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TITLE: Multivariate GREML analysis reveals shared genetic architecture between brain regions and behavioral traits

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ABSTRACT:
Genome-based Restricted Maximum Likelihood (GREML) estimation has been developed to estimate the SNP-heritability of traits using observed genetic similarities among unrelated individuals in a population. The bivariate extension of this method enables the estimation of the genetic correlation between two traits. One often combines

the estimates of pairwise combinations of traits into a multivariate genetic correlation matrix in case one is interested in the genetic correlation across more than two traits. However, this "pairwise bivariate" approach may result in a genetic correlation matrix which is not internally consistent. Besides, the corresponding standard errors of this genetic correlation matrix are not completely correct as they do not reflect the full data structure. Therefore, we developed a multivariate extension of the GREML method which guarantees the internal consistency of the resulting genetic correlation matrix using a Cholesky decomposition. To deal with the computational complexity of the model, we developed an optimization procedure which is more efficient than the present "pairwise bivariate" approach (reducing complexity from order $(NP)^3$ to NP^3).

We used the multivariate GREML method to analyze the shared genetic architecture of the human brain (76 cortical and subcortical structures) and 10 behavioral traits. Using a sample of approximately 14,000 unrelated individuals from the UK Biobank, one of our main findings is that two genetically distinct clusters in the brain are associated with intelligence. Besides the empirical value of these findings, the resulting multivariate genetic correlation matrix can also be used as input for methods such as genomic structural equation modeling (Genomic-SEM).

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