# Heritability of large-scale functional brain network

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Abstract Submission

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**Introduction:**

The twin study design offers an effective way of determining heritability of the human brain. The extent to which heritability influences the functional brain network is not clearly established. Very few brain imaging studies that ever looked at the heritability of the brain network focused on the small number of well-known regions. In this study, we propose to map the heritability of large-scale functional brain networks at the voxel-level resolution by taking each voxel as a network node. We show that the functional network on monetary reward is mostly inherited.

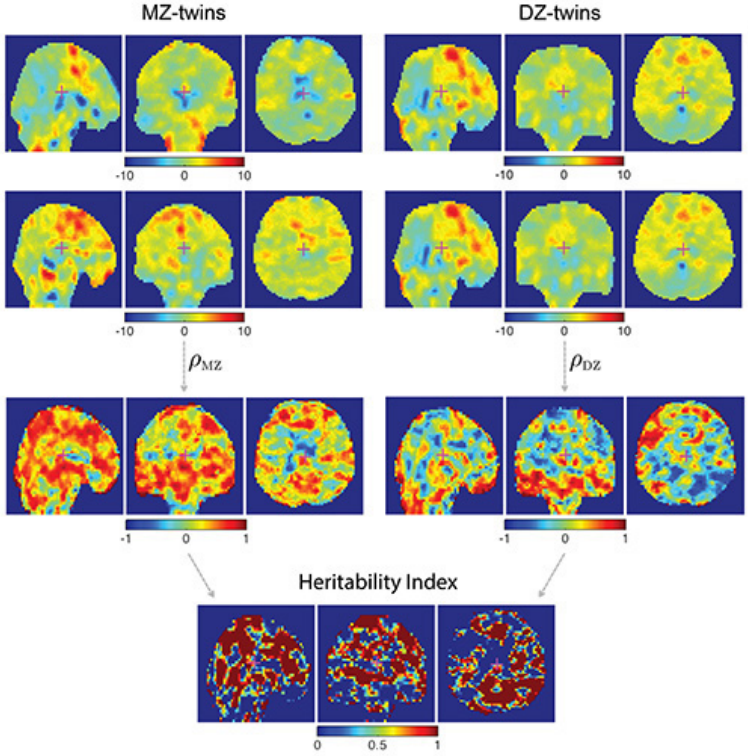



Figure 1. Top: Representative MZ- (left) and DZ-twin (right) pairs of the contrast maps obtained from the first level analysis testing the significance of the delay in hitting the response button in $5 reward in contrast to $0 reward. Middle: The correlation of the contrast maps within twins. Bottom: heritability index measures the genetic contribution in %.

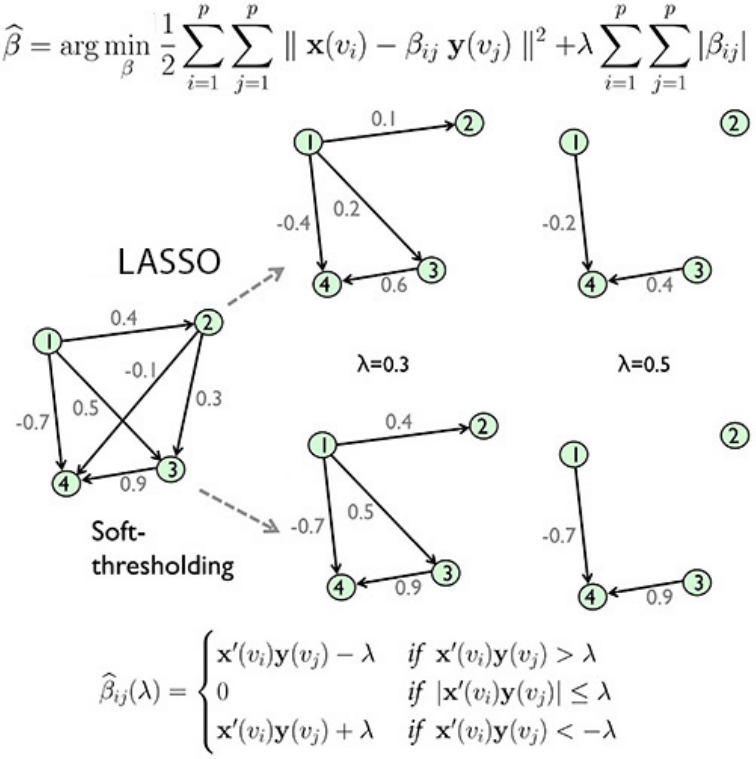



Figure 2. Schematic showing the equivalence of constructed binary graphs using existing LASSO and the proposed soft-thresholding method. Top: The sparse cross-correlations are estimated using LASSO. Bottom: the equivalent binary graph can be obtained by simply thresholding the cross-correlations at sparse parameter $\lambda$.

**Methods:**

Experiment: The study consists of 11 monozygotic (MZ) and 9 same-sex dizygotic (DZ) twin pairs of 3T fMRI. Subjects went through a reward experiment of 3 runs of 40 trials. A total 120 trials consisting of 40 $0, 40 $1 and 40 $5 rewards were randomly split into 3 runs. The aim of the task is to respond to a target on time in order to earn rewards. Trials begin with a cue indicating the amount of money for that specific trial, and then there is delay between the cue and the target (white star) in which participants prepare for the target to appear. Then a target flashes rapidly on the screen. If the participants hit the response button while the star is on the screen they will have succeeded in winning the money. If they hit too late, they will not win the money.

First level analysis: fMRI data went through the standard SPM pipeline. We are interested in knowing the extent of the genetic influence on the functional brain networks of these participants while anticipating the high reward as measured by activity during the delay that occurs between the reward cue and the target. After fitting a general linear model at each voxel, we obtained the contrast map testing the significance of activity in the delay period for $5 trials relative to the no reward control condition (Figure 1). The contrast maps were then used in the proposed study.

We computed the heritability index (HI), which is the twice the difference of the within twin correlations between MZ- and DZ-twins, at each voxel. HI measures the amount of genetic variations in a phenotype in percentage (or probability). Significant parts of the brain show very high genetic influence (Figure 1).

We determined the genetic influence on the fMRI network. This requires computing the cross-correlations among every possible voxel within each twin group. The resulting more than 1 billion cross-correlations are too dense for analysis and interpretation. The proposed sparse cross-correlation network model (Chung, 2016) was used to sparsely select significant cross-correlations. The optimization involving billion connections was easily solved by soft-thresholding (Chung, 2015) (Figure 2).

Graph filtration features (Lee, 2011) such as the number of clusters and the size of the largest clusters are then used to quantify the constructed sparse networks (Figure 3). The significance of any two sparse networks can be quantified using the Kolmogorov-Smirnov (KS) like test statistic (Chung, 2016) on these topological features (Figure 4).

We propose the heritability graph index (HGI), which generalizes HI to networks. HGI is defined as the twice the difference in the within twin cross-correlations between MZ and DZ twins (Figure 5). HGI at the node level is exactly HI. HGI is displayed using a custom brain network visualization pipeline (Figure 5). The statistical significance of HGI can be determined using the KS-like test statistic.

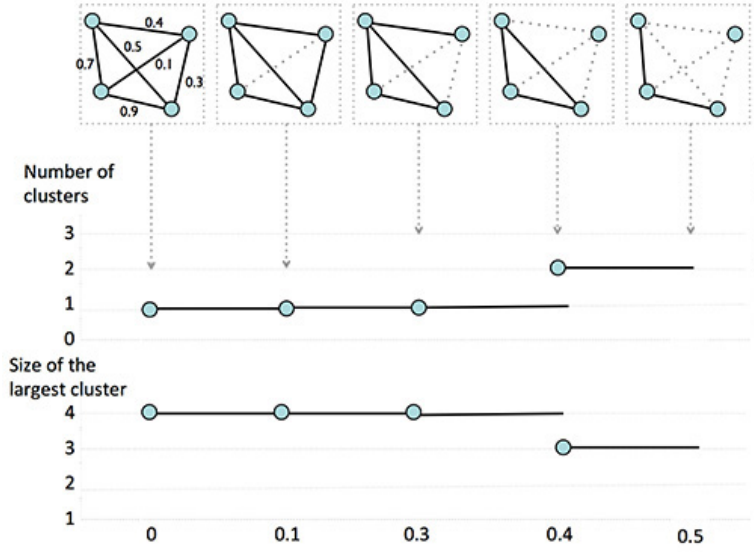
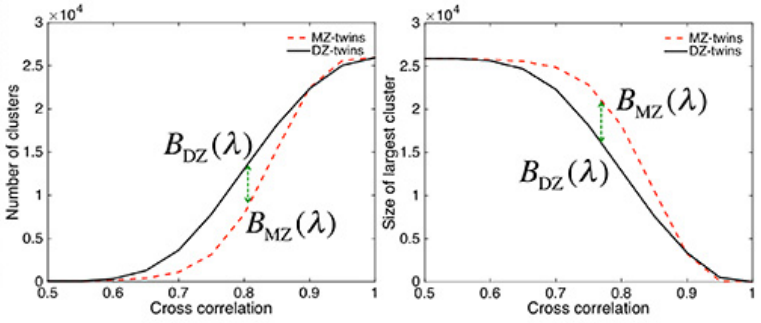



Figure 3. Schematic of graph filtrations. The edge weights of the sparse network is given by the sparse parameter s that threshold the edge. Any edge below the sparse parameter will be deleted. The number of clusters and the size of the largest cluster are tabulated over the sparse parameter.

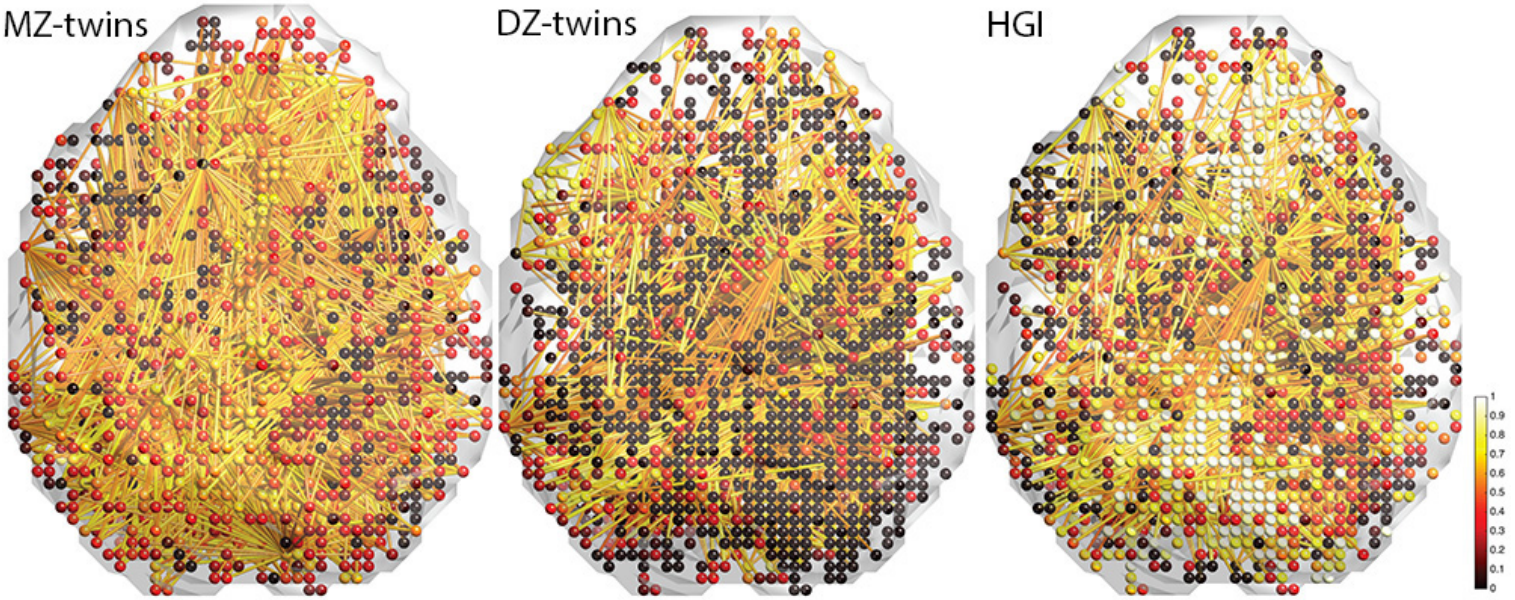



$$p\text{-value} = P\left(\max_{\lambda}\left|B_{MZ}(\lambda) - B_{DZ}(\lambda)\right| \geq \sqrt{2(p-1)d}\right) \approx 2e^{-2d^2} + \ldots$$

Figure 4. Topological inference of graph filtrations on sparse cross-correlations of MZ- and DZ-twins. The number of disjoint clusters (left) and the size of largest cluster (right) are plotted over the sparse parameter $\lambda$ between 0.5 and 1. At given $\lambda$, MZ-twins have smaller number of clusters but larger cluster size indicating many higher correlation edges are still present within larger clusters ($p$-value $< 0.00002$).

**Results:**

For the number of clusters and the size of largest clusters, the p-values are respectively less than 0.00002 and 0.00001 indicating very strong significance of HGI. The results are also displayed in a new visualization pipeline (Figure 5).




$$\mathrm{HI}(v_i) = 2\left[\rho_{\mathrm{MZ}}(v_i) - \rho_{\mathrm{DZ}}(v_i)\right]$$

$$\mathrm{HGI}(v_i, v_j) = 2\left[\rho_{\mathrm{MZ}}(v_i, v_j) - \rho_{\mathrm{DZ}}(v_i, v_j)\right]$$

$$\mathrm{HGI}(v_i, v_i) = \mathrm{HI}(v_i)$$

Figure 5. The genetic map of the whole brain network. Node colors are correlations of MZ- (**left**) and DZ-twins (**middle**). The edge colors are cross-correlations between nodes thresholded at 0.5. **Right**: Node values are heritability indices (HI). Edge values are heritability graph indices (HGI) thresholded at 0.5. MZ-twins show higher correlations at the both voxel and network levels compared to DZ-twins. Some low HI nodes have high HGI. The voxel-level feature HI will fail to detect such subtle genetic effects on the brain network.

**Conclusions:**

The study provides the large-scale baseline heritability map for planning and guiding future genetic studies. Numerous hub nodes are automatically identified that can be further selected for additional more refined connectivity analysis with smaller number of nodes.

**Genetics:**

Genetic Modeling and Analysis Methods [1]

**Imaging Methods:**

BOLD fMRI

**Modeling and Analysis Methods:**

fMRI Connectivity and Network Modeling [2]

**Keywords:**

Other - Twins

[1|2]Indicates the priority used for review

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Functional MRI

**For human MRI, what field strength scanner do you use?**

3.0T

**Which processing packages did you use for your study?**

SPM
Other, Please list - Custom visualization pipeline

**Provide references in author date format**

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