

## **Genomic Kinship Construction to Enhance Genetic Analyses in the Human Connectome Project Data.**

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## **Abstract**

Imaging genetic analyses quantify genetic control over quantitative measurements of brain structure and function using coefficients of relationship (CR) that code the degree of shared genetics between subjects. CR can be inferred through self-reported relatedness or calculated empirically using genome-wide SNP scans. We hypothesized that empirical CR provides a more accurate assessment of shared genetics than self-reported relatedness. We tested this in 1,046 participants of the Human Connectome Project (HCP) (480M/566F) recruited from the Missouri twin registry. We calculated the heritability for seventeen quantitative traits drawn from four categories (brain diffusion and structure, cognition and body physiology) documented by the HCP. We compared the heritability and genetic correlation estimates calculated using self-reported and empirical CR methods Kinship-based INference for GWAS (KING) and weighted allelic correlation (WAC). The polygenic nature of traits was assessed by calculating the empirical CR from chromosomal SNP sets. The heritability estimates based on whole-genome empirical CR were higher but remain significantly correlated ( $r > 0.85$ ) with those obtained using self-reported values. Population stratification in the HCP sample have likely influenced the empirical CR calculations and biased heritability estimates. Heritability values calculated using empirical CR for chromosomal SNP sets were significantly correlated with chromosome length ( $r \sim 0.7$ ) suggesting a polygenic nature of these traits. The chromosomal heritability patterns were correlated among traits from the same knowledge domains; among traits with significant genetic correlations; and among traits sharing biological processes without being genetically related. The pedigree structures generated in our analyses are available online as a web-based calculator ([www.solar-eclipse-genetics.org/HCP](http://www.solar-eclipse-genetics.org/HCP)).

## Introduction

International collaborations and biobanks such as the Human Connectome Project (HCP) are collecting large multimodal datasets to identify genetic and environmental factors that underlie normal and illness-related variances in the brain and body (Glasser, et al. 2013; Van Essen, et al. 2013). Genetic analyses use coefficients of relationship (CR) to characterize the degree of shared genetic variance among study participants to partition the phenotypic variance into genetic and environmental sources. Traditionally, CR is approximated based on self-reported relationships. For example, a pair of individuals may identify themselves as parent and child, siblings, or as cousins. This method requires knowing all relationships among study participants. Self-reported relatedness values can be inaccurate (e.g., mistaken zygosity in the case of same-sex twins or mistaken paternity) and this can bias genetic analyses. Alternatively, CR can be measured empirically from high-throughput genome-wide single nucleotide polymorphism (SNP) scans (Ramstetter, et al. 2017; Toro, et al. 2014; Wood, et al. 2014; Yang, et al. 2010). We hypothesized that empirical CR provides more accurate estimates of shared genetic variance (heritability) than self-reported values. We tested this hypothesis using the quantitative brain and body measurements collected by the HCP collaboration.

The analysis of heritability based on modeling of mixed effects divides the phenotypic variance into additive genetic and environmental components in order to quantify the degree of genetic variance. This mixed effect model uses an  $N \times N$  matrix of CR values (where  $N$  is the sample size), and is known as the pedigree matrix. Self-reported CR values are calculated as the length of the shortest ancestral path (kindship) between two individuals. Each kinship type is a fixed number: 1 for the self and a monozygotic twin;  $\frac{1}{2}$  for parents, full siblings and dizygotic twins;  $\frac{1}{4}$  for grandparents or half-siblings;  $\frac{1}{8}$  for cousins; and 0 for unrelated individuals. It codes the *expected* degree of shared genomic variance for a kinship type. However, no two siblings share exactly 50% of the genome-wide genetic polymorphisms (Visscher, et al. 2007; Visscher, et al. 2006), and seemingly *unrelated* individuals residing in the same geographical area may have a non-zero degree of shared genetic variance.

CR values can also be inferred empirically by quantifying the similarity in the whole-genome or chromosomal SNP sets among the study participants. The complex traits used in this analysis are expected to have a highly polygenic architecture, with genetic factors residing on all chromosomes. Traits may share chromosomal heritability patterns due to pleiotropy (directly shared genetic variance) and/or due to similarity in the chromosomal distribution of genes that regulate similar functions. For instance, genetic analyses of hypertension, arterial stiffening and cerebral white matter integrity converged on a 1q24 region that harbors the constellation of genes that code for cell adhesion (*SELP*, *SELL*, and *SELE*) protein and the coagulation factor V (*F5*) (Kochunov, et al. 2009; Kochunov, et al. 2012; Mitchell, et al. 1996; Turner, et al. 2005)

We used four empirical CR methods with different normalization approaches. The Kinship-based INference for Genome wide association study (KING) method was developed to approximate self-reported CR values. It is frequently used to verify self-

reported relationships in family samples (Manichaikul, et al. 2010). In our study, KING was used to verify zygosity for same-gendered twins. A second method, the Weighted Allelic Correlation (WAC) approach, was developed to study the “missing heritability” of complex phenotypes. The WAC approach produces CR values that are weighted by minor allelic frequency (MAF) using a parameter,  $\alpha$ , which is assigned values of 1, -1, or 0 (Speed, et al. 2017a; Speed, et al. 2012). **A weighting of  $\alpha=1$  calculates CR by up-weighting on common variants, whereas a weighting of  $\alpha=-1$  up-weights CR on the low MAF variants.** CR values independent of MAF are calculated using  $\alpha=0$ .

We hypothesized that empirical CR will provide a more accurate assessment of shared genetic variance than the self-reported values. To test our hypothesis, we chose seventeen quantitative traits that represented four knowledge domains ascertained by HCP: diffusion and structural imaging measures of brain integrity, neurocognitive assessment and physical health. We selected traits based on the expectation of significant heritability and the potential for shared genetic variance across the knowledge domains. Five diffusion traits were analyzed using standard Diffusion Tensor Imaging (DTI) and advanced White Matter Tract Integrity (WMTI) models (Ades-Aron, et al. 2018; Jelescu, et al. 2014) to assess the integrity and microstructure of cerebral white matter (WM). Structural brain integrity measurements included average gray matter (GM) thickness and regional gray and white matter volumes. We chose four neuropsychological traits consisting of two working memory and two processing speed measurements. In previous research, these traits have shown high heritability and significant genetic correlation with measures of brain integrity (Glahn, et al. 2013; Kochunov, et al. 2016; Kochunov, et al. 2015). We also considered body mass index (BMI) and systolic and diastolic blood pressures based on research linking body adiposity to cerebral integrity (Kochunov, et al. 2011b; Ryan, et al. 2017; Spieker, et al. 2015).

We tested two hypotheses: (1) Empirical CR derived from whole genome genotyping will provide more accurate heritability measurements than self-reported CR; and (2) Empirical CR derived from the chromosomal sets of SNPs can be used to probe the polygenic nature of quantitative traits (Visscher, et al. 2007; Visscher, et al. 2006). We show that heritability analyses produce higher estimates of additive genetic variance using empirical rather than self-reported CR. The chromosomal heritability patterns suggest genes that influence phenotypes with related biological functions may have similar chromosomal distribution patterns of alleles. Our analyses can be repeated using the pedigrees found online at NITRC.org and the heritability calculator for self-reported and empirical pedigrees at solar-eclipse-genetics.org/HCP.

## Methods

### *Subjects*

Heritability and genetic correlation analyses were performed on data from 1,046 (480/566 M/F) participants in the Human Connectome Project (HCP) for whom the scans and data had been released (humanconnectome.org) after passing the HCP quality control and assurance standards (Marcus, et al. 2013). Details of this release are available in the HCP

reference manual. The participants in the HCP study were recruited from the Missouri Family and Twin Registry of individuals born in Missouri (Van Essen, et al. 2013). All HCP participants were deliberately selected as belonging to young adult sibships of average size 3–4 that include MZ or DZ twin pairs and siblings. Participants ranged in age from 22 to 36 years (average age,  $28.7 \pm 3.68$  years). This age range was chosen because it corresponds to the period when neurodevelopment is largely complete and the onset of neurodegeneration has not yet occurred. The full set of inclusion and exclusion criteria is detailed elsewhere (Van Essen, et al. 2013). In short, the HCP subjects are healthy individuals free from major psychiatric or neurological illnesses. They are drawn from ongoing longitudinal studies (Edens, et al. 2010; Sartor, et al. 2010), where they received extensive previous assessments including history of drug use and emotional and behavioral problems. All subjects provided written informed consent on forms approved by the Institutional Review Board of Washington University in St. Louis.

### ***Genotyping***

The genotyping data for sample size of 1141 subjects that were released by HCP and available through dbGAP database ([https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs001364.v1.p1](https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001364.v1.p1)) was used. Briefly, all subjects were genotyped using Illumina Multi-Ethnic Global Array (MEGA) SNP-array that provides extended coverage in European, East Asian, and South Asian populations. We used genotyped 1,580,642 snps that satisfied the quality control conditions following exclusions of SNPs with MAF < 1%, genotype call rate < 95% and Hardy-Weinberg equilibrium <  $1 \times 10^{-6}$ .

### ***Quantification of the degree of relationship.***

SOLAR-Eclipse uses coefficients of relationship ( $r_{i,j}$ ) (equal to twice the coefficients of kinship) to code the probability that two alleles from individuals  $i$  and  $j$  are identical by descent. The coefficient of relationship is a function of identity by descent sharing statistics,  $r_{i,j} = \pi_{1i,j}/2 + \pi_{2i,j}$ , where  $\pi_{1i,j}$  and  $\pi_{2i,j}$  are the probabilities that two individuals share one and two alleles through a common ancestry.

Self-reported coefficients of relationship between individuals  $i$  and  $j$  are calculated as  $r_{i,j} = 1/2^n$  where  $n$  is the length of the ancestral path that connects them. Common  $n$  values include  $n=1$  for parents, full siblings and dizygotic twins;  $n=2$  for grandparents, half-siblings;  $n=3$  for cousins; and increasing  $n$  values for more distance relatives. Unrelated individuals assumed to share no ancestral variance and are coded with CR=0. The self-reported CR coefficients may be subject to mistaken zygosity for same sex twins. Therefore, the self-reported CR values for HCP were coded after correcting for mistaken zygosity values using the *Robust-KING* empirical CR method. The zygosity for thirty-six twin pairs was changed from self-reported dizygotic (CR=0.5) to monozygotic (CR=1).

Empirical  $r_{i,j}$  were calculated using methods implemented in SOLAR-Eclipse software ([www.solar-eclipse-genetics.org](http://www.solar-eclipse-genetics.org)). The *empirical\_pedigree* function takes the allelic data stored in a PLINK file as an input and produces a pedigree file. All empirical methods infer  $r_{i,j}$  based on the average identity by state statistics while weighting the result by sample-level allele frequency at each SNP. We calculated four empirical pedigrees using two methods: robust Kingship based INference for Genome-wide studies (robust-

KING)(Manichaikul, et al. 2010) and weighted allelic correlation (WAC) approaches(Hayes, et al. 2009).

#### *Robust-KING.*

The robust relationship inference KING method was developed for fast  $r_{ij}$  calculations in familial samples. The method is described in details in the original publication (Manichaikul, et al. 2010). Briefly, the coefficients of relatedness are calculated using Equation 1.

$$r_{i,j} = 1 - \frac{N_{Aa}^i + N_{Aa}^j}{2N_{Aa}^i} + \frac{N_{Aa,Aa} - 2N_{AA,aa}}{N_{Aa}^i} \quad (1)$$

Where  $N_{Aa}^{ij}$  are the total number of heterozygotes for the i-th and j-th individuals and  $N_{Aa,Aa}$  and  $N_{AA,aa}$  are the total number of SNPs at which both individuals of the pair are hetero- and homozygous. The KING method is computationally efficient because the N coefficients are computed using binary logic operations (AND and OR).

#### *Weighted Allelic Correlation (WAC)*

The WAC approach (Hayes, et al. 2009) calculates the coefficient of relationship using the correlation coefficient among the allelic scores and weighting it by the minor allele frequency factor:  $p(1-p)^\alpha$  using equation 2.

$$r_{i,j} = \frac{1}{N} \sum_{n=1}^N (G_{i,n} - 2p_n)(G_{j,n} - 2p_n)(p_n(1 - p_n))^\alpha \quad (2)$$

Where  $G_{i,n}$  and  $G_{j,n}$  are the allelic scores (0, 1 or 2) for the n-th SNP for the i-th and j-th individuals,  $p_n$  is the minor allele frequency (MAF) for this SNP calculated for the sample and N is the total number of SNPs. The parameter  $\alpha$  determines the weightings of the coefficient of relationship proportional to MAF ( $\alpha > 0$ ), irrespective of MAF ( $\alpha = 0$ ) and inversely proportional to MAF ( $\alpha < 0$ ). We calculated the pedigree matrix for three common settings  $\alpha = 1, 0$  and  $-1$ . The setting of 1 up-weights CR on the similarity in common alleles; the setting of  $-1$  up-weights CR on similarity in rare alleles; and a setting of 0 calculates CR independent of allelic frequency.

#### *Quantitative Traits*

We selected traits from four domains: diffusion, structure, neuropsychology and physiology (Table 1). The traits within each domain were chosen based on the expected correlation among the traits within and across the domains. Diffusion weighted imaging (DWI) traits were calculated using standard diffusion tensor imaging (DTI) and White

Matter Tract Integrity (WMTI) models. All other traits were obtained from the public section of the HCP database (db.humanconnectome.org). The structural traits included whole-brain average gray matter (GM) thickness, whole-brain and cortical GM volume, and whole brain white matter (WM) volume. Four neuropsychological traits were chosen to be sensitive to cognitive processing speed and working memory. Working memory performance was assessed using accuracy scores on the list sorting (Accuracy working memory) and dimensional change card sort (Card Sorting) tasks. Processing speed was assessed using the Pattern Completion Processing Speed from the NIH Toolbox (<http://www.nihtoolbox.org>) (Carlozzi, et al. 2013) and reaction time (Barch, et al. 2014). Physiological traits included body mass index (BMI) and systolic and diastolic blood pressure (BPSys, BPDias) (Table 1).

*Diffusion data collection and preprocessing.* Diffusion data was collected at Washington University St. Louis using a customized Siemens Magnetom Connectome 3 Tesla scanner with a 100 mT/m maximum gradient strength and a 32-channel head coil. Details on the scanner, image acquisition and reconstruction are provided elsewhere (Ugurbil, et al. 2013) and found online at <https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release>). Briefly, diffusion data were collected using a single-shot, single refocusing spin-echo, echo-planar imaging sequence with 1.25 mm isotropic spatial resolution (TE/TR=89.5/5520 ms, FOV=210x180 mm). Three gradient tables of 90 diffusion-weighted directions and six b=0 images each, were collected with right-to-left and left-to-right phase encoding polarities for each of the three diffusion weightings (b=1000, 2000, and 3000 s/mm<sup>2</sup>). The total imaging time for collection of diffusion data was approximately one hour.

Diffusion data were preprocessed using a modified HCP Diffusion pipeline (Glasser, et al. 2013; Sotiropoulos, et al. 2013). The pipeline first corrected for thermal noise by applying the Marchenko-Pastour Principle Component Analysis (MPPCA) (Veraart, et al. 2016a; Veraart, et al. 2016b; Veraart, et al. 2016c), and was followed by the normalization of b0 image intensity across runs. Corrections for Gibbs ringing (Kellner, et al. 2016) and Rician bias (Gudbjartsson and Patz 1995) were applied as well as corrections for EPI susceptibility and eddy-current-induced distortions, gradient-nonlinearities, and subject motion. Lastly, a brain mask was applied.

*Diffusion data modeling.*

Diffusion data were analyzed using two approaches: a standard diffusion tensor fitting and an advanced White Matter Tract Integrity model. Standard DTI-FA values were obtained by fitting the diffusion tensor model (first two terms in equation 3) using the FSL-FDT toolkit (Behrens, et al. 2003). WMTI is an extension of DTI that uses a model-independent diffusion kurtosis signal representation and the kurtosis term to account for non-Gaussian behavior of the diffusion signal (Eq. 3) (Jensen and Helpern 2010; Jensen, et al. 2005; Lu, et al. 2006). WMTI derives both the diffusion and kurtosis tensors using the second-order expansion of the multi *b*-shell diffusion-weighted signal decay as a function of the *b*-value:

$$\ln S(\mathbf{b}, \mathbf{g}) = \ln S(\mathbf{0}) - b \sum_{i,j=1}^3 g_i g_j D_{ij} + \frac{b^2}{6} \left( \sum_{i=1}^3 \frac{D_{ii}}{3} \right)^2 \sum_{i,j,k,l=1}^3 g_i g_j g_k g_l W_{ijkl} + O(b^3) \quad (3)$$

with  $g_i$  the  $i$ th component of gradient direction  $\mathbf{g}$  and  $S(0)$  the nondiffusion-weighted signal intensity.  $D_{ij}$  is the  $ij$ th element of the fully symmetric diffusion tensor  $\mathbf{D}$ , characterized by six independent elements and  $W_{ijkl}$  denotes an element of the diffusion kurtosis tensor  $\mathbf{W}$ , which is fully parameterized by 15 independent elements. During the WMTI fit, multivariate regression was used to estimate the eigenvalues for the diffusion ( $L_{1,2,3}$ ) and kurtosis ( $K_{1,2,3}$ ) tensors. The three eigenvalues for the diffusion tensor were converted to axial ( $L_{\parallel}$ ), radial, ( $L_{\perp}$ ), and DKI-FA. Similarly, the three eigenvalues of the kurtosis tensor were converted to axial ( $K_{\parallel}$ ), radial, ( $K_{\perp}$ ), and kurtosis anisotropy (KA) values (Poot, et al. 2010). WMTI calculates two additional parameters: axonal water fractions (AWF) and tortuosity of the extra-axonal space (TORT), Eq. 4 and 5

$$AWF = \frac{K_{\max}}{K_{\max} + 3} \quad (4)$$

$$TORT = \frac{D_{e,\parallel}}{D_{e,\perp}} \quad (5)$$

AWF is hypothesized to constitute the fraction of diffusion signal that originates from intra-axonal water.  $K_{\max}$  is the maximum kurtosis along all directions, and  $D_{e,\parallel}$  and  $D_{e,\perp}$  are the apparent axial and radial diffusivities of the extra-axonal space (Jelescu, et al. 2014).

Whole-brain average diffusion parameters were obtained using the ENIGMA-DTI protocol ([https://www.nitrc.org/projects/enigma\\_dti](https://www.nitrc.org/projects/enigma_dti)) (Jahanshad, et al. 2013). Briefly, DTI-FA images were non-linearly registered to the ENIGMA-DTI target brain using FSL's *FNIRT* (Jahanshad, et al. 2013). This target was created as a “minimal deformation target” based on images from the participating studies as previously described (Jahanshad, et al. 2013). The data were processed using FSL's tract-based spatial statistics (*TBSS*; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>) analytic method (Smith, et al. 2006) modified to project individual FA values onto the hand-segmented ENIGMA-DTI skeleton mask. The DTI-FA projection maps were used to project DKI-FA, KA, AWF and TORT maps onto the skeleton to ensure that all values corresponded to the same voxels. The whole-brain average traits were calculated by averaging values across the skeleton.

#### ***Heritability and genetic correlation: Analysis of additive genetic variance and covariance.***

Heritability ( $h^2$ ) is the proportion of the total phenotypic variance ( $\sigma_p^2$ ) that can be explained by the genetic effects of genes ( $\sigma_g^2$ ), Equation 6.

$$h^2 = \sigma_g^2 / \sigma_p^2. \quad (6)$$



SOLAR-Eclipse's heritability calculations are accelerated using the Fast Permutation Heritability Inference (FPHI) approach (polygenic –fphi command). It uses a single step estimation to produce an asymptotically unbiased estimate (Ganjgahi, et al. 2015). The FPHI provides a significant ( $10^3$ ) computational acceleration relative to the standard iterative maximum likelihood estimation in SOLAR-Eclipse.

We used a bivariate genetic analysis to calculate the magnitude and significance of the genetic correlation coefficient ( $\rho_G$ ).  $\rho_G$  corresponds to the proportion of variability that results from shared additive genetic effects. The overall phenotypic correlation ( $\rho_P$ ) between two traits (represented by A and B in Equation 7) is equal to  $\rho_G$  and the residual correlation ( $\rho_E$ ) that represents shared environmental effects.

$$\rho_P = \sqrt{h_A^2} \sqrt{h_B^2} \cdot \rho_G + \sqrt{1-h_A^2} \sqrt{1-h_B^2} \cdot \rho_E \quad (7)$$

Where,  $h_A^2$  and  $h_B^2$  denote the heritability for each of the traits. If  $\rho_G$  is significantly different from zero, then a significant proportion of the variance in two traits results from the shared genetic factors (Almasy, et al. 1997). All genetic analyses were conducted with age, sex, age\*sex, age<sup>2</sup>, age<sup>2</sup>\*sex included as covariates.

#### ***Chromosomal heritability estimates.***

We partitioned the genotyping data into individual chromosomes to examine the distribution of empirical heritability across the genome. We estimated the coefficients of relationship using SNPs from each chromosome (22 in total) and used pedigree matrices constructed from these coefficients to estimate the empirical heritability.

## Results

### *Empirical versus self-reported coefficients of relationship.*

The scatter plots of the empirical and self-reported coefficients of relationship (off-diagonal elements) are shown in Figure 1. The KING approach faithfully approximated the average coefficients of relationship:  $0.99 \pm 0.001$  for identical twins (self-reported coefficient=1.0);  $0.50 \pm 0.02$  for fraternal twins/siblings (self-reported coefficient=1.0); and  $0.25 \pm 0.04$  for half-siblings (self-reported coefficient=0.25). The KING coefficients showed a slight negative bias ( $-0.05 \pm 0.05$ ) for the unrelated individuals (self-reported coefficient=0). The correlation between KING and self-reported coefficients was positive and significant  $r^2=0.95$  ( $p < 10^{-10}$ ).

The relationship coefficients calculated by WAC, under the three different situations, were lower than the self-reported values. For identical twins, the coefficients of relationship were  $0.79 \pm 0.05$ ,  $0.70 \pm 0.09$  and  $0.65 \pm 0.20$  for  $\alpha=1, 0$  and  $-1$ , respectively. For fraternal twins/siblings the coefficients were  $0.48 \pm 0.06$ ,  $0.43 \pm 0.08$  and  $0.40 \pm 0.10$  for  $\alpha=1, 0$  and  $-1$ . For half-siblings, these coefficients were  $0.31 \pm 0.05$ ,  $0.31 \pm 0.09$  and  $0.26 \pm 0.10$  for  $\alpha=1, 0$  and  $-1$ . The coefficients for unrelated individuals had a zero bias with standard deviation of 0.05, 0.05 and 0.06 for  $\alpha=1, 0$  and  $-1$ .

The highest correlation between empirical and self-reported relationships were observed for WAC  $\alpha=1$  ( $r^2=0.98$ ,  $p < 10^{-10}$ ), followed by  $\alpha=0$  ( $r^2=0.97$ ,  $p < 10^{-10}$ ). The lowest was observed for WAC  $\alpha=-1$  ( $r^2=0.74$ ,  $p < 10^{-10}$ ).

### *Heritability.*

Heritability estimates calculated using self-reported and empirical coefficients are shown in Table 1 and Figure 2. Heritability estimates using the empirical relationship, as a group, were significantly higher than those derived from self-reported relationships (ANOVA  $p=0.001$ ). The average heritability for 19 traits was  $h^2=0.71 \pm 0.22$ ,  $0.73 \pm 0.23$ ,  $0.75 \pm 0.22$ ,  $0.77 \pm 0.21$ ,  $0.81 \pm 0.17$  for self-reported, KING and WAC  $\alpha=1, 0, -1$ , respectively (Figure 2).

When compared to self-reported coefficients, WAC  $\alpha=-1$  showed a significant 15% increase in heritability estimates ( $p=10^{-8}$ ). The KING approach also provided heritability estimates that were 1.5% higher than those obtained using the self-reported coefficients ( $p = 0.04$ ). The pattern of heritability values was consistent for all approaches ( $r^2 > 0.98$ ) and with similar standard errors (Figure 2).

### *Genetic correlation.*

Genetic correlation analysis was used to calculate the phenotypic ( $\rho_P$ ), genetic ( $\rho_G$ ) and environmental ( $\rho_E$ ) bivariate correlation coefficients (Figure 3). We observed significant correlation patterns for within-domain correlations. Notable observations include significant correlations between FA values calculated using DTI and WMTI approaches ( $\rho_P=0.89$ ,  $\rho_G=0.91$ ,  $\rho_E=0.89$ , all  $p < 10^{-6}$ ) and strong correlations between DTI-FA and KA ( $\rho_P=0.82$ ,  $\rho_G=0.89$  and  $\rho_E=0.57$ ). The correlation results for self-reported pedigree were similar ( $r^2 > 0.95$ ) to these produced with the four empirical approaches.

***Chromosomal heritability estimates.***

Heritability estimates using coefficients of relationship calculated for each of the 22 chromosomes using the WAC approach are shown in Figure 4. The heritability values were highest for WAC  $\alpha=-1$  ( $p<0.01$ ). The average heritability values for all seventeen traits were significantly correlated with the chromosomal length ( $r=0.76, 0.70$  and  $0.55$ ,  $p<0.01$  for  $\alpha=1, 0$  and  $-1$ ) (Figure 4, bottom graph).

Partial correlation analysis was used to calculate bivariate correlations for twenty-two chromosomal heritability values among the seventeen traits, while correcting for the chromosomal length (Figure 5). This analysis tested the similarities among the variance explained by genetic variability encoded by each of the chromosomes. The patterns produced by this analysis were significantly correlated for off diagonal elements among the three  $\alpha$  weighting values (all  $r>0.80$ , all  $p<10^{-5}$ ). The pattern of chromosomal correlation values was not correlated with phenotypic, genetic or environmental correlation patterns (all  $r<0.10$ , all  $p>0.3$ ). They replicated significant within-domain correlations (Figure 5). They also showed that some traits with hypothetically overlapping biological function, such as white matter volume and diffusion domain measurements had a significant similarity in the chromosomal heritability patterns in the absents of significant phenotypic or genetic correlation between them (Figure 5). Heritability estimates for the chromosomal pedigrees were not available for the KING approach due to numerical failures of chromosomal heritability estimates.

## Discussion

The empirical coefficients of relationship (CR) derived from high-density genome scans may improve heritability estimates in the complex phenotypes collected by the Human Connectome Project (HCP). We used four empirical CR approaches and seventeen quantitative traits selected from the four knowledge domains collected by the HCP. We observed that heritability values calculated using empirical CR values were highly correlated with heritability estimates obtained using self-reported CR. The weighted allelic correlation (WAC) approach that up-weighted CR coefficients based on sharing of low MAF alleles ( $\alpha=-1$ ) produced higher heritability estimates. This may suggest that the variance in complex neuroimaging, neuropsychological and body health traits is influenced by low MAF alleles or that the low frequency variants may provide more informative CR. However, post-hoc analyses showed that WAC  $\alpha=-1$  approach was more sensitive to the ancestral/ethnic differences in this mixed sample and this may have biased heritability estimates. Heritability estimates obtained using chromosomal CR were correlated with the length of the chromosome ( $r>0.5$ ), suggesting the expected highly polygenetic inheritance mechanism for complex traits. The patterns of chromosomal heritability estimates for the HCP traits suggested that genes that influence phenotypes with closely related biological functions, such as brain volume and axonal geometry, might have a similar chromosomal distribution of alleles that influence these traits. The heritability calculator for self-reported and empirical pedigrees is available online ([solar-eclipse-genetics.org/HCP](http://solar-eclipse-genetics.org/HCP)) and the pedigrees are shared via [NITRC.org](http://NITRC.org).

Inferring relatedness in family samples, such as HCP, is an essential component of imaging genetic analyses. We compared the relatedness estimates for four empirical CR approaches and found them highly correlated with the self-reported CR values ( $r=0.86-0.99$ ). The Kinship-based INference for Gwas (KING) approach was developed to approximate self-reported CR in family samples. This method faithfully matched the self-reported CR values in relatives but showed a negative bias (average CR=-0.05) for unrelated individuals (expected CR=0). In other studies, this approach was 92-99% accurate in estimating relatedness in first- to third-degree relatives, but likewise showed a negative bias (underestimated relatedness) in more distant relatives, due to the deviations from the Hardy-Weinberg approximation (Ramstetter, et al. 2017; Visscher, et al. 2007).

**Here, we used empirical CR methods that were developed for performing snp-based heritability analyses in unrelated samples and implemented in LDAK(Speed, et al. 2017b) and GCTA(Visscher, et al. 2007; Visscher, et al. 2006), approaches. Snp-based heritability analyses are usually performed in unrelated individuals where relatives (CR>0.025) are routinely removed. The rational for removing related individuals from large samples of unrelated individuals was to prevent potential biases due to shared environment and focus on the variance explained by common genetic variants. The empirical CR matrix estimates the genetic relatedness amongst a set of individuals and the variance component methods are appropriate for both unrelated and related individuals(Zaitlen, et al. 2013). The snp-heritability approaches in related sample changes this type of inference in favor of the estimate of the total additive genetic variance (from both common and rare sources). The use**

**of related individuals leads to a more statistically powerful inference of total additive genetic variance as demonstrated here where the empirical heritability estimates were similar or higher than these obtained using self-reported values.**

CR calculated using the weighted allelic correlation (WAC) method showed lower correlation with self-reported values when the weighting emphasis shifted from alleles with common to lower MAF ( $r=0.99, 0.98$  and  $0.86$  for  $\alpha=1,0,-1$ ). All WAC approaches showed zero bias for the unrelated subjects (average CR=0.00). **The CR values calculated using WAC approach were sensitive to the ethnic diversity of the HCP sample. Post-hoc analyses were performed to investigate the bi-modal distribution in CR coefficients that was most apparent for the  $\alpha=-1$  setting (Figure 1). The variance in the WAC  $\alpha=-1$  CR values for monozygotic twins was significantly affected (adjusted  $r=0.80$ ) by the variance captured by the first four genetic-distance clusters calculated using the multidimensional scaling analysis. This dependence was lower but significant for both WAC  $\alpha=0$  and  $1$  (adjusted  $r^2=0.70$  and  $0.57$ , respectively). In all instances, cluster 1 scores showed the greatest explained variance and were significant for all three  $\alpha$  settings. Multidimensional scaling scores for clusters 2 and 3 were significant for  $\alpha=-1$ , while cluster 3 scores were significant for  $\alpha=0$ . Multidimensional scaling analysis captures the “genetic distance” between subjects and is sensitive to population stratification in ethnically diverse samples such as HCP. The variance in multidimensional scaling scores was not significantly correlated with the traits and repeating heritability analyses with the scores included as covariates produced no difference in outcome.**

Empirical CR approaches produced higher heritability values than these obtained using self-reported CR. The KING method produced a ~1.5% improvement over self-reported data. Higher  $h^2$  values were seen with increased weighting on the low MAF ( $0.5\% < \text{MAF} < 10\%$ ) SNPs with the highest heritability estimates for the WAC  $\alpha=-1$  method. This may suggest that the phenotypic variance in complex traits may be linked to lower rather than higher MAF variants (Speed, et al. 2017a). It may also suggest that ethnic differences in the sample may bias the heritability estimates produced using empirical CR calculated WAC approach. We observed a high ( $r>.90$ ) correlation between measurements of the shared genetic and environmental variance among the traits. The partitioning of shared phenotypic variance is the function of the joint heritability. The heritability values were highly correlated between empirical and self-reported approaches and therefore the results of the genetic correlation analyses were similar for all methods.

We observed significant genetic correlation among the traits within each of the domains. All the traits within the diffusion domain were highly inter-correlated on both genetic and environmental estimates. This included high genetic ( $\rho_G=0.81, p<10^{-10}$ ) correlation between fractional anisotropy (FA) values calculated using DTI and WMTI approaches despite the differences in the underlying models. Likewise, all structural volumetric measurements showed high genetic correlations (all  $\rho_G>0.70$ , all  $p<10^{-3}$ ). However, cortical GM thickness showed only modest genetic correlation with cortical GM and WM volumes ( $\rho_G=0.31$  and  $0.20, p<0.001$ ), replicating previous observations (Winkler, et al. 2010). BMI showed the expected shared genetic variance with both systolic ( $\rho_G=0.60$ ,

$p < 10^{-9}$ ) and diastolic ( $\rho_G = 0.48$ ,  $p < 10^{-7}$ ) blood pressure (Figure 3). Significant genetic correlation was observed between the scores of working memory tests (Accuracy and Picture Sequencing  $\rho_G = 0.62$ ,  $p < 10^{-10}$ ; Accuracy and Card Sorting  $\rho_G = 0.63$ ,  $p < 10^{-10}$ ) and processing speed and reaction time ( $\rho_G = -0.62$ ,  $p < 10^{-10}$ ) despite the differences in the measurement procedure: i.e., computer test vs. fMRI experiment (Figure 3). The genetic correlations between traits from different domains were sparse. We replicated a significant correlation between FA and Processing speed ( $\rho_G = 0.44$  and  $0.34$ ,  $p < 10^{-6}$  for FA measured using DTI and WMTI approaches) and FA and reaction time ( $\rho_G = -0.27$  and  $-0.22$ ,  $p < 0.01$ ) (Kochunov, et al. 2010; Kochunov, et al. 2015). Likewise, we replicated a significant negative correlation between BMI and KA ( $\rho_G = -0.22$ ,  $p = 0.0001$ ) (Ryan, et al. 2017). We also observed previously reported significant genetic correlation between DTI-FA and WMTI-KA values ( $\rho_G = 0.21$  and  $0.22$ ,  $p < 0.0001$ ) (Kochunov, et al. 2011a).

Heritability analyses were performed using CR calculated for each individual chromosome. The highest average  $h^2$  values were again observed for the WAC  $\alpha = -1$  method. There was a positive correlation between the length of the chromosome and the  $h^2$  values derived from its CR matrix. The correlation with chromosomal length was numerically higher for an  $\alpha$  weighting that emphasized similarity on common alleles ( $r = 0.76$  vs  $0.55$  for  $\alpha = 1$  and  $-1$ , respectively), but this difference was not significant ( $p > 0.1$ ). There were strong similarities in the patterns of per-chromosome  $h^2$  values for some traits (Figure 5). The chromosomal  $h^2$  correlation matrix was visually similar but uncorrelated with the patterns of genetic and environmental correlations. Traits with significant genetic correlation showed strong correlation of the chromosomal  $h^2$  values. Traits from overlapping biological functions had highly correlated chromosomal heritability patterns even in the absence of genetic or environmental correlation. For instance, the axonal water fraction (AWF) and WM volumes showed a significant ( $r = 0.92$ ,  $p < 10^{-8}$ ) correlation between chromosomal heritability patterns in the absence of significant genetic or environmental correlations ( $\rho_G = 0.08$ ,  $p = 0.08$ ;  $\rho_E = 0.03$ ,  $p = 0.7$ ). The processing speed and reaction times showed heritability patterns that overlapped with cognitive, diffusion and structural traits, yet there was no overlap with the heritability patterns for BMI or blood pressure. Overall, the chromosomal data indicates that the genetic architecture of complex quantitative traits is reflected by similarity for low MAF SNPs, where the density of the loci may also vary across chromosomes.

## Limitations

Empirical CR methods have biological limitations. All four of the empirical methods we evaluated produced negative CR values for some unrelated individuals. The negative CR reflects violations of Hardy-Weinberg equilibrium such as ancestral differences in linkage disequilibrium structures, overlapping generations and deviations from the assumption that genotype frequencies in a population will remain constant from generation to generation (Visscher, et al. 2007). We retained negative CR values in the analysis because selecting a threshold for empirical CR may bias the likelihood calculations (Visscher, et al. 2007). Empirical CR values may vary by both the method and the genotyping approach and this may alter the heritability results. We show that heritability and genetic correlation patterns demonstrated a high ( $r > 0.9$ ) correlation

regardless of the CR approach, which suggests the high overall reproducibility of these analyses.

**Empirical CR methods should be used with caution in ethnically diverse samples due to potential for population stratification. We observed that CR coefficients calculated using the WAC approaches were sensitive to the ethnicity-related genetic distance among subject. HCP is a multiethnic sample and genetic distance among the subjects calculated using a multidimensional scaling approach explained significant variance in the CR. The association was the highest for the WAC  $\alpha=-1$  that up-weighted CR estimates on the low minor allele frequency variants. This has likely biased the pedigree matrix and led to higher heritability values by incorporating ethnicity-specific genetic distance in the calculation of additive genetic variances.**

Empirical CR methods also have methodological limitations. The empirical CR matrix is more densely populated than self-reported matrix and this increased (by a factor of 10-20) the computational time for the classical maximum likelihood methods. The computation time remained the same for FPHI while producing an accurate approximation of  $h^2$  values (within 1-3%). Another methodological limitation were convergence issues in chromosomal CR values produced by the KING approach which prevented the use of these values in the analyses. This convergence issue was observed during the inversion of the chromosomal CR matrix in both the classical ML and FPHI methods.

## **Conclusions**

We compared heritability calculations based on empirically measured genetic variance among participants in HCP and observed them to be significantly higher than those calculated using self-reported CR. The highest  $h^2$  values were observed for the CR method that weighted on the sharing of low-MAF alleles. However, the population stratification caused by ethnic differences among subjects has likely biased this approach, producing higher heritability estimates. Nonetheless, the heritability values were highly correlated between empirical and self-reported CR. The genetic correlation pattern mirrored the pattern of shared phenotypic variance and was similar across all CR methods. Empirical CR values can be calculated for whole-genome or individual chromosomes. Further research may focus on heritability estimates calculated for specific SNP sets such as these selected for protein coding genes and regulatory regions. The heritability values for HCP traits can now be computed using self-reported and empirical pedigrees online at <http://www.solar-eclipse-genetics.org/HCP>





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Traits	Trait Description	Heritability ( $h^2$ ) estimates				
<i>Diffusion Domain</i>		Self-reported	KING	WAC $\alpha=1$	WAC $\alpha=0$	WAC $\alpha=-1$
AWF	Axonal water fractions calculated using WMTI model	0.91±0.02 ( $p<10^{-26}$ )	0.91±0.01 ( $p<10^{-26}$ )	0.93±0.01 ( $p<10^{-26}$ )	0.94±0.01 ( $p<10^{-26}$ )	0.96±0.01 ( $p<10^{-26}$ )
DKI-FA	Fractional Anisotropy of water diffusion (FA) calculated using white matter tract integrity (WMTI) model (fits diffusion and kurtosis tensor)	0.85±0.02 ( $p<10^{-26}$ )	0.86±0.02 ( $p<10^{-26}$ )	0.89±0.02 ( $p<10^{-26}$ )	0.92±0.01 ( $p<10^{-26}$ )	0.93±0.02 ( $p<10^{-26}$ )
DTI-FA	Fractional Anisotropy of water diffusion (FA) calculated using diffusion tensor model (fits diffusion tensor only)	0.86±0.02 ( $p<10^{-26}$ )	0.85±0.02 ( $p<10^{-26}$ )	0.88±0.02 ( $p<10^{-26}$ )	0.91±0.02 ( $p<10^{-26}$ )	0.94±0.02 ( $p<10^{-26}$ )
KA	Kurtosis Anisotropy calculated from the WMTI model	0.86±0.02 ( $p<10^{-26}$ )	0.87±0.02 ( $p<10^{-26}$ )	0.90±0.02 ( $p<10^{-26}$ )	0.91±0.01 ( $p<10^{-26}$ )	0.94±0.02 ( $p<10^{-26}$ )
TORT	Tortuosity of the extra cellular space calculated using WMTI model	0.79±0.02 ( $p<10^{-26}$ )	0.77±0.03 ( $p<10^{-26}$ )	0.82±0.03 ( $p<10^{-26}$ )	0.85±0.02 ( $p<10^{-26}$ )	0.90±0.03 ( $p<10^{-26}$ )
<i>Structural Imaging Domain</i>						
GM Thickness	Average thickness of cortical gray matter (GM) ribbon	0.80±0.02 ( $p<10^{-26}$ )	0.80±0.03 ( $p<10^{-26}$ )	0.83±0.02 ( $p<10^{-26}$ )	0.85±0.02 ( $p<10^{-26}$ )	0.88±0.02 ( $p<10^{-26}$ )
Cortical GM Volumes	Volume of cortical GM	0.93±0.01 ( $p<10^{-26}$ )	0.97±0.02 ( $p<10^{-26}$ )	0.96±0.03 ( $p<10^{-26}$ )	0.99±0.01 ( $p<10^{-26}$ )	0.99±0.02 ( $p<10^{-26}$ )
GM Volume	Volume of cerebral GM	0.93±0.01 ( $p<10^{-26}$ )	0.98±0.02 ( $p<10^{-26}$ )	0.99±0.01 ( $p<10^{-26}$ )	0.99±0.01 ( $p<10^{-26}$ )	0.99±0.01 ( $p<10^{-26}$ )
WM Volume	Volume of cerebral WM	0.94±0.01 ( $p<10^{-26}$ )	0.95±0.01 ( $p<10^{-26}$ )	0.95±0.01 ( $p<10^{-26}$ )	0.96±0.01 ( $p<10^{-26}$ )	0.94±0.01 ( $p<10^{-26}$ )
<i>Body physiology Domain</i>						

BMI	Body mass index	0.72±0.04 (p=10 <sup>-26</sup> )	0.73±0.04 (p<10 <sup>-26</sup> )	0.76±0.04 (p<10 <sup>-26</sup> )	0.78±0.03 ( p<10 <sup>-26</sup> )	0.82±0.01 (p<10 <sup>-26</sup> )
BP Sys	Systolic blood pressure	0.40±0.05 (p=10 <sup>-12</sup> )	0.40±0.05 (p=10 <sup>-13</sup> )	0.45±0.06 (p=10 <sup>-14</sup> )	0.48±0.06 (p=10 <sup>-15</sup> )	0.56±0.06 (p=10 <sup>-16</sup> )
BP Dias	Diastolic blood pressure	0.46±0.05 (p=10 <sup>-16</sup> )	0.50±0.05 (p=10 <sup>-17</sup> )	0.56±0.05 (p=10 <sup>-18</sup> )	0.59±0.05 (p=10 <sup>-18</sup> )	0.65±0.06 (p=10 <sup>-19</sup> )
<i>Neurocognitive Domain</i>						
Accuracy-WM	Accuracy scores on the list sorting working memory task	0.53±0.04 (p<10 <sup>-26</sup> )	0.51±0.04 (p<10 <sup>-26</sup> )	0.49±0.00 (p<10 <sup>-26</sup> )	0.57±0.05 (p<10 <sup>-26</sup> )	0.65±0.05 (p<10 <sup>-26</sup> )
Reaction Time	Reaction time measured in the attention task	0.41±0.06 (p=10 <sup>-12</sup> )	0.40±0.06 (p=10 <sup>-11</sup> )	0.43±0.06 (p=10 <sup>-13</sup> )	0.47±0.06 (p=10 <sup>-14</sup> )	0.60±0.06 (p=10 <sup>-15</sup> )
Processing Speed	Pattern Completion Processing Speed Scores	0.38±0.06 (p=10 <sup>-11</sup> )	0.35±0.06 (p=10 <sup>-10</sup> )	0.39±0.06 (p=10 <sup>-14</sup> )	0.42±0.06 (p=10 <sup>-15</sup> )	0.51±0.07 (p=10 <sup>-16</sup> )
Picture Sequence	Scores on the picture sequence working memory task	0.50±0.05 (p=10 <sup>-21</sup> )	0.52±0.04 (p<10 <sup>-26</sup> )	0.55±0.05 (p<10 <sup>-26</sup> )	0.58±0.05 ( p<10 <sup>-26</sup> )	0.65±0.05 ( p<10 <sup>-26</sup> )
Card Sorting	Scores of the dimensional change card sort task	0.40±0.06 (p=10 <sup>-12</sup> )	0.45±0.05 (p=10 <sup>-15</sup> )	0.49±0.06 (p=10 <sup>-16</sup> )	0.53±0.05 (p=10 <sup>-17</sup> )	0.64±0.05 (p=10 <sup>-19</sup> )

**Table 1.** Heritability values ( $\pm$ standard error) for quantitative traits from four knowledge domains ascertained by HCP calculated using self-reported and empirical coefficients of relationship.



### Figure Legend

**Figure 1.** Scatter plot of coefficients of relationship (CR) obtained using empirical approaches vs. self-reported values (off-diagonal elements only). The linear fit between empirical and self-reported parameter was characterized by intercept (A), slope (B) and the correlation coefficient squared ( $r^2$ ).

**Figure 2.** Scatter plot of heritability values calculated using empirical relationship (CR) vs. these obtained from self-reported CR, including linear fit lines, equations and correlation coefficients.

**Figure 3.** The phenotypic ( $\rho_p$ ), left, genetic ( $\rho_G$ ), center, and environmental ( $\rho_E$ ), right, correlation coefficients calculated among the quantitative traits.

**Figure 4.** Heritability estimates (top panel) calculated for chromosomal SNPs showed significant dependence on the length of the chromosome.

**Figure 5.** The partial correlation coefficients calculated for chromosomal weighted allelic correlation (WAC) heritability patterns while correcting for chromosomal length. The partial correlation maps show significant within and across domains similarity in heritability patterns for traits that encode measurements with overlapping biology such as the white matter volume (WM) and the diffusion domain measurements.

