

Mining Correlation between Fluid Intelligence and Whole-brain Large Scale Structural Connectivity

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Abstract

Exploring the neural basis of intelligence and the corresponding associations with brain network has been an active area of research in network neuroscience. Up to now, the majority of explorations mining human intelligence in brain connectomics leverages whole-brain functional connectivity patterns. In this study, structural connectivity patterns are instead used to explore relationships between brain connectivity and different behavioral/cognitive measures such as fluid intelligence. Specifically, we conduct a study using the 397 unrelated subjects from Human Connectome Project (Young Adults) dataset to estimate individual level structural connectivity matrices. We show that topological features, as quantified by our proposed measurements: Average Persistence (AP) and Persistent Entropy (PE), has statistically significant associations with different behavioral/cognitive measures. We also perform a parallel study using traditional graph-theoretical measures, provided by Brain Connectivity Toolbox, as benchmarks for our study. Our findings indicate that individual's structural connectivity indeed offers reliable predictive power of different behavioral/cognitive measures, including but not limited to fluid intelligence. Our results suggest that structural connectomes provide complementary insights (compared to using functional connectomes) in predicting human intelligence and warrants future studies on human intelligence and/or other behavioral/cognitive measures involving multi-modal approach.

Introduction

Connectome analyses of the human brain's structural and functional architecture provide a non-invasive and valuable tool to understand the variety of human brain phenotypes, including but not limited to intelligence. Big data initiatives such as the Human Connectome Project (HCP) acquire connectomic and phenotypic data from a large number of individuals in an effort to understand how brain networks relate to individual behaviour¹. Connectomes can represent either structural connectivity (SC) given by the white matter inter-regional pathways estimated from diffusion-weighted MRI (dwMRI) or functional connectivity (FC) defined by the patterns of temporal dependencies between regional activity measurements such as blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) time series. The most commonly studied form of FC, resting-state FC (rsFC), is measured in the absence of an explicit task.

In an attempt to investigate the neural basis of intelligence and to understand the individual differences in general cognitive ability, several studies have been conducted on the fluid intelligence scores from the behavioral testing components of the Human Connectome Project. Most of these studies rely either solely on functional connectivity or integration of both functional and structural connectivity. These studies include, but not limited to, prediction of individual differences in human intelligence by characterizing features of the brain's intrinsic network architecture with a functional whole-brain large scale approach², mapping of structural and functional connectivity on cognition³, predictive biomarker of fluid intelligence from the white-matter functional connectivity patterns⁴, integrated neuroimaging, connectomics, and machine learning approaches for functional and structural brain connectivity⁵, to name a few. There are also a number of studies performed to understand the link between cognitive decline and dementia severity from structural network efficiency⁶⁻⁹.

In fact, the connection between fluid intelligence and network structure and efficiency is a rather debated topic. While most studies found some association between brain network connectivity measurements¹⁰ and cognitive functions, a study¹¹ on the 1200 Human Connectome Project subjects shows that general crystallized and fluid intelligence are *not* associated with functional global network efficiency.

In the recent years, a new set of toolbox for measuring network connectivity has emerged: Persistence homology¹². Persistence homology, intuitively speaking, measures the "persistence" of "holes" in each dimension. Classical graph-

theoretic measures are usually local and mainly based on differences between either node or edge measurements or correlations without considering the topology of networks, whereas persistence homology takes a holistic approach to understand the network architecture.

Here we conduct a parallel study using both classical connectivity toolbox as well as persistence homology tools, on Human Connectome Project Young Adults (HCP-YA) data, to understand the correlation between the fluid intelligence and structural connectivity. We also use a less known tool, persistent entropy^{13,14}, which hasn't been used before to explore relationship between brain's structural connectivity and cognition. Our findings indicate predictive power of brain structural connectivity for fluid intelligence, even when we use a simple model (ordinary least square linear regression) and a small set of features.

Materials and Methodology

Structural connectome extraction from HCP-YA data

The Human Connectome Project for Young Adults (HCP-YA) aims to characterize brain connectivity in young adults and enables detailed comparisons between brain circuits, behaviors, and genetics at the individual subject level¹. Here we access the preprocessed imaging data through the ConnectomeDB and extract the structural connectomes using the pipeline described in Fig.1 of Zhang et al.¹⁵. For each subject in HCP-YA, we have the dMRI and T1 data. This includes 6 runs, using 3 different gradient tables, with each table acquired once with right-to-left and left-to-right phase encoding polarities, respectively. Each gradient table includes approximately 90 diffusion weighting directions plus 6 b_0 acquisitions interspersed throughout each run. Within each run, there are three shells of $b = 1000, 2000$, and 3000 s/mm^2 interspersed with an approximately equal number of acquisitions on each shell. The scans were done by using the spin echo EPI sequence on a 3T customized Connectome Scanner. Such settings give the final acquired image an isotropic voxel size of 1.25 mm, and 270 diffusion weighted scans distributed equally over 3 shells and the T1 image has 0.7 mm^3 isotropic resolution. See Van Essen et al.¹ for more details about the data acquisition and the minimal preprocessing. A population-based structural connectome mapping (PSC¹⁵) was applied to the minimally preprocessed dMRI and T1 data to extract the structural connectome for each subject. PSC uses a reproducible probabilistic tractography algorithm¹⁶ to generate an individual's whole-brain tractography data, which borrows anatomical information from high-resolution T1 image to reduce bias in the tractography.

We use Desikan-Killiany (DK) atlas¹⁷ to define the ROIs corresponding to the nodes in the structural connectome. The DK parcellation contains 68 cortical surface regions with 34 nodes in each hemisphere, and 19 subcortical regions. For each pair of ROIs, the streamlines connecting them are extracted using the following procedure: 1) each gray matter ROI is dilated to include a small portion of white matter regions, 2) streamlines connecting multiple ROIs are cut into pieces so that we could extract the correct and complete pathway and 3) apparent outlier streamlines are removed. In total, 1065 brain structural connectomes are extracted from the latest release of the HCP-YA dataset. From this dataset we separate out 397 subjects which are neither twins nor siblings using the demographic data on parental identifiers, and the present study is reported on this subset of HCP-YA dataset.

Fluid intelligence scores

The fluid intelligence markers studied here are Penn Matrix Test (PMAT24), Oral Comprehension, Picture Vocabulary Test, Penn Word Memory Test (CPW) and Pattern Comparison Processing Speed Test (Pattern Comp Spd). PMAT24 is a measure of abstraction and mental flexibility, Penn Word Memory (CPW) is a test for verbal episodic memory and Pic.Vocab.Test measures receptive vocabulary of the subject.

Brain connectivity graph-theoretical measures

Brain Connectivity Toolbox¹⁰ (BCT) is widely used by researchers for complex brain-network analysis. Here we computed four network-level graph theoretical measures using BCT. For global measures, we computed global efficiency (GE) and global clustering coefficient (GCC, also known as transitivity). For node level information, we used mean clustering coefficient (MCC) and average nodal betweenness centrality (ANBC). Note that global efficiency and average betweenness centrality are integrative measures whereas transitivity and mean clustering coefficients are

segregative measures.

Persistence Homology and Persistence Entropy

Topology is the branch of geometry that studies shapes and classifies objects according to some intrinsic essential invariants (properties that do not change under certain feasible transformations) of their shapes. Topological features like homology can be seen as quantification of geometric properties such as proximity and continuity and, therefore, can be useful tools for shape analysis¹⁸, pattern recognition^{19,20}, and network analysis, in particular brain networks^{12,21}. Topological Data Analysis (TDA) helps to understand brain networks in a holistically and to analyse network functionalities from higher order interactions (rather than just pairwise) in the system, to paint a global picture.

The brain network is usually constructed by estimating the connectivity matrix and thresholding it at an arbitrary level, and traditional methods do not have any generally agreed upon criteria for determining a proper threshold. Persistence homology models brain networks generated over every possible threshold and enables us to quantify various persistent topological features at different scales in a coherent manner. In this framework, a barcode is used to quantify and visualize the evolutionary changes of topological features such as the components and cycles over different scales. For 0-th dimension, this persistence quantifies the rise and fall of different components, with length of the bar in the D -Dim barcode signifying the life-time of a component. For 1-Dim, the persistence of a bar quantifies the birth and death of different cycles (also referred as circuits in graph theory), with length of the bar signifying the life-time of a cycle. For a detailed overview of persistence homology, see Sizemore et al.²¹ but its standard workflow is the following:

- Start with a dataset, for example, a point cloud, endowed with some notion of proximity or metric.
- Build a simplicial complex and a filter function on it. Compute a nested sequence of increasing subcomplexes which encapsulate features from data using the filter function.
- Compute the homology of each subcomplex (intuitively, homology captures the “holes” of the underlying space)
- Study how they *evolve and dissolve* in the sequence aka persistence diagram

While studying *bars* from these barcodes individually as features is meaningful and informative, often they give rise to a very high dimensional feature space compared to sample size. To make these persistent barcodes applicable for data mining and prediction purposes, we can use summary statistics associated with them. While average length of the bars (signifying life time of a component or cycle) associated with a network, gives us some valuable insight, understanding the *distribution* of the bars requires more effort. Following the definition of entropy, introduced by Claude Shannon’s foundational work²² in information science, persistence entropy¹³ is defined for persistent homological barcodes. Essentially, entropy measures the expectation of the *surprisal* in the distribution. Instead of treating each barcode as an individual feature, the entropy gives a cumulative significance or summary statistics of the persistence.

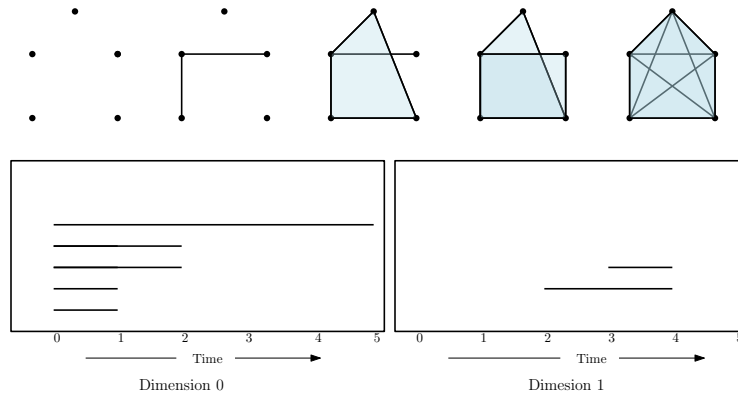


Figure 1: Top: Example of a filtration. Bottom: 0-Dim and 1-Dim Persistence Barcodes

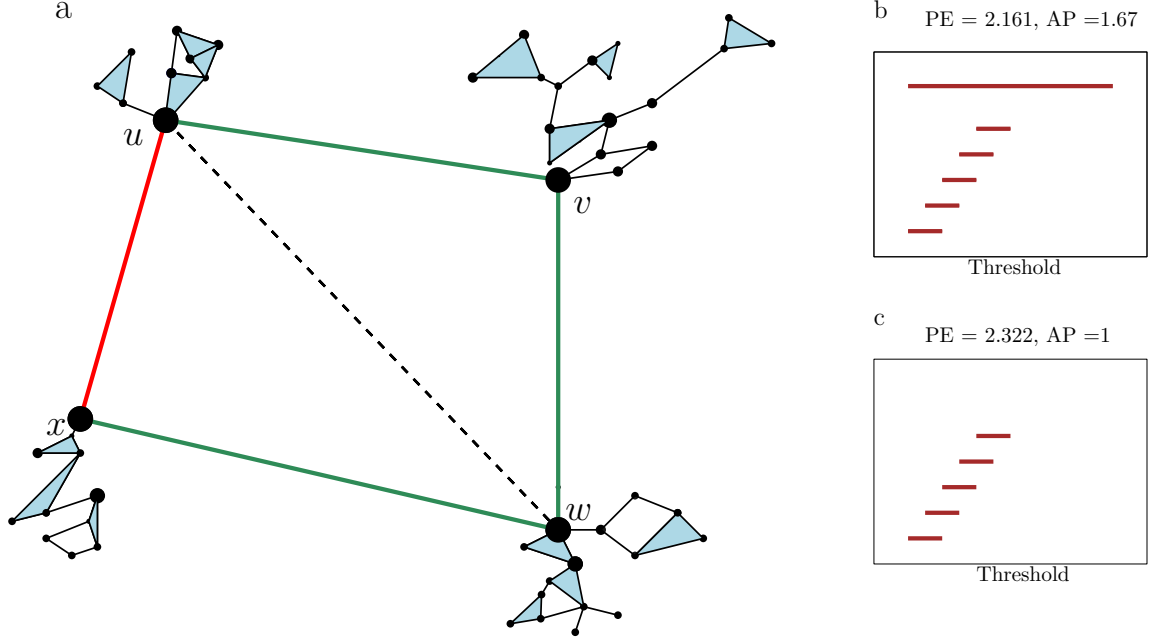


Figure 2: (a) A schematic diagram demonstrating persistence entropy change with edge deletion

Let $\mathcal{B} = (b_i, d_i)_{i=1}^n$ be the set of persistence barcode associated with a network $\mathcal{N}$. Then the *life* of the bar or persistence of (b_i, d_i) is defined by $l_i = d_i - b_i$. The mean life or average persistence (AP) of $\mathcal{B}$ is given by:

$$\text{AP}(\mathcal{N}) = \frac{1}{n} \sum_{i=1}^n l_i \quad (1)$$

Let $L = \sum_{i=1}^n l_i$ be the sum of the lengths of all the bars in barcode $\mathcal{B}$. Then the persistence entropy (PE) for the network $\mathcal{N}$ is defined by the formula:

$$\text{PE}(\mathcal{N}) = - \sum_{i=1}^n \frac{l_i}{L} \log\left(\frac{l_i}{L}\right) \quad (2)$$

Entropy captures how individual bars are different from each other and provides a summary statistics for the probability distribution, what mean and variance alone cannot capture. For example, a schematic diagram of a network with 4 modules shown in Fig. 2. If we remove the edge between vertex u and x (shown in red), we will lose the cycle joining u, v, w and x . We also note that this edge deletion process will raise the entropy of the network, see Fig. 2.

Fig. 3 illustrates how persistence diagrams and persistence entropy vary along with the structural connectivity matrices, using the real data from HCP. Fig. 3(a) shows heat-maps of brain connectivity for the subjects with maximum and minimum 0-dimensional persistence entropy and corresponding persistence profile in Fig. 3(b). Similarly, Fig. 3(c) shows the heat-maps of brain connectivity for the subjects with maximum and minimum 1-dimensional persistence entropy and Fig. 3(d) shows the corresponding persistence diagram. We note that connectivity patterns for maximum and minimum 1-dimensional persistence entropy are visually different. See the Discussion section for plausible interpretations.

Results

We use ordinary least square regression to predict the cognitive scores using two different set of network measurements: traditional graph theoretic connectivity measures and topological connectivity measures. For the traditional

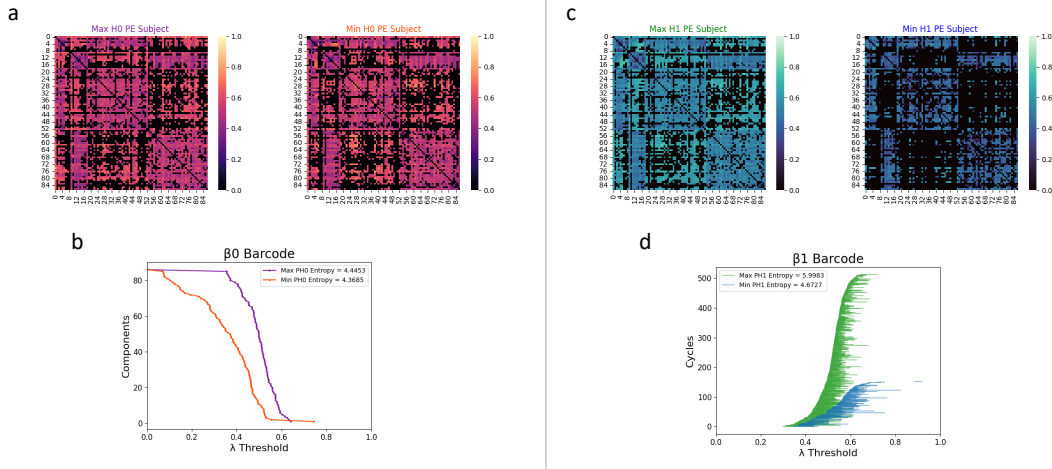


Figure 3: Connectivity matrix and persistence entropy

brain connectivity measures, we use global efficiency (GE), global clustering coefficient (GCC), mean clustering coefficient (MCC), and average nodal betweenness centrality (ANBC). For topological measurements, we use two features: average persistence (AP) and persistence entropy (PE).

Firstly for each cognitive measure, we use our feature vectors to train our model with 80% subjects, chosen at random, and use the rest of 20% (test subjects) to predict the cognitive score. Then we calculate the Pearson correlation between the predicted value and the actual value (obtained from HCP-YA database). To remove the bias originating from this random selection, we repeat this process of splitting data into training and testing subjects 1000 times and perform. In each simulation, we use a different randomization seed; hence, with high probability, we get a different correlation value, which results in an empirical distribution, shown in color blue in Fig. 4. We denote the mean of this distribution by μ_1 . Next, per simulation, we also shuffle/permute the cognitive scores of the 20% test subjects, so that each person is randomly assigned a cognitive score. Then we calculate the Pearson correlation between the randomly assigned score and the predicted score, which again gives us another normal distribution, shown in color orange in Fig. 4. We denote mean of this distribution by μ_0 . We repeated this computation for both 0-dim homology and 1-dim homology, for both average persistence life and persistence entropy. We observe maximum prediction power when we use the two features: average 0D-persistence (i.e. average life of a component) and 1D-persistent entropy.

Table 1 shows us the mean correlations μ_1 along with coefficients of linear regression for the features GE, GCC, MCC and ANBC for each cognitive measure. The value μ_0 is the mean of the shuffled distribution and the p-value

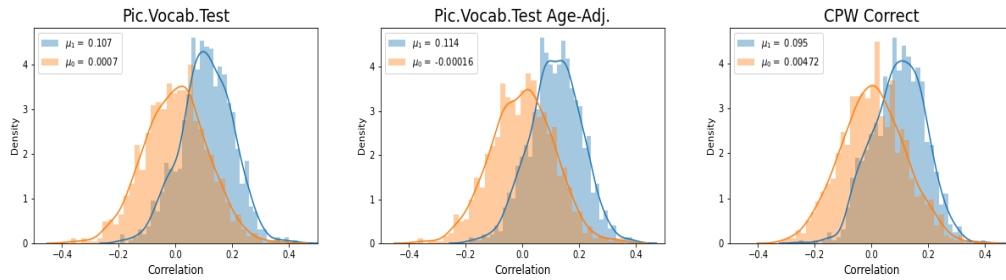


Figure 4: Association between network topology and fluid intelligence

Table 1: Correlation of Fluid intelligence with graph theoretic measurements for connectivity

Cognitive Measure	μ_1	μ_0	p-val	GE	GCC	MCC	ANBC
Oral Comp.	0.06	-0.00085	4.28e-36	$-0.122 \pm 3.4e-03$	$0.111 \pm 3.5e-03$	$-0.106 \pm 8.7e-04$	$-0.127 \pm 1.0e-03$
Pic.Vocab.Test	0.068	-0.00026	7.41e-47	$-0.128 \pm 3.2e-03$	$0.122 \pm 3.2e-03$	$-0.138 \pm 9.0e-04$	$-0.089 \pm 9.5e-04$
Pic.Vocab.Test Age-Adj.	0.075	-0.00012	6.87e-55	$-0.125 \pm 3.2e-03$	$0.127 \pm 3.2e-03$	$-0.147 \pm 9.5e-04$	$-0.074 \pm 9.6e-04$
CPW Correct	0.09	0.00208	3.62e-75	$-0.086 \pm 3.3e-03$	$0.218 \pm 3.4e-03$	$-0.025 \pm 8.3e-04$	$-0.028 \pm 9.1e-04$
CPW Med. Time	0.126	-0.00373	1.55e-150	$-0.112 \pm 3.3e-03$	$-0.034 \pm 3.5e-03$	$0.107 \pm 8.9e-04$	$-0.012 \pm 7.8e-04$
Pattern Comp. Spd.	0.114	-0.00266	1.71e-119	$-0.015 \pm 3.7e-03$	$0.091 \pm 3.7e-03$	$-0.162 \pm 9.0e-04$	$-0.107 \pm 8.9e-04$

Table 2: Correlation of Fluid intelligence with mean persistence life and persistence entropy

Cognitive Measure	μ_1	μ_0	p-val	AP	PE
Oral Comp.	0.054	0.0033	1.72e-27	$-0.039 \pm 8.10e-04$	$-0.077 \pm 8.11e-04$
Pic.Vocab.Test	0.107	0.0007	3.83e-106	$-0.075 \pm 8.02e-04$	$-0.096 \pm 7.10e-04$
Pic.Vocab.Test Age-Adj.	0.114	-0.00016	1.23e-121	$-0.079 \pm 8.10e-04$	$-0.101 \pm 7.15e-04$
CPW Correct	0.095	0.00472	7.27e-79	$-0.047 \pm 7.85e-04$	$-0.127 \pm 8.26e-04$
CPW Med. Time	0.122	-0.00128	1.94e-132	$0.143 \pm 8.06e-04$	$0.067 \pm 8.31e-04$
Pattern Comp. Spd.	0.102	0.00368	5.01e-87	$-0.103 \pm 8.30e-04$	$-0.105 \pm 8.12e-04$

comes from comparison between these two distribution using Student's t-test. We note that the randomized shuffle distribution has mean μ_0 close to zero, as we would expect.

Similarly in Table 2 we have μ_1 and μ_0 as the means for the correlations with actual cognitive score and shuffled cognitive score respectively, along with corresponding p-values. The coefficients for average persistence(AP) and persistence entropy(PE) in the linear regression model are given in the last two columns. Results in Table 1 and 2 show that there is a statistically significant association between cognitive performance and network measurements, by both graph-theoretic as well as topological connectivity measures.

Discussion

Connectivity measurement tools have long been used to investigate network efficiency and clustering as means to quantify integration and segregation properties in brain networks¹⁰. Since efficient connectivity of a network ensures smooth transmission of information, it has been hypothesised that it is also related with fluid, crystallized, general intelligence²³⁻²⁵. Alzheimer's and other neurodegenerative diseases are believed to be structural disruptions that lead to functional impairments. In such vein, we attempt to investigate structural network topology and its associations with various cognitive and behavioral measures.

For persistence homology features, longer persistence suggests more relevant features to cognitive and behavioral measures such as intelligence. Shorter persistence features, as shown by AP measure, are hypothesized to be white noise from the whole-brain connectivity profile. However, an open question is how to select and determine if a feature is indeed signal (versus noise) and where it is possible to quantify topological feature persistence. Even though persistence entropy does not give an definitive answer to the aforementioned quest, it does, however, offer an insightful summary statistic pertaining the distribution of one dimensional cycle persistence. Persistence entropy captures how individual bars (in the bar code diagram 1) are different from each other and provides a summary statistics for the probability distribution, what first and second moment statistical summary of bar code lengths cannot capture.

Per Fig. 2, let us assume that there are two subjects whose whole-brain structural connectivity is shown by the figure. The only structural difference between the two subjects is the edge ux . We see that it has 4 modules (communities), and that 4 nodes u, v, w and x belong exclusively to each of the module. Structurally, if we delete the edge between vertex u and x (shown in red), we lose the cycle joining u, v, w and x . This results in some disconnection in the sense that now u and x are in 3-degrees of separation. In other words, the shortest path to get to u to x (and vice versa) are 3 (instead of 1, should the edge ux exist). Not only now there is no direct path between u and x , but the number of paths between u and w are reduced from two to one. Since this is a schematic diagram, for the sake of simplicity, we can assume the persistence life of the five small bars are equal and persistence life of the large bar (corresponding to the big cycle) is 5 times the persistence life of the small ones. In that case, the result of deletion of edge ux will cause

an increase in persistence entropy from 2.161 to 2.322, shown in Fig. 2, even though the rest of network architecture remains the same.

From Table 2, we see that coefficients average persistence (AP) for components and persistent entropy (PE) for cycles in the linear regression model are negative, suggesting these parameters are inversely correlated with the investigated cognitive measures in this paper. The inverse proportion between AP and cognitive/behavioral measures suggest that the persisting "holes" (in our case, zeroth or first dimensional holes as characterized by corresponding cycles) suppress the effectiveness of global communication (e.g., integration) between brain regions of interest. For instance, a 1D cycle made of 4 nodes is annihilated as soon as there is an edge born between 2 nodes in the cycle (that currently has no connection between them). The fact that this edge is born allows the shortest path between the two nodes to be 1 instead of 2 if information between them is passed along the edges of current cycle. On the other hand, if there is one large persisting cycle (which lowers the PE measure), as in Fig. 2, this would actually result in a more efficient global integration of information (hence, higher intelligence). In summary, average persistence and persistence entropy provide, collectively, comprehensive summary statistics for structural brain network and has proven predictive power for the investigate cognitive/behavioral measures such as fluid intelligence.

The proposed work and subsequent analyses were completed with some acknowledged limitations. First, our analysis did not take into account the functional connectivity domain which limits our comprehensive understanding of intelligence from a multi-modal point of view. Typically, intelligence is studied, at least in the brain connectomics domain, using insights from whole-brain large scale functional connectivity patterns. Future studies should integrate multi-modal approach to investigate intelligence properties (and perhaps, other cognitive/behavioral measures). Secondly, the estimation of whole-brain structural connectivity is sensitive to data processing parameters such as the number of streamlines used. As this is an effort to understand behavioral measures from a structural perspective, future studies should also investigate the sensitivity of the proposed topological features (e.g., AP and PE).

Conclusions

We did a parallel study on relationship between graph theoretic and topological connectivity measures for brain networks and different cognitive scores. We explored four well-known graph theoretic network properties as well as less known topological features of persistence entropy and average length of persistence. We found that both set of measurements have some predictive power for fluid and crystallized intelligence measures such as pattern computation speed, verbal episodic memory and picture vocabulary association. Our results suggest that structural connectomes provide valuable insights in predicting human intelligence and probes future studies on human intelligence and/or other behavioral/cognitive measures involving multi-modal approach.

Disclosure statement

The authors have no actual or potential conflicts of interest.

Acknowledgements

This work was supported in part by the National Institutes of Health grants RF1 AG068191, R01 AG071470, U01 AG068057 and T32 AG076411, and the National Science Foundation grant IIS 1837964.

Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH09-1657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

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