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Heritability Estimation of Reliable Connectomic Features*

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Abstract

Brain imaging genetics is an emerging research field to explore the underlying genetic architecture of brain structure and function measured by different imaging modalities. However, not all the changes in the brain are a consequential result of genetic effect and it is usually unknown which imaging phenotypes are promising for genetic analyses. In this paper, we focus on identifying highly heritable measures of structural brain networks derived from diffusion weighted imaging data. Using the twin data from the Human Connectome Project (HCP), we evaluated the reliability of fractional anisotropy measure, fiber length and fiber number of each edge in the structural connectome and seven network level measures using intraclass correlation coefficients. We then estimated the heritability of those reliable network measures using SOLAR-Eclipse software. Across all 64,620 network edges between 360 brain regions in the Glasser parcellation, we observed ~5% of them with significantly high heritability in fractional anisotropy, fiber length or fiber number. All the tested network level measures, capturing the network integrality, segregation or resilience, are highly heritable, with variance explained by the additive genetic effect ranging from 59% to 77%.

Keywords

Structural Connectivity; Heritability; Reliability; HCP

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1 Introduction

Brain imaging genetics is an emerging research field that integrates genotyping and neuroimaging data to explore the underlying genetic architecture of brain structure and function. Genetic analysis of imaging measures not only allows the detection of risk variants associated with diseases, but also provides insights into the underlying biological mechanism of preclinical brain changes. However, not all the changes in the brain are a consequential result of genetic effect. It is usually unknown which imaging phenotypes are promising for genetic analyses. Therefore, prior to that, it is important to quantify the degree to which brain imaging phenotypes can be attributed to genetic effect using heritability analysis.

Recently, substantial attention has been drawn to the genetic influence on structural brain connectivity, which appeared to be altered in heritable diseases (e.g. Alzheimer's disease [13]). One widely analyzed measure is fractional anisotropy (FA), an measure of fiber integrity very sensitive to the white matter changes in various diseases [9]. Brain-wide, regional and voxel level FA measures have all been found to be highly and significantly heritable [9,1]. Other features that have been investigated include white matter fiber tract shapes [8], white matter volume, network level characteristic path length and clustering coefficient [1], and fiber orientation distribution [15]. However, these studies mostly focus on the heritability of tracts (i.e. white matter ROIs) themselves, but not the resulting anatomical connections of the human brain (i.e. connectome). To this end, the heritability of brain connectomic features remains largely unknown.

To bridge this gap, we propose to perform a comprehensive heritability analysis of anatomical brain networks using the twin data from the Human Connectome Project (HCP) [19]. We employ a new brain parcellation defined based on functional MRI (fMRI) to generate brain networks with improved anatomical precision, enabling us to examine the genetic influence on the structural coordination within/between functional brain circuits. With three sessions of diffusion weighted imaging (DWI) scans for each individual, we first evaluate the reliability of three edge-level measures, including fractional anisotropy, fiber length and fiber number, and seven network-level measures using intraclass correlation coefficients (ICC). The heritability of those reliable network measures were then estimated using Sequential Oligogenic Linkage Analysis Routines (SOLAR)-Eclipse software. Across all 64,620 edges between 360 ROIs, ~5% of them show significantly high heritability in fractional anisotropy, fiber length or fiber number. Top functional brain circuits connected by these heritable edges include visual and default mode network (DMN). All the tested network level measures, capturing the integrity, segregation or resilience of brain networks, are highly heritable with variance explained by the additive genetic effect ranging from 59% to 77%.

2 Method

HCP data

We downloaded high spatial resolution DWI data from the Human Connectome Project (HCP) [19]. In total, there are 179 pair of twins (Age: 29.1 ± 3.68), including 136 mono-

zygotic females, 98 mono-zygotic males, 68 di-zygotic females and 56 di-zygotic males. DWI data was processed following the MRtrix3 guidelines [18]. More specifically, we first generated a tissue-segmented image appropriate for anatomically constrained tractography [16]. Then, we estimated the multi-shell multi-tissue response function [3] and performed the multi-shell, multi-tissue constrained spherical deconvolution [7]. Afterwards, we generated the initial tractogram with 10 million streamlines (maximum tract length = 250, FA cutoff = 0.06) and applied the successor of Spherical-deconvolution Informed Filtering of Tractograms (SIFT2) methodology [17]. Compared to SIFT, SIFT2 generates more biologically accurate measures of fiber connectivity whilst making use of the complete streamlines reconstruction [17]. Finally, we mapped the SIFT2 output streamlines onto the Glasser atlas with 360 ROIs [5] to produce the structural connectome. The final brain networks were constructed using fibers going through white matter and connecting Glasser ROIs. In this project, we focused on three edge-level measures, including fractional anisotropy (FA), length of fibers (LOF) and number of the fibers (NOF). In addition, we binarized the brain network and calculated seven network-level topological features characterizing the integrity, segregation and resilience of brain networks [14] (see Table 1).

Reliability of connectomic features

Tractography-based networks is known to have an issue on measurement reliability. To investigate the precision of connectomic features, we estimated the test-retest reliability by comparing three DWI data sets of the same individuals acquired at different time points. We calculated intraclass correlation coefficients (ICC) for each brain connectomic feature to evaluate their reliability [12]. All connectomic features with good/excellent reliability (ICC≥0.75) are included for the subsequent heritability analysis [10].

Heritability analysis

Heritability is defined as the proportion of phenotypic variance attributable to genetic effect. In this project, we estimated the heritability of brain connectomoic features extracted from twin subjects in the HCP cohort without using any genetic data. SOLAR-Eclipse software tool is chosen over traditional ACE modal due to its capability in evaluating the covariate effects, significance of heritability and standard error for each trait [9, 4]. It requires three inputs: phenotype traits, covariates measures and a kinship matrix indicating the pairwise relationship between twin individuals. A maximum likelihood variance decomposition method is applied to estimate the variance explained by additive genetic factors and environmental factors respectively. The output from SOLAR-Eclipse includes heritability (h^2), standard error and the corresponding significance p-value for each feature. We estimated the heritability of all brain connectomic features, including FA, LOF, NOF of 64,620 edges and 7 network level measures (Table. 1). Network level measures are derived from binarized brain network in a way that the weight of the link is set to one when it exists and zero otherwise[14]. Prior to the heritability analysis, inverse Gaussian transformation was applied to ensure normality of all the measures. Since many previous studies have reported the effect of age (linear/nonlinear), gender and their interactions on structural brain connectivity [2,22,6,11], all heritability analyses were conducted with age at scan, age^2, sex, age×sex and age^2×sex as covariates. In addition, we extracted the total variance explained by all covariate variables.

3 Results

Reliability of brain connectomic features

Shown in Fig. 1(a) is the scatter plot of edge-level reliability against heritability estimated in SOLAR-Eclipse. Each dot corresponds to one edge and the color indicates the significance of the heritability. For FA, LOF and NOF measures, 11.13%, 9.95% and 45.54% of total edges respectively show consistency across three sessions with good/excellent reliability score (ICC ≥ 0.75). In total, 43,051 out of 193,860 edge-level features passed the reliability test and their heritability patterns will be further analyzed. All tested network level measures show very good reproducibility across sessions, with the ICC value ranging from 0.85 to 0.92 (see Table 1). Since we focus on the features reproducible across three sessions, the heritability analysis was only performed on the DWI data from one session.

Heritability of edge-level measures

After excluding the edges without passing reliability test, there are 5105 edges whose FA show significantly high heritability after stringent Bonferroni correction ($p \leq 0.05/(64,620 \times 3) = 2.58e-7$). For LOF and NOF measures, there are 2687 edges and 7311 edges passing the significance threshold respectively. From Fig. 1(b), we observe that the heritability (h^2) of FA measure is between 0.4 and 0.85. LOF and NOF measures show similar heritability distribution, but there is much less edges with very high heritability ($h^2 \geq 0.8$).

Shown in Fig. 1(c) are the heatmaps of anatomical connection matrix with ICC≥0.75 and $p \leq 2.58e{-}7$ for FA, LOF and NOF measures respectively. Glasser brain regions were reordered to form seven functional groups defined in Yeo parcellation (Fig. 2) [21]. Subcortical part was added to complement Yeo atlas. For all three edge-level measures, the majority of those significantly heritable and reliable edges are located within default mode network, within visual circuit, or connecting default mode network with other circuits, such as Ventral Attention and Frontal-Parietal. Edges connecting Visual and Somato-Motor circuits show the highest average heritability ($h^2 = 0.69$) in FA measure. For LOF and NOF, the edges with the highest average heritability are from Limbic system ($h^2 = 0.64$ for LOF and $h^2 = 0.49$ for NOF).

For each type of measures, we further ranked the edges based on their her- itability (h^2) and examined the brain regions connected by those top heritable edges. In Fig. 3(a) are the heatmaps showing the heritability of top 0.5% edges in FA, LOF and NOF respectively. In the brain connectivity map (Fig. 3(b)), we observed that many top heritable edges are within the frontal lobe. several brain regions in occipital lobe (primary visual cortex) as hubs connected by some highly heritable edges for FA and LOF. These fiber tracts belong to white matter region inferior longitudinal fasciculus, whose regional FA value is previously identified to be highly heritable [9]. In addition, we found that the length of Cingulum tracts (vertical lines in the middle of the brain) are also largely controlled by the genetic factors, with h^2 around 0.65. Its FA measure was also previously reported to be heritable with $h^2 = 0.81$ [9]. For NOF, top heritable edges show a different spatial pattern and are more evenly distributed across the whole brain. Functional brain circuits that are mostly connected by these top heritable edges are DMN and FP (Fig. 3(c)). Finally, we examined the expression

patterns of those brain regions involved in the DMN circuit in Allen Human Brain Atlas, including medial prefrontal cortex, angular, precuneus, posterior cingulate cortex and hippocampus. Interestingly, many of these brain regions connected by heritable edges show very similar gene expression patterns.

Heritability of network-level measures

For each individual, we extracted seven network-level topological features to evaluate the integrity, segregation and resilience of brain network, including assortativity coefficient, modularity, local efficiency, cluster efficiency, transitivity, characteristic path length and its inverse measure global efficiency. The detailed description of these measures is available in [14]. Shown in Table. 1 is the summary of estimated heritability for all topological features. Five covariates can explain ~15% variance of all topological features except for assortativity coefficient and characteristic path length. Sex and age^2× sex are the only factors that exhibit significant influence on the network topology heritability. Assortativity coefficient has the highest reliability, but only 58% of variance can be attributed to the additive genetic effect. The other six features are estimated to have similar heritability around 0.75. These findings are consistent with previous studies, e.g. characteristic path length and clustering coefficient of anatomical brain network are highly heritable [1]. Our heritability estimation is slightly higher than theirs, possibly due to the selection of different brain parcellation schemes.

4 Conclusion

We performed a comprehensive heritability analysis for both edge-level and network-level brain connectomic features. Unlike previous studies that largely focus on the tracts (i.e. white matter ROIs), we used a new brain parcellation to construct brain networks (connectome) with improved anatomical precision. Our results show the degree to which the genetic factors may influence the structural coordination between/within functional brain circuits. Many edges/tracts were found to be highly heritable, particularly those connecting default mode network circuit or visual circuit. This is consistent with another finding that hub regions in the default mode network have very similar gene expression patterns [20]. All seven tested network-level features are reliable and significantly heritable. Future effort is warranted to investigate the genetic variations underlying these heritable connectomic features.

Acknowledgments

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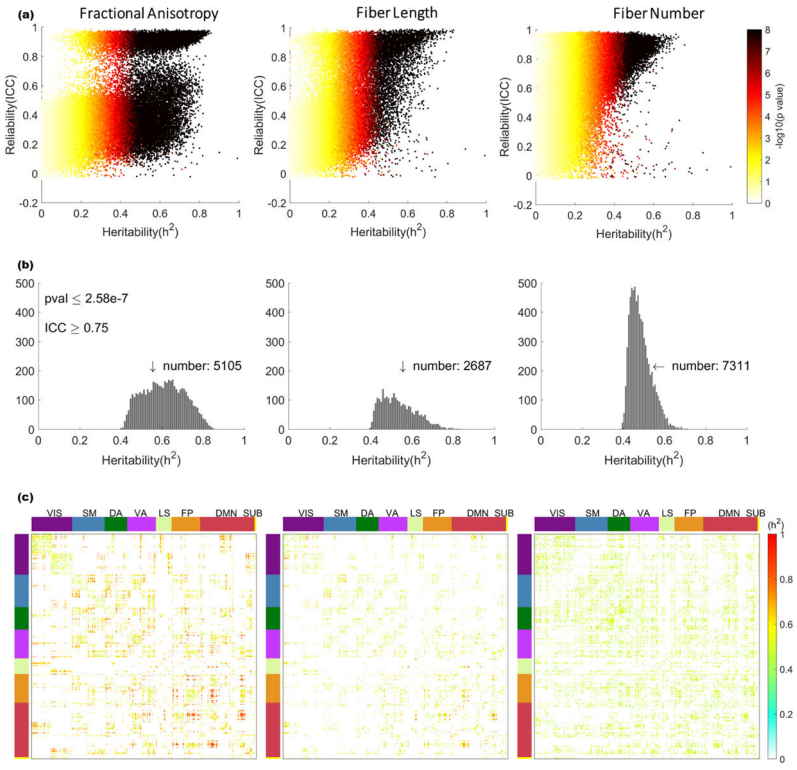

Fig. 1.

Heritability distribution of all significant and reliable edges. (a) Scatter plots of reliability against heritability. Dot color indicates log-transformed p-value. (b) Histogram for reliabe edges. (c) Heatmap of anatomical connection matrix. Rows and columns are reordered to form seven functional groups corresponding to Yeo parcellation. Top and side color panels indicate the corresponding Yeo parcellation of each ROI. The last subcortical (SUB) group is added to complement the Yeo atlas.

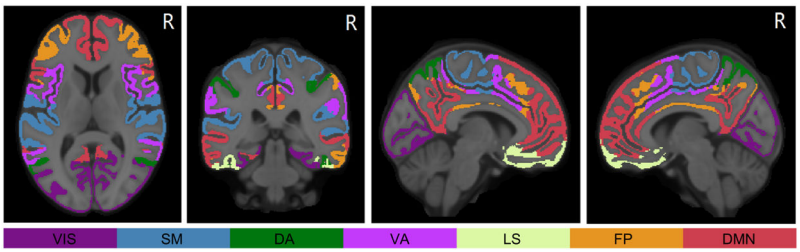

Fig. 2.

Brain map of Yeo parcellation in MNI space. From left to right: axial view, coronal view, sagittal view (Left) and sagittal view (Right). The bottom color panel indicates the color scheme of different regions: Visual (VIS), Somato-Motor (SM), Dorsal Attention (DA), Ventral Attention (VA), Limbic system (LS), Fronto-Parietal (FP) and Default Mode Network (DMN).

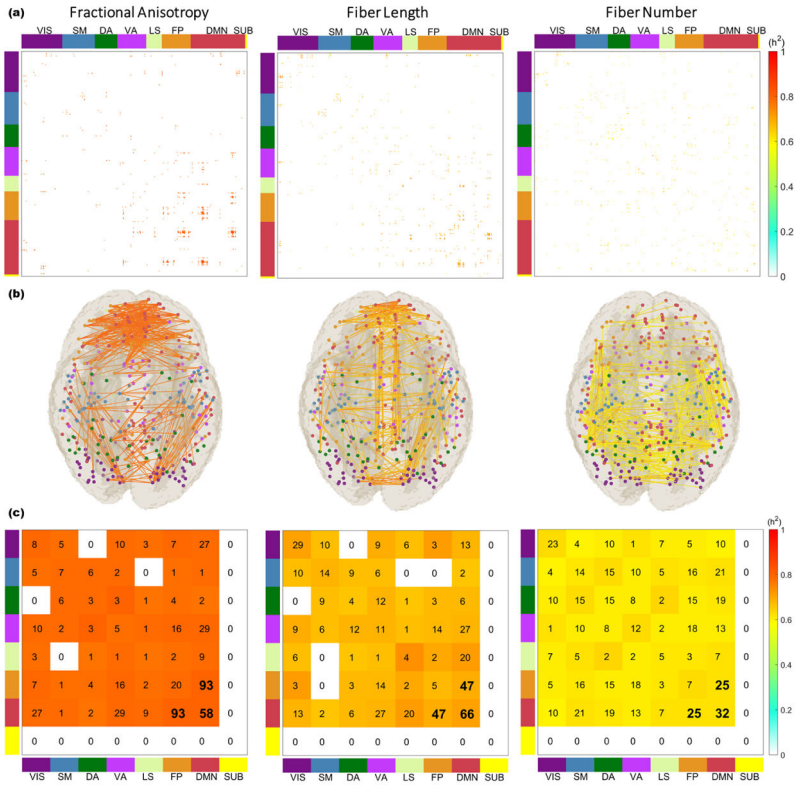

Fig. 3.

Heritability of top 0.5% edges ranked by h^2. (a) Heatmap of anatomical connection matrix. (b) Heritability of edge-level measures in the brain map. Node color indicates different Yeo functional groups. (c) Heatmap showing total number and average h^2 value of edges connecting each pair of functional groups in Yeo parcellation. Top and side color panels indicate the corresponding Yeo parcellation of each ROI. The last subcortical (SUB) group is added to complement the Yeo atlas.

Table 1.

Heritability of topological features derived from brain networks.

Topological Features	ICC	h^2	Std. Error	P-value	Variance (Covariates)
Assortativity Coefficient	0.92	0.59	0.06	3.50×10^{-13}	0.04
Local Efficiency	0.89	0.76	0.04	1.36×10^{-24}	0.18
Modularity	0.87	0.70	0.05	3.02×10^{-19}	0.11
Transitivity	0.89	0.77	0.04	3.90×10^{-24}	0.16
Cluster Coefficient	0.89	0.76	0.04	1.37×10^{-24}	0.17
Global Efficiency	0.87	0.75	0.04	4.88×10^{-23}	0.16
Characteristic Path Length	0.85	0.72	0.04	5.71×10^{-23}	0.02