Heritability of Structural Brain Connectivity Measures in 188 Twins

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Background

It is well-established that many aspects of brain structure, including structural connectivity, are heritable [1,2]. **Graph theory** is a new method that assesses brain connectivity by treating the brain as a collection of nodes (regions) and edges (connections). A number of parameters exist to describe the relationship between these nodes and edges. Characteristic path length (**CPL**) is an average measure of the path length in a network. Mean clustering coefficient (**MCC)** is a measure of how many neighbors of a given node are also connected to each other. Global efficiency (**EGLOB)** the inverse of CPL; networks with lower CPL are more efficient than those with greater CPL. Small-worldness (**SW)** represents the balance between network differentiation and network integration. Modularity (**MOD)** is the degree to which a system can be subdivided into smaller networks [3].

Methods

Participants - 188 twins (54 MZ pairs and 40 same-sex DZ pairs; 62 men/126 women, mean age 23.25+/-1.83SD years)
Tractography – Tractography was performed as described in [4], resulting in 70x70 matrices of the fiber density (normalized for total number of fibers traced) between 35 cortical regions in the left and right hemispheres.
Graph theory metrics – We used the Brain Connectivity Toolbox (https://sites.google.com/a/brain-connectivity-toolbox.net/bct/Home, [3]) to calculate 5 standard measures of connectivity: CPL, MCC, EGLOB, SW, and MOD. These were calculated for whole brain and left and right hemispheres separately. We calculated these over a range of sparsities (.1-.3, in .01 increments), and calculated the area under the curve of those 20 data points to generate an integrated score for each measure. This was done to generate more stable scores. These scores were entered into an **ACE structural equation model** to estimate the proportion of variance due to additive genetic (A), common (C) and unique (E) environmental factors, with age and sex as covariates.

Scan – 4T Bruker Medspec MRI. Anatomical (T1) parameters: inversion recovery rapid gradient echo sequence; TI/TR/TE=700/1500/3.35ms; flip angle=8 degrees; slice thickness=0.9mm, 256x256x256; HARDI parameters: single-shot echo planar imaging with twice-refocused spin echo sequence to reduce eddycurrent induced distortions; 23cm FOV, TR/TE=6090/91.7ms, 128x128; each 3D volume consisted of 55 2-mm thick axial slices with no gap and 1.79x1.79 mm2 in-plane resolution. 105 images per subj: 11 with no diffusion sensitization (iT2-weighted b0 images) and 94 diffusion weighted (DW) images (*b*=1159 s/mm2) with gradient directions evenly distributed on the hemisphere.

Results

For whole brain, left and right graph theory metrics, a comparison of the p values for the ACE and AE model yielded no significant differences, thus we used the AE model for each of these. Results are shown in **Table 1.**

	Whole Brain	***Left***	***Right***
CPL	**0.50 (.14)**	**0.40 (.36)**	**0.45 (.53)**
MCC	0.53 (0.00081)	0.13 (1)	**0.14 (.19)**
EGLOB	**0.58 (.88)**	**0.24 (.67)**	**0.65 (.22)**
SW	0.51 (0.018)	0.18 (0.010)	**0.19 (.60)**
MOD	**0.46 (.15)**	0.17 (0.011)	**0.50 (.72)**

Table 1. Heritability results for graph theory metrics whole brain and in left and right hemispheres separately. A *p* value above 0.05 indicates the model is a good fit.

For the whole brain, EGLOB was most heritable, followed by CPL and MOD (58%, 50%, 46%). In the left hemisphere, CPL and EGLOB were heritable (40%, 24%). In the right hemisphere, EGLOB was most heritable, followed by MOD, CPL, SW, and MCC (65%, 50%, 45%, 19%, 14%). **Figure 1** depicts the structural network averaged across subjects.

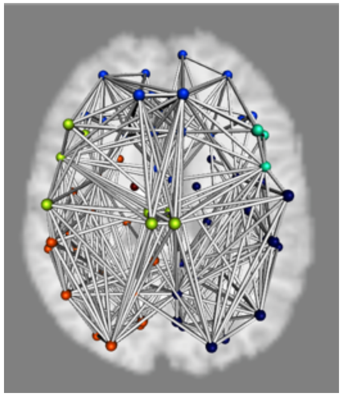

Figure 1. Structural network averaged across subjects. Color indicates membership in different modules, a trait that was heritable across the whole brain and in the right hemisphere, generated at sparsity 0.2 using the UCLA Multimodal Connectivity Package (https://github.com/jbrown81/umcp)

To understand why we found such differences in heritability between the hemispheres we looked at the MZ and DZ correlations, charted in **Figure 2**.

Results – cont.

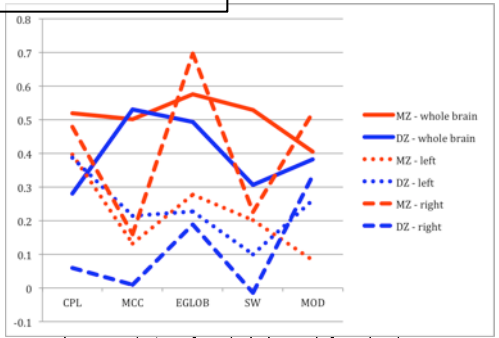

Figure 2. MZ and DZ correlations for whole brain, left and right hemisphere calculations of CPL, MCC, EGLOB, SW, and MOD

Conclusions

In this study we establish that graph theory metrics of structural brain connectivity are heritable in a sample of 188 twins. We found that a number of graph theory parameters were heritable, and that these results differed when considering the whole brain versus the hemispheres separately. Finding of less heritability in the left hemisphere is surprising and appears to be driven by both higher rDZ and lower rMZ in the left hemisphere than in the right.
One limitation of this study is the relatively small sample size for considering questions of heritability. This study is on-going, with a projected end of N=1150. With a larger sample we will be more confident in our findings.
This work establishes basic properties of graph theory metrics and and offers promising targets for quantitative genetic analysis of brain connectivity.

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