ICC for the components of cross-individual variation are notably higher. Focusing on the 100-component basis set, which performed well in phenotypic prediction, the mean ICC is 0.78.

Some of this improvement might be due to chance, as aggregates tend to be more stable than the elements that are aggregated. To test this possibility, we calculated the mean ICC for random permutations of these 100 components (1000 permutations of each component). Mean ICC for permuted components was 0.65, so the boost in ICC seen in the actually observed 100 components is substantially over and above what can be explained by simply aggregating random collections of edges.

4 Discussion

In resting state fMRI, the presence of low rank structure in intra-individual variation is well known: a small set of fundamental units—ICNs such as DMN and FPN—account for a sizable portion of variation in the BOLD signal across time within a scanning session. In this study, we extend the search for useful low rank structure to inter-individual connectomic variation. We found convergent evidence that a modest number of fundamental units, roughly 50-150, capture a sizable share of how the resting state functional connectomes of any two healthy adults differ. Moreover, we found these components exhibit high levels of network community structure (aiding interpretability) and they have very good test-retest reliability. We propose that the fundamental connectivity units identified in this study form an effective basis set for quantifying and interpreting systematic inter-individual connectomic differences, and for predicting behavioral and clinical phenotypes.

The fundamental units of inter-individual variation reflect ICN structure A remarkable feature of the connectomic components that emerged in this study is that they strongly reflect ICN structure. ICN boundaries are determined from a strictly intra-individual phenomenon: coherence of the resting state BOLD time series across regions within a person during a scanning session [40, 14, 3]. There is no necessity that ICNs should be implicated in across-

individual differences in functional connectomes; the set of edges that make individuals different could just have easily have crossed ICN boundaries freely. That is not what we found, however, based both on qualitative observation as well as quantitative assessment.

The finding that there is extensive ICN structure in these components jointly helps to illuminate two issues. First, it helps to explain why we were successful in finding low rank structure in the first place. Second, it potentially illuminates the mechanisms by which the inter-individual differences we observed arose. Both of these points warrant elaboration.

There is growing understanding of the maturational trajectories of large-scale ICNs and principles by which they take shape. Resting state imaging studies in infants suggest at least some important ICNs are in a highly immature state in the fetal and infant brain with weak intra-network connectivity and low levels of network separation [41, 42, 43]. Over the course of childhood to early adolescence, massive changes occur: integration of connections within ICNs [44, 45], segregation of DMN from attention/control networks [46, 47, 18], and cross-modal linkages in which structural connections co-develop with functional connections [48].

The overall picture, then, involves highly complex and choreographed developmental processes that shape large populations of interconnections between ICNs. Suppose, now, that there are factors, for example, genetic factors or environmental influences, that modulate these neurodevelopmental ICN-shaping processes, and these factors operate differently across individuals. For example, suppose DMN and attention/control network segregation is modulated by some factor that exhibits a graded level of expression across individuals, and similarly for the other intra- and inter-ICN changes observed during youth.

A model along these lines in which developmental processes impart cohesive changes to large populations of ICN-to-ICN connections is well suited for explaining the findings we actually observed. In particular, such a model readily explains why we observed significant low rank structure in inter-individual variation in connectomes, as such structure necessarily exists if individuals systematically differ at large aggregates of connections. In addition, the model explains the patterns we observed in the connectomic components themselves. These components exhibit extensive ICN structure, which is predicted if the neurodevelopmental generative processes that produce inter-individual connectomic differences impart aggregate intra-ICN and inter-ICN alterations.

In short, then, we propose that adult inter-individual connectomic variation—especially the meaningful aspects of this variation that is relevant to explaining neurocognitive and behavioral phenotypes—importantly reflects the legacy of individual-differences in ICN development. This hypothesis invites detailed future investigation, ideally in longitudinal datasets that permit precise quantification of ICN maturational trajectories as well as adult connectomic variation.

Success at Phenotypic Prediction and Test-Retest Reliability The BBS modeling approach leverages a modest number of units of inter-individual variation—in this study we focuses on a 100-component basis set. Yet we found this method predicts HCP phenotypic variables (such as executive functioning, processing speed, and externalizing) just as well, or in some cases better than, CPM, an alternative highly successful method that is trained on every edge of the connectome [4]. The most likely explanation for this result is that systematic connectomic differences across individuals really do have substantial low rank structure. Thus restricting one's predictor set to a modest number of connectomic components, which is sufficient to capture this structure, yields strong phenotypic prediction.

An additional complementary explanation emphasizes the issue of signal-to-noise ratio and test-retest reliability. While the inter-session test-retest reliability of individual edges of the resting state functional connectome has been found to only fair [39, 49], the connectomic components identified in this study exhibit substantially better reliabilities. This improvement arises, most likely, because high eigenvalue components—i.e., components that explain a large portion of inter-individual connectomic variation—are more likely to be latching onto "real" brain differences, i.e., stable cross-individual differences that genuinely exist in nature. In contrast, connectivity features that explain only a tiny portion of inter-individual variation have a greater probability of reflecting noise, which, by definition, lacks test-retest reliability. It follows that restricting analysis to a modest number of high eigenvalue components can boost the signal-to-noise ratio of the included predictors, contributing to better prediction of unseen data (see [50] for a related argument).

Implications for connectomic statistical analysis Our results have broader implications for methods of statistical analyses of connectomes, especially methods aimed at predicting phenotypic differences across individuals and between groups [51, 52]. A persistent challenge in individual differences research has been the shear size of functional connectomes [53]. This sometimes forces researchers to choose between focusing on a small set of "connections of interest" or else undertake a whole connectome statistical search and pay a substantial price in terms of multiple comparisons correction. Our results suggest that the tradeoffs need not be so stark. There is a massive amount of dependence among edges in connectomes across individuals. Thus a basis set with a modest number of components allows researchers interested in individual differences to undertake whole-connectome inquiry while dramatically reducing the multiple comparison cost.

More broadly, there is a pressing need to leverage prior knowledge about the nature, kind, and extent of inter-individual variation in functional connectomes to further guide and constrain statistical models in neuroimaging individual differences research. Our observation of extensive low rank structure, i.e., a modest number of components account for a sizable portion of cross-individual differences, represents one kind of prior knowledge. Our observation of prominent

ICN structure within these components, discussed earlier, is also highly relevant in this context. Future studies should leverage this observation, for example using block structure-based regularization, to inform and constrain statistical models of inter-individual differences, and thereby increase the chances of robust out-of-sample generalization.

In sum, this study identified fundamental units in cross-individual differences in functional connectomes. These fundamental units constitute a highly effective and interpretable basis set for phenotypic prediction and they open the door to novel methods for detecting and quantifying individual differences. Our results invite further research into the neurodevelopmental processes that shape ICNs, which could help to explain why adult inter-individual connectomic differences take these characteristic forms.

Note: Supplement will be available soon.

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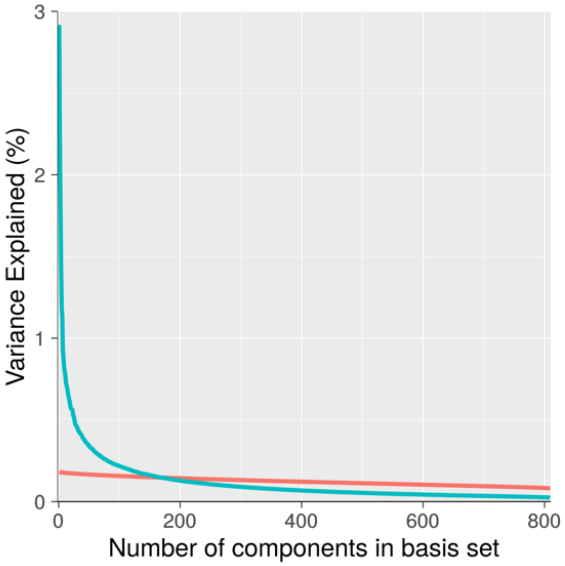

Figure 1: Percent Variance Explained For Components Derived From Actual Versus Random Data. For observed components (blue), percent variance explained of early components is much larger than mean percent variance explained of components derived from random data (red). This pattern is suggestive of substantial low rank structure in observed connectomes.

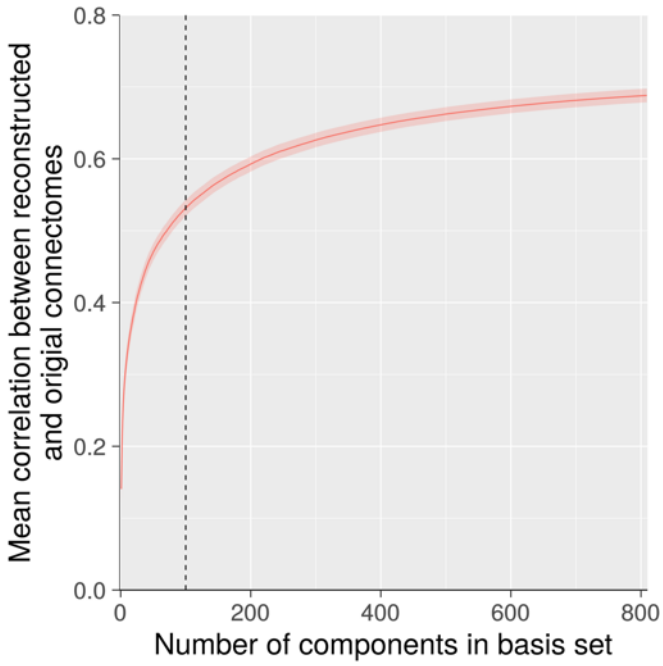

Figure 2: Out of Sample Reconstruction of Connectomes. With 100 components (dashed line), the correlation between actual and reconstructed connectomes is 0.50. Importantly, this correlation is only 0.68 using all 809 components, so a basis set consisting of 100 components achieves roughly three fourths of the "ceiling" correlation that is achievable.

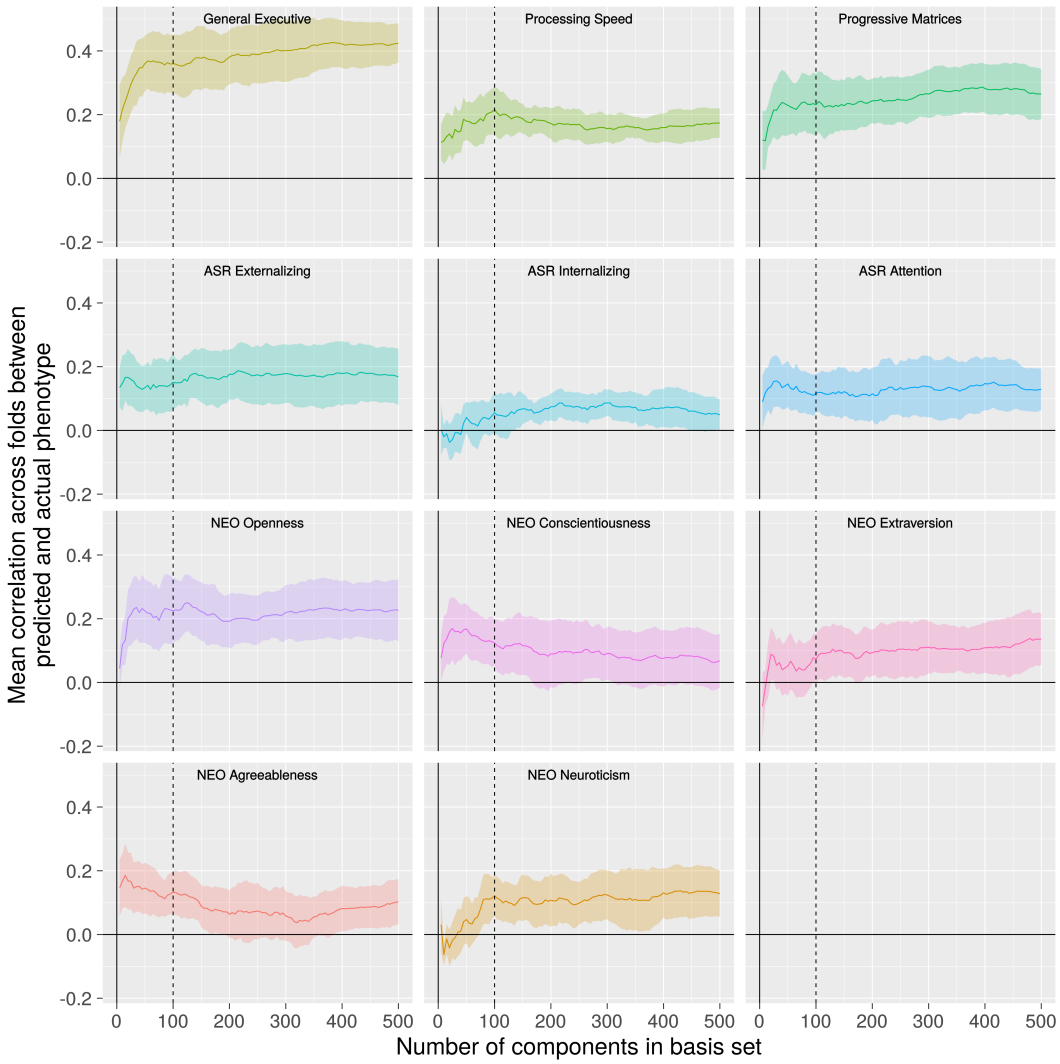

Figure 3: Phenotype Predictive Accuracy as a Function of Basis Set Size. For most phenotypes, there is a plateau after 50 to 100 components (dotted line) after which adding further components to the prediction model basis set does not appreciably improve performance.

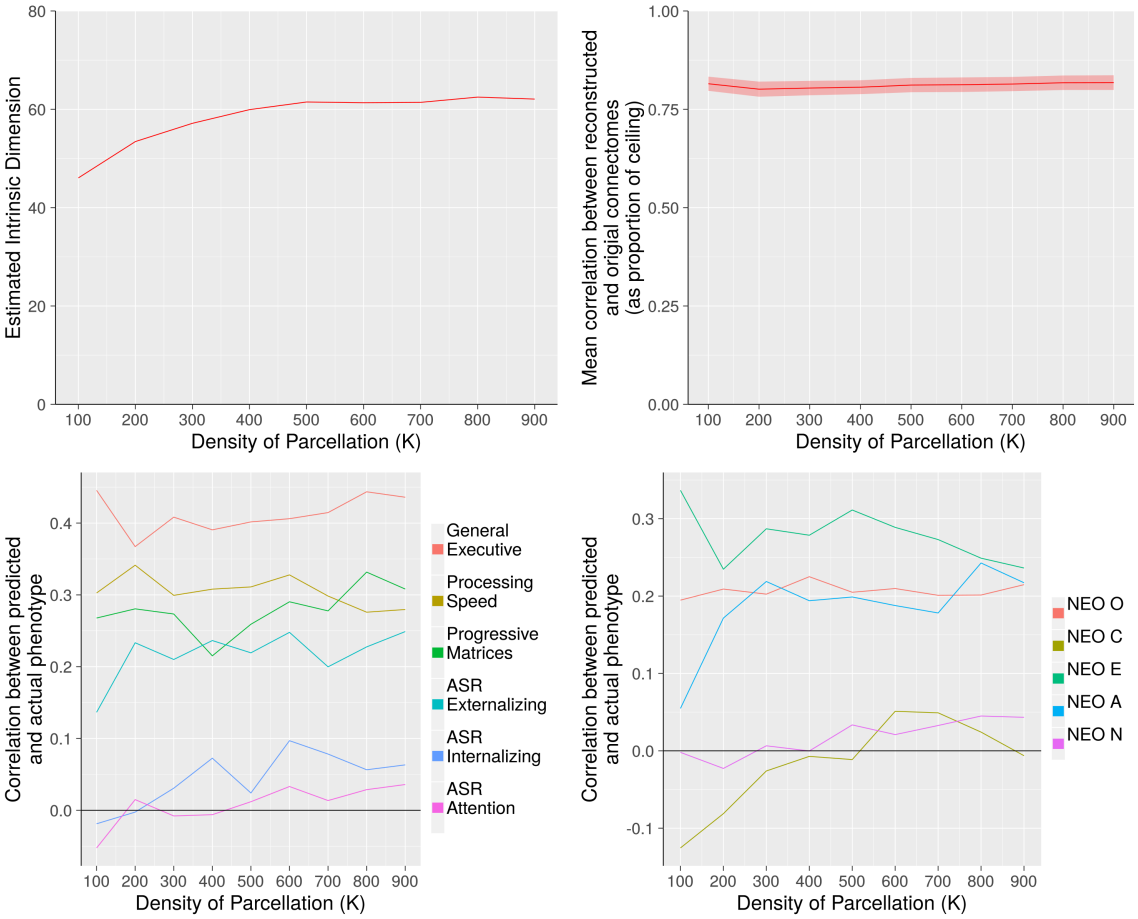

Figure 4: Assessing Role of Parcellation Density. Three methods for identifying low rank structure yielded stable results across parcellations of varying density. Panel A: Estimation of intrinsic dimensionality with the method of Levina and Bickel [26]. Panel C: Out-of-sample reconstruction. Panels D and E: Predictive accuracy with respect to 11 HCP phenotypes. All above analyses used a 100-component basis set, with additional analyses for the 50 and 150 component basis set in the Supplement).

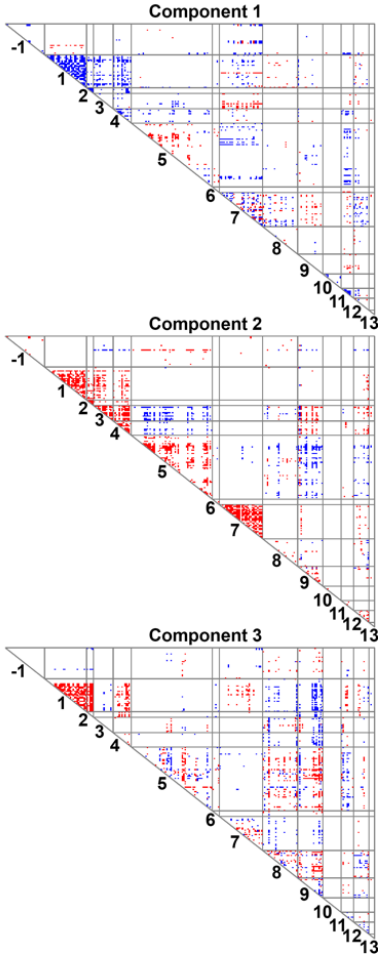

Figure 5: Components 1, 2, and 3. The first three components of inter-individual connectomic variation are displayed, with nodes organized by membership in 13 ICNs according to assignments of Power *et al.* [14]. The boundaries of ICNs are determined from a strictly intra-individual phenomenon: coherence of the BOLD time series within a person across time. It is notable, then, that inter-individual connectomic differences clearly involve substantial ICN structure (which we further corroborate utilizing a novel quantitative approach based on stochastic block modeling). 1=Somatomotor-hand; 2= Somatomotor -faces; 3=Cingulo-opercular; 4=Auditory; 5=Default; 6=Memory retrieval; 7=Visual; 8=Fronto-parietal; 9=Salience; 10=Subcortical; 11=Ventral Attention; 12=Dorsal Attention; 13=Cerebellum

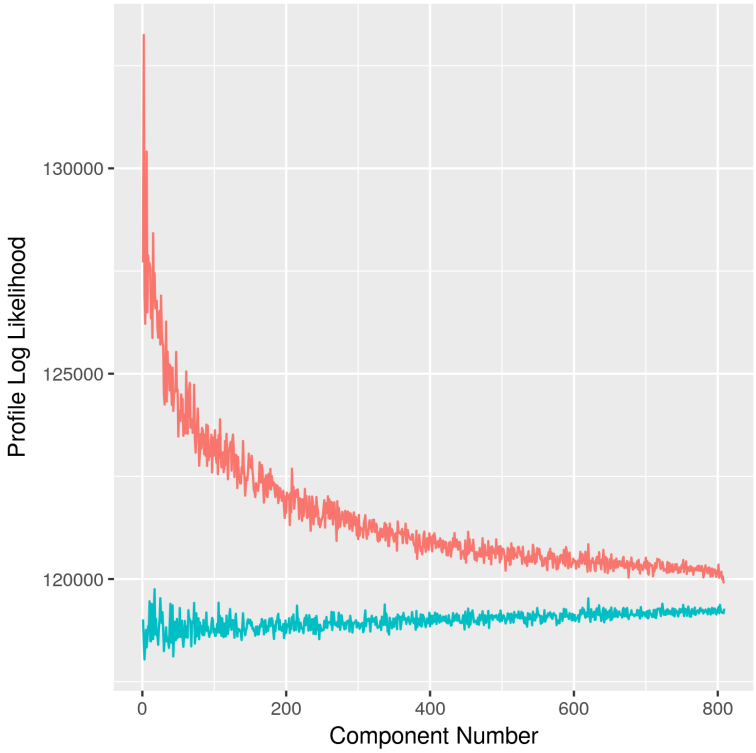

Figure 6: Profile log-likelihood of ICN-based community structure in each component. This statistic serves to quantify presence of ICN structure in each component using a stochastic block model (SBM) framework. The red trace is the profile log-likelihood from the SBM according to the community assignments given in Power *et al.* [14]. The blue trace is the median profile log-likelihood across many shufflings of the community assignments. See Appendix A for details. ICN structure is most prominent in early (high eigenvalue) components.

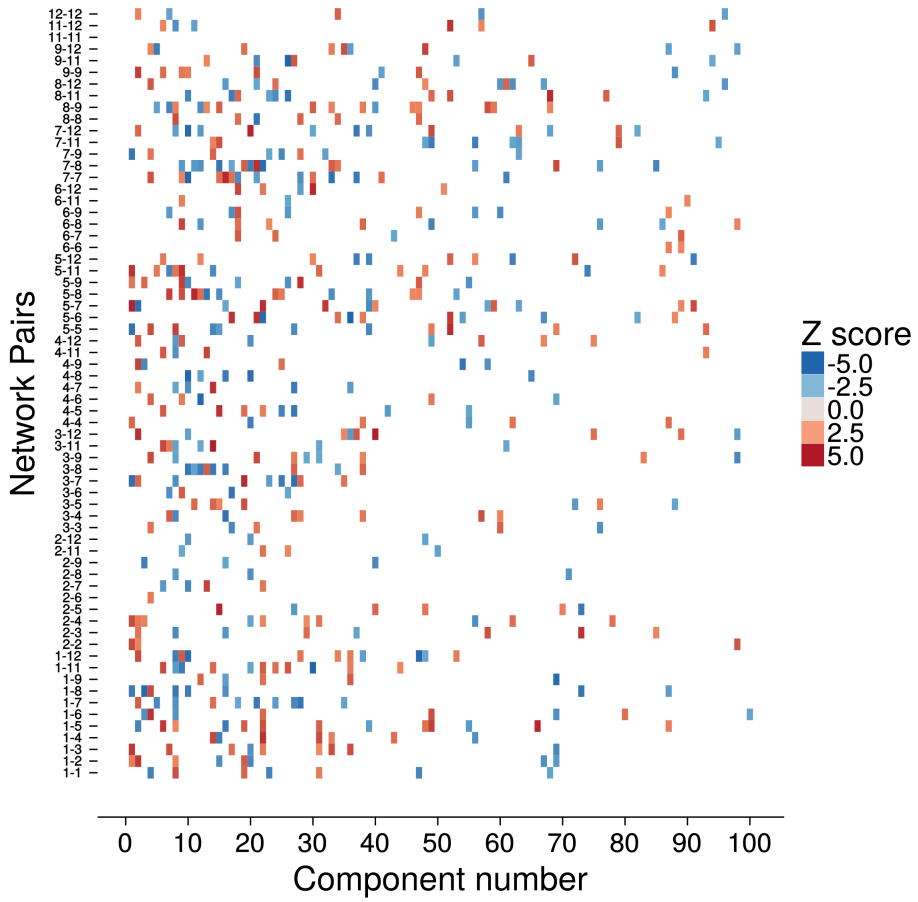

Figure 7: Network Structure of the Connectomic Components. For the first 100 components, altered connectivity patterns are shown using colored squares. Each square represents altered mean connectivity among connections linking pairs of networks. 1=Somatomotor-hand; 2= Somatomotor -faces; 3=Cingulo-opercular; 4=Auditory; 5=Default; 6=Memory retrieval; 7=Visual; 8=Fronto-parietal; 9=Salience; 10=Subcortical; 11=Ventral Attention; 12=Dorsal Attention; 13=Cerebellum.

References

[1] Koene R A Van Dijk et al. "Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization". In: *Journal of neurophysiology* 103.1 (Jan. 2010), pp. 297–321. ISSN: 1522-1598. DOI: 10.1152/jn.00783.2009. URL: http://www.ncbi.nlm.nih.gov/pubmed/19889849 (visited on 06/02/2012).

[2] Randy L. Buckner, Fenna M. Krienen, and B. T. Thomas Yeo. "Opportunities and limitations of intrinsic functional connectivity MRI". eng. In: *Nature Neuroscience* 16.7 (July 2013), pp. 832–837. ISSN: 1546-1726. DOI: 10.1038/nn.3423.

[3] B T Thomas Yeo et al. "The organization of the human cerebral cortex estimated by intrinsic functional connectivity". In: *Journal of neurophysiology* 106.3 (Sept. 2011), pp. 1125–1165. ISSN: 1522-1598. DOI: 10.1152/jn.00338.2011.

[4] Xilin Shen et al. "Using connectome-based predictive modeling to predict individual behavior from brain connectivity". eng. In: *Nature Protocols* 12.3 (Mar. 2017), pp. 506–518. ISSN: 1750-2799. DOI: 10.1038/nprot.2016.178.

[5] Angela R Laird et al. "Behavioral interpretations of intrinsic connectivity networks". In: *Journal of cognitive neuroscience* 23.12 (Dec. 2011), pp. 4022–4037. ISSN: 1530-8898. DOI: 10.1162/jocn_a_00077.

[6] F. Xavier Castellanos et al. "Clinical applications of the functional connectome". In: *NeuroImage* 80 (Oct. 2013), pp. 527–540. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.04.083. URL: http://www.sciencedirect.com/science/article/pii/S1053811913004308 (visited on 10/08/2013).

[7] Choong-Wan Woo et al. "Building better biomarkers: brain models in translational neuroimaging". en. In: *Nature Neuroscience* 20.3 (Mar. 2017), pp. 365–377. ISSN: 1546-1726. DOI: 10.1038/nn.4478. URL: https://www-nature-com.proxy.lib.umich.edu/articles/nn.4478 (visited on 03/03/2018).

[8] Clare Kelly et al. "Characterizing variation in the functional connectome: promise and pitfalls". In: *Trends in Cognitive Sciences* 16.3 (Mar. 2012), pp. 181–188. ISSN: 1364-6613. DOI: 10.1016/j.tics.2012.02.001. URL: http://www.sciencedirect.com/science/article/pii/S1364661312000332 (visited on 03/03/2018).

[9] Sophia Mueller et al. "Individual Variability in Functional Connectivity Architecture of the Human Brain". In: *Neuron* 77.3 (Feb. 2013), pp. 586–595. ISSN: 0896-6273. DOI: 10.1016/j.neuron.2012.12.028. URL: http://www.sciencedirect.com/science/article/pii/S0896627313000044 (visited on 03/26/2018).

[10] Evan M. Gordon et al. "Individual-specific features of brain systems identified with resting state functional correlations". In: *NeuroImage* 146 (Feb. 2017), pp. 918–939. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2016.08.032. URL: http://www.sciencedirect.com/science/article/pii/S1053811916304177 (visited on 03/26/2018).

[11] Christian F. Beckmann et al. "Investigations into resting-state connectivity using independent component analysis". en. In: *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 360.1457 (May 2005), pp. 1001–1013. ISSN: 0962-8436, 1471-2970. DOI: 10.1098/rstb.2005.1634. URL: http://rstb.royalsocietypublishing.org.proxy.lib.umich.edu/content/360/1457/1001 (visited on 03/05/2018).

[12] Michael D. Greicius et al. "Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI". en. In: *Proceedings of the National Academy of Sciences* 101.13 (Mar. 2004), pp. 4637–4642. ISSN: 0027-8424, 1091-6490. DOI: 10.1073/pnas.0308627101. URL: http://www.pnas.org.proxy.lib.umich.edu/content/101/13/4637 (visited on 03/05/2018).

[13] Vincent G. van de Ven et al. "Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest". en. In: *Human Brain Mapping* 22.3 (July 2004), pp. 165–178. ISSN: 1097-0193. DOI: 10.1002/hbm.20022. URL: http://onlinelibrary.wiley.com.proxy.lib.umich.edu/doi/10.1002/hbm.20022/abstract (visited on 03/05/2018).

[14] Jonathan D. Power et al. "Functional Network Organization of the Human Brain". In: *Neuron* 72.4 (Nov. 2011), pp. 665–678. ISSN: 0896-6273. DOI: 10.1016/j.neuron.2011.09.006. URL: http://www.sciencedirect.com/science/article/pii/S0896627311007926 (visited on 07/02/2013).

[15] Steven L Bressler and Vinod Menon. "Large-scale brain networks in cognition: emerging methods and principles". In: *Trends in cognitive sciences* 14.6 (June 2010), pp. 277–290. ISSN: 1879-307X. DOI: 10.1016/j.tics.2010.04.004.

[16] Vinod Menon. "Large-scale brain networks and psychopathology: a unifying triple network model". In: *Trends in cognitive sciences* 15.10 (Oct. 2011), pp. 483–506. ISSN: 1879-307X. DOI: 10.1016/j.tics.2011.08.003.

[17] Deanna M. Barch. "Brain network interactions in health and disease". ENG. In: *Trends in Cognitive Sciences* 17.12 (Dec. 2013), pp. 603–605. ISSN: 1879-307X. DOI: 10.1016/j.tics.2013.09.004.

[18] Daniel Kessler, Michael Angstadt, and Chandra Sripada. "Brain Network Growth Charting and the Identification of Attention Impairment in Youth". In: *JAMA Psychiatry* 73.5 (2016), pp. 481–489.

[19] Daniel Kessler et al. "Modality-spanning deficits in attention-deficit/hyperactivity disorder in functional networks, gray matter, and white matter." In: *Journal of Neuroscience* 34.50 (Dec. 2014), pp. 16555–16566.

[20] David C. Van Essen et al. "The WU-Minn Human Connectome Project: An overview". In: *NeuroImage*. Mapping the Connectome 80 (Oct. 2013), pp. 62–79. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.05.041. URL: http://www.sciencedirect.com/science/article/pii/S1053811913005351 (visited on 03/29/2018).

[21] Matthew F. Glasser et al. "The minimal preprocessing pipelines for the Human Connectome Project". In: *NeuroImage*. Mapping the Connectome 80 (Oct. 2013), pp. 105–124. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.04.127. URL: http://www.sciencedirect.com/science/article/pii/S1053811913005053 (visited on 03/26/2018).

[22] Gholamreza Salimi-Khorshidi et al. "Automatic denoising of functional MRI data: Combining independent component analysis and hierarchical fusion of classifiers". In: *NeuroImage* 90 (Apr. 2014), pp. 449–468. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.11.046. URL: http://www.sciencedirect.com/science/article/pii/S1053811913011956 (visited on 03/26/2018).

[23] Joshua S. Siegel et al. "Data Quality Influences Observed Links Between Functional Connectivity and Behavior". eng. In: *Cerebral Cortex (New York, N.Y.: 1991)* 27.9 (Sept. 2017), pp. 4492–4502. ISSN: 1460-2199. DOI: 10.1093/cercor/bhw253.

[24] Yashar Behzadi et al. "A component based noise correction method (CompCor) for BOLD and perfusion based fMRI". In: *NeuroImage* 37.1 (Aug. 2007), pp. 90–101. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2007.04.042. URL: http://www.sciencedirect.com/science/article/pii/S1053811907003837 (visited on 07/01/2013).

[25] Jonathan D. Power et al. "Methods to detect, characterize, and remove motion artifact in resting state fMRI". eng. In: *NeuroImage* 84 (Jan. 2014), pp. 320–341. ISSN: 1095-9572. DOI: 10.1016/j.neuroimage.2013.08.048.

[26] Elizaveta Levina and Peter J. Bickel. "Maximum Likelihood estimation of intrinsic dimension". In: *Proceedings of the 17th International Conference on Neural Information Processing Systems*. Vancouver, British Columbia, Canada: MIT Press, 2004, pp. 777–784.

[27] Yunjin Choi, Jonathan Taylor, and Robert Tibshirani. "Selecting the number of principal components: Estimation of the true rank of a noisy matrix". EN. In: *The Annals of Statistics* 45.6 (Dec. 2017), pp. 2590–2617. ISSN: 0090-5364, 2168-8966. DOI: 10.1214/16-AOS1536. URL: http://projecteuclid.org/euclid.aos/1513328584 (visited on 04/23/2018).

[28] Jonathan E. Taylor, Joshua R. Loftus, and Ryan J. Tibshirani. "Inference in adaptive regression via the Kac–Rice formula". EN. In: *The Annals of Statistics* 44.2 (Apr. 2016), pp. 743–770. ISSN: 0090-5364, 2168-8966. DOI: 10.1214/15-AOS1386. URL: http://projecteuclid.org/euclid.aos/1458245734 (visited on 04/23/2018).

[29] Noelle E. Carlozzi et al. "The NIH Toolbox Pattern Comparison Processing Speed Test: Normative Data". In: *Archives of Clinical Neuropsychology* 30.5 (Aug. 2015), pp. 359–368. ISSN: 0887-6177. DOI: 10.1093/arclin/acv031. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542749/ (visited on 05/15/2018).

[30] T.M. Achenbach. *The Achenbach System of Empirically Based Assessment (ASEBA): Development, Findings, Theory and Applications.* Burlington, VT: University of Vermont Research Center for Children, Youth and Families, 2009.

[31] Robert R. McCrae and Paul T. Costa. "A contemplated revision of the NEO Five-Factor Inventory". In: *Personality and Individual Differences* 36.3 (Feb. 2004), pp. 587–596. ISSN: 0191-8869. DOI: 10.1016/S0191-8869(03)00118-1. URL: http://www.sciencedirect.com/science/article/pii/S0191886903001181 (visited on 04/23/2018).

[32] Emily S. Finn et al. "Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity". en. In: *Nature Neuroscience* 18.11 (Nov. 2015), pp. 1664–1671. ISSN: 1546-1726. DOI: 10.1038/nn.4135. URL: https://www-nature-com.proxy.lib.umich.edu/articles/nn.4135 (visited on 03/03/2018).

[33] Feilong Ma, J. Swaroop Guntupalli, and James Haxby. *Hyperalignment improves prediction of fluid intelligence from functional connectivity.* 2017.

[34] Monica D. Rosenberg et al. "A neuromarker of sustained attention from whole-brain functional connectivity". eng. In: *Nature Neuroscience* 19.1 (Jan. 2016), pp. 165–171. ISSN: 1546-1726. DOI: 10.1038/nn.4179.

[35] Roger E. Beaty et al. "Robust prediction of individual creative ability from brain functional connectivity". en. In: *Proceedings of the National Academy of Sciences* (Jan. 2018), p. 201713532. ISSN: 0027-8424, 1091-6490. DOI: 10.1073/pnas.1713532115. URL: http://www.pnas.org/content/early/2018/01/09/1713532115 (visited on 03/30/2018).

[36] Craddock R. Cameron et al. "A whole brain fMRI atlas generated via spatially constrained spectral clustering". In: *Human Brain Mapping* 33.8 (July 2011), pp. 1914–1928. ISSN: 1065-9471. DOI: 10.1002/hbm.21333. URL: https://onlinelibrary-wiley-com.proxy.lib.umich.edu/doi/full/10.1002/hbm.21333 (visited on 03/26/2018).

[37] Paul W. Holland, Kathryn Blackmond Laskey, and Samuel Leinhardt. "Stochastic blockmodels: First steps". In: *Social Networks* 5.2 (June 1983), pp. 109–137. ISSN: 0378-8733. DOI: 10.1016/0378-8733(83)90021-7. URL: http://www.sciencedirect.com/science/article/pii/0378873383900217 (visited on 03/26/2018).

[38] P. E. Shrout and J. L. Fleiss. "Intraclass correlations: uses in assessing rater reliability". eng. In: *Psychological Bulletin* 86.2 (Mar. 1979), pp. 420–428. ISSN: 0033-2909.

[39] Stephanie Noble et al. "Influences on the Test–Retest Reliability of Functional Connectivity MRI and its Relationship with Behavioral Utility". en. In: *Cerebral Cortex* 27.11 (Nov. 2017), pp. 5415–5429. ISSN: 1047-3211. DOI: 10.1093/cercor/bhx230. URL: https://academic-oup-com.proxy.lib.umich.edu/cercor/article/27/11/5415/4139668 (visited on 03/03/2018).

[40] M. D. Fox et al. "The human brain is intrinsically organized into dynamic, anticorrelated functional networks". In: *Proc Natl Acad Sci USA* 102 (2005). 27, pp. 9673–8. ISSN: 0027-8424 (Print). DOI: 0504136102[pii] 10.1073/pnas.0504136102. URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15976020.

[41] Marion I. van den Heuvel and Moriah E. Thomason. "Functional Connectivity of the Human Brain in Utero". In: *Trends in Cognitive Sciences* 20.12 (Dec. 2016), pp. 931–939. ISSN: 1364-6613. DOI: 10.1016/j.tics.2016.10.001. URL: http://www.sciencedirect.com/science/article/pii/S1364661316301541 (visited on 03/28/2018).

[42] Kristin Keunen, Serena J. Counsell, and Manon J. N. L. Benders. "The emergence of functional architecture during early brain development". In: *NeuroImage*. Functional Architecture of the Brain 160 (Oct. 2017), pp. 2–14. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2017.01.047. URL: http://www.sciencedirect.com/science/article/pii/S105381191730054X (visited on 03/28/2018).

[43] David S. Grayson and Damien A. Fair. "Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature". In: *NeuroImage*. Functional Architecture of the Brain 160 (Oct. 2017), pp. 15–31. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2017.01.079. URL: http://www.sciencedirect.com/science/article/pii/S1053811917301027 (visited on 03/28/2018).

[44] Damien A. Fair et al. "The maturing architecture of the brain's default network". en. In: *Proceedings of the National Academy of Sciences* 105.10 (Mar. 2008), pp. 4028–4032. ISSN: 0027-8424, 1091-6490. DOI: 10.1073/pnas.0800376105. URL: http://www.pnas.org.proxy.lib.umich.edu/content/105/10/4028 (visited on 07/01/2013).

[45] Damien A. Fair et al. "Functional Brain Networks Develop from a "Local to Distributed" Organization". In: *PLoS Comput Biol* 5.5 (May 2009), e1000381. DOI: 10.1371/journal.pcbi.1000381. URL: http://dx.doi.org/10.1371/journal.pcbi.1000381 (visited on 04/21/2014).

[46] Damien A Fair et al. "Development of distinct control networks through segregation and integration". eng. In: *Proceedings of the National Academy of Sciences of the United States of America* 104.33 (Aug. 2007), pp. 13507–13512. ISSN: 0027-8424. DOI: 10.1073/pnas.0705843104.

[47] Jeffrey S Anderson et al. "Connectivity gradients between the default mode and attention control networks". In: *Brain connectivity* 1.2 (2011), pp. 147–157. ISSN: 2158-0022. DOI: 10.1089/brain.2011.0007. URL: http://www.ncbi.nlm.nih.gov/pubmed/22076305 (visited on 09/11/2012).

[48] Kaustubh Supekar et al. "Development of functional and structural connectivity within the default mode network in young children". In: *NeuroImage* 52.1 (Aug. 2010), pp. 290–301. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2010.04.009. URL: http://www.sciencedirect.com/science/article/pii/S1053811910004039 (visited on 12/04/2013).

[49] Rasmus M. Birn et al. "The effect of scan length on the reliability of resting-state fMRI connectivity estimates". In: *NeuroImage* 83 (Dec. 2013), pp. 550–558. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.05.099. URL: http://www.sciencedirect.com/science/article/pii/S1053811913006010 (visited on 03/03/2018).

[50] Enrico Amico and Joaquín Goñi. "The quest for identifiability in human functional connectomes". In: *arXiv:1707.02365 [q-bio]* (July 2017). arXiv: 1707.02365. URL: http://arxiv.org/abs/1707.02365 (visited on 03/03/2018).

[51] Djalel Eddine Meskaldji et al. "Comparing connectomes across subjects and populations at different scales". In: *NeuroImage*. Mapping the Connectome 80 (Oct. 2013), pp. 416–425. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.04.084. URL: http://www.sciencedirect.com/science/article/pii/S105381191300431X (visited on 03/03/2018).

[52] Gaël Varoquaux and R. Cameron Craddock. "Learning and comparing functional connectomes across subjects". In: *NeuroImage*. Mapping the Connectome 80 (Oct. 2013), pp. 405–415. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2013.04.007. URL: http://www.sciencedirect.com/science/article/pii/S1053811913003340 (visited on 03/03/2018).

[53] Andrew Zalesky et al. "Connectivity differences in brain networks". In: *NeuroImage* 60.2 (Apr. 2012), pp. 1055–1062. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2012.01.068. URL: http://www.sciencedirect.com/science/article/pii/S1053811912000857 (visited on 03/03/2018).

Appendices

A Details Regarding Assessment of Community Structure

A.1 The Stochastic Block Model

The SBM [1] is a well-established generative model for networks with communities. Under the SBM, each of the n nodes is independently assigned to one of K communities, with probability of assignment to community k given by π_k, $\sum_{i=1}^{K} \pi_k = 1$. Given a realization of the community assignments vector c, where c_i is the community label of node i, the SBM generates edge weights A_{ij} between nodes i and j independently, from a distribution depending only on the community labels c_i and c_j. If the distribution is parameterized by a parameter θ_{c_i,c_j}, the distribution of the entire network is determined by the set of parameters θ_{kl}, $k, l = 1, \ldots, K$, with $\theta_{kl} = \theta_{lk}$ if the network is symmetric, as it is in our case. In the classical formulation of the SBM, the adjacency matrix is assumed to be binary, in which case the distribution of A_{ij} is Bernoulli and $\theta_{kl} = P(A_{ij} = 1 | c_i = k, c_j = l)$. In our case, because we work with weighted matrices and the weights are Fisher-transformed correlations, we model the distribution of A_{ij} as normal, determined by parameters $\theta_{kl} = (\mu_{kl}, \sigma^2_{kl})$.

A.2 Calculating profile likelihood under the SBM

In our setting, we have an a priori community membership as given by the Power *et al.* parcellation [2]. The log-likelihood of the observed weights for a given community assignment, c, is given by

$$\begin{aligned}
\log \mathcal{L}(\theta, \pi | A) &= \sum_{k=1}^{K} n_k \log(\pi_k) + \sum_{i=1}^{n} \sum_{j=1}^{i-1} \log f(A_{ij}; \theta_{c_i,c_j}), \\
&= \sum_{k=1}^{K} n_k \log(\pi_k) + \sum_{i=1}^{n} \sum_{j=1}^{i-1} \left[-\frac{1}{2} \log(2\pi) - \log \sigma_{c_i,c_j} - \frac{(A_{ij} - \mu_{c_i,c_j})^2}{2\sigma^2_{c_i,c_j}}, \right]
\end{aligned}$$

where n_k is the number of nodes in community k, and $f(\cdot; \theta_{kl})$ is the probability density function of $N(\mu_{kl}, \sigma^2_{kl})$.

Maximizing the likelihood of the SBM over community assignments is an NP-hard problem, but for a given c, maximizing over π and θ is easy and there is a closed form solution. Let S_{kl} denote the set of node pairs connecting community k to community l, $S_{kl} = \{i < j : c_i = k, c_j = l\}$, and let $n_{kl} = |S_{kl}|$ denote the number of such pairs. Then the maximum likelihood estimates of parameters for a given c are

$$
\begin{aligned}
\hat{\pi}_k &= \frac{n_k}{n} \ , \\
\hat{\mu}_{kl} &= \frac{1}{n_{kl}} \sum_{(i,j) \in S_{kl}} A_{ij} \ , \\
\hat{\sigma}^2_{kl} &= \frac{1}{n_{kl}} \sum_{(i,j) \in S_{kl}} (A_{ij} - \hat{\mu}_{kl})^2 \ ,
\end{aligned}
$$

the usual MLEs under the normal distribution. Plugging in these values into the profile likelihood gives the maximized profile likelihood, which we use as the test statistic.

To carry out the test, we need to compare the value of the observed profile log-likelihood, $\hat{l}$, to the distribution of profile log-likelihoods under the null hypothesis of no community structure in the data. We obtain this distribution empirically, shuffling the labels of the given parcellation c randomly and recomputing the profile log-likelihood in the same way, $m = 20{,}000$ times in total, to obtain the values l_j, $j = 1, \ldots, m$. Finally, we estimated empirically the probability that a profile log-likelihood L sampled from this null distribution will exceed $\hat{l}$, as

$$
P(L \geq \hat{l}) = \max \left(\frac{1}{m}, \ \frac{1}{m} \sum_{i=1}^{m} I(l_i \ \geq \hat{l}) \right),
$$

where I is the indicator function.

Note that permutation of the labels does not change the number of nodes in each community, so the terms involving $\hat{\pi}_k$'s can omitted.

This procedure is repeated for each of the 809 components of interest, and the resulting 809 p-values are Bonferroni-corrected for multiple comparisons. The number of permutations was selected such that it would be mathematically possible to achieve Bonferroni-corrected significance at $\alpha = .05$.

In addition, for each component we retained both the profile log-likelihood under the Power *et al.* parcellation [2] and the median profile log-likelihood across the m shufflings, and plotted these as a function of the component number (see Figure 6. Because of the use of logs, the ratio of likelihoods is proportional to the difference of log-likelihoods, and one may descriptively interpret the "gap" between the two traces as some indication of the magnitude of the divergence from the null.

References

[1] Paul W. Holland, Kathryn Blackmond Laskey, and Samuel Leinhardt. "Stochastic blockmodels: First steps". In: *Social Networks* 5.2 (June 1983), pp. 109–137. ISSN: 0378-8733. DOI: 10.1016/0378-8733(83)90021-7. URL: http://www.sciencedirect.com/science/article/pii/0378873383900217 (visited on 03/26/2018).

[2] Jonathan D. Power et al. "Functional Network Organization of the Human Brain". In: *Neuron* 72.4 (Nov. 2011), pp. 665–678. ISSN: 0896-6273. DOI: 10.1016/j.neuron.2011.09.006. URL: http://www.sciencedirect.com/science/article/pii/S0896627311007926 (visited on 07/02/2013).