

HERITABILITY OF STRUCTURAL CONNECTIONS FROM HCP DIFFUSION MRI DATA

Stamatios N Sotiropoulos¹, Xu Chen², Stephen M Smith¹, David C Van Essen³, Timothy E Behrens¹, Thomas E Nichols², and Saad Jbabdi¹

¹FMRI Centre, University of Oxford, Oxford, United Kingdom, ²Department of Statistics, University of Warwick, Coventry, United Kingdom, ³Department of Anatomy & Neurobiology, Washington University, St Louis, MO, United States

Target Audience: This work will be of interest to scientists studying diffusion MRI tractography and brain anatomical connectivity in large populations.

Purpose: There is great interest in understanding population variability of brain connectivity patterns, and the genetic contributions to this variability, e.g. as studied by the ENIGMA consortium [1] and the Human Connectome Project (HCP)[2]. Heritability, the proportion of variability attributable to genetic sources, is a quantitative measure that allows the identification and ranking of phenotypes. In this work, we examine the heritability of structural connections using diffusion MRI data from the HCP. Previous work has illustrated heritability of functional connections [3], as well as heritability of DTI-extracted measures [4,5]. We utilise the HCP state-of-the-art anatomical and diffusion MRI datasets [6,7] to obtain whole-brain structural connectivity matrices and infer on heritability using permutation testing [8]. Importantly, we localise regions with most heritable connections across different cortical “geographic” (folding-based) parcellations and compare to heritability trends of cortical morphological features.

Methods: Minimally-preprocessed [9] anatomical and diffusion MRI (dMRI) data [6,7] were obtained from the HCP (www.humanconnectome.org). These corresponded to 170 subjects with 29 monozygotic (MZ), 22 dizygotic (DZ) twin pairs and their non-twin siblings (SIB).

Structural Connectivity Estimation: For each subject, the multi-shell, high spatial and high angular resolution dMRI data were used for fiber orientation estimation through a multi-shell parametric deconvolution model [10]. Inference was performed via a Bayesian framework, with a likelihood that accounts for the Rician nature of the MRI signal. The number of identifiable fiber bundle orientations (up to three) per voxel was determined using automatic relevance determination, in the form of a sparsifying prior that penalizes fibre complexity [11]. The inferred orientations were then used to estimate long-range connections using the probabilistic tractography tool in FSL [11,12]. Streamline particles (N=3,000) were seeded from every voxel in white and gray matter. A measure of path probability was obtained between every pair of a standardized set of vertices [9] from the WM/GM boundary surface (~30,000 vertices/hemisphere). The cortical pial surface was used as a termination mask and CSF-filled regions as exclusion masks. To encourage estimation of direct connections, streamlines were not allowed to enter and subsequently exit basal ganglia nuclei, but instead were terminated upon exit (unless they originated from the basal ganglia) [13]. Similarly, they were terminated when crossing the WM/GM boundary surface with the same direction (e.g. going from outside the surface to inside) more than once. The 60K x 60K “dense” connectomes were reduced to connectome versions using two standard bilateral Feesurfer parcellations [14] (Fig. 1, a coarser one with 34 and a finer one with 75 parcels). “Homologue” regions belonging to the same parcel were divided to two individual parcels resulting in 68 and 150 parcels respectively. Average path probabilities between each pair of the parcellated schemes were then obtained. To remove insignificant connections, the probabilities were averaged across subjects and, for each parcel, those below the 10th percentile were set to zero.

Heritability Estimation: We computed heritability in two ways. (i) An “aggregate heritability” was computed based on the connectome-wide correlation between subject pairs. For each MZ, DZ or SIB-pair, a correlation is computed between the pair’s parcellated connectomes after demeaning. The MZ and DZ correlations were then compared in a two-sample t-test (a valid test of any heritability). Twice the difference of MZ and DZ correlations provides a rough estimate of mean heritability [14]. (ii) Heritability of each connectome element was computed using an ACE model [15]. This variance components model estimates the proportion of variance due to Additive genetics (A), Common (C) and unshared Environmental (E) effects; for this extended twin design, the “C” effect was defined by family. To discount major deterministic effects, age, total gray matter and total white matter volume were used as nuisance regressors. Often estimated by iterative and error-prone maximum likelihood, we instead fit the ACE model with a fast, non-iterative method implemented in the APACE toolbox [8]. P-values are computed with permutation (1000 perms.), as under the null hypothesis of no heritability, MZ and DZ families of the same size can be randomly exchanged. Inference over the network matrix is corrected for multiple comparisons with family-wise error correction (FWE rate=0.05).

Results & Discussion: Fig. 2A shows boxplots of the pair-wise correlations used to compute aggregate heritability, for the finer Destrieux parcellation. Aggregate heritabilities were significant, with $h^2=0.256$ ($p=0.01$) and $h^2=0.298$ ($p=0.001$) for the coarser and finer parcellations, respectively. Fig. 2B shows the results of the edgewise heritability analysis from the ACE model, as the histogram of non-zero h^2 values (84% and 83% edges had $h^2>0$ for each parcellation, when 50% would be expected by chance). The mean edgewise h^2 was highly significant, as revealed by the empirical distribution built by permutation testing, with $\langle h^2 \rangle = 0.253$ (95% conf. interval: [0.17, 0.3], $p=0.003$) and $\langle h^2 \rangle = 0.237$ (95% conf. interval: [0.17, 0.275], $p=0.001$) for the two parcellations. These results suggest that structural connectivity, for both parcellation levels, is heritable.

We further identified which brain regions have the most heritable connections. Fig. 3A illustrates the average heritability of connections arising from each parcel. For both parcellations, inferior parietal and superior temporal regions exhibited bilaterally high average heritability, along with the left cuneus (not seen in the presented lateral views). Regions around the lateral fissure and the middle and inferior temporal areas also exhibited moderate-to-high heritability (depending on the parcellation). To interpret these findings, it is important to consider whether they genuinely reflect genetic influences in the underlying fibre patterns or whether they are driven by confounding factor(s). We explored here whether the gyral bias in tractography [16] (the fact that streamlines are biased towards the gyral crowns rather than gyral walls and sulci) impacts the results. If that were the case, we would expect the cortical surface curvature to be heritable in similar regions as the connections. We performed a similar heritability analysis using cortical mean curvature as a trait. Fig. 3B illustrates the mean heritability of cortical curvature for each parcel. As it can be seen, this follows a different pattern than in Fig. 3A, with the most heritable regions being around the central sulcus, the orbitofrontal cortex, the fusiform/parahippocampal area and the calcarine sulcus. Some partial overlap is observed around the lateral fissure, it is therefore unlikely that such a cortical feature drives the connection heritability. Further exploration of potential confounds (e.g. parcel size/location) to heritability of structural connections is needed. We will examine such possibilities in the future by discounting these effects using sharper cross-subject alignment [16].

Conclusion: Heritability of structural connections in the healthy adult brain has been shown using the HCP dMRI data. We illustrated that these heritability estimates are consistent across different cortical parcellations and that they are not (at least completely) determined by cortical curvature.

References: 1. Stein et al, Nature Genetics 44:552-61, 2012. 2. Van Essen et al, NeuroImage 62:2222-31, 2012. 3. Smith et al, OHBM, 1719, 2014. 4. Chiang et al, J. Neuroscience, 29:2212-24, 2009. 5. Kochunov et al, NeuroImage 53:1109-16, 2010. 6. Ugurbil et al, NeuroImage 80:80-104, 2013. 7. Sotiropoulos et al, NeuroImage 80:125-143, 2013. 8. Chen et al, OHBM, 3410, 2014, <http://warwick.ac.uk/tenichols/APACE>. 9. Glasser et al, NeuroImage 80:105-124, 2013. 10. Jbabdi et al, MRM 68:1846-55, 2012. 11. Behrens et al, NeuroImage 34: 144-55, 2007. 12. Smith et al, NeuroImage 2004. 13. Smith et al, NeuroImage 62:1924-38, 2012. 14. Fischl et al, Cerebral Cortex 14:11-22, 2004. 15. Neale & Maes, Methodology of genetic studies of twins and families, Kluwer, 2004. 16. Chen et al, OHBM, 3524, 2014. 15. Van Essen et al, Diffusion MRI (2nd Edition), Elsevier, 337-358, 2013. 16. Robinson et al, NeuroImage 100:414-26, 2014.

Acknowledgement: We acknowledge support from the WashU-UMinn Human Connectome Project (NIH 1U54MH091657-01).

