

Heritability Estimation Methods of Multiple Brain Measures: A Preliminary MRI Study in Twins

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Abstract. Heritability is the proportion of total phenotypic variance due to genetic influence. To estimate heritability, Falconer's formula (FF) and structural equation modeling (SEM) are used. However, compared to FF, SEM is hardly applicable for neuroimaging analysis because the SEM tools such as Mx cannot calculate numerous data simultaneously nor sequentially. We developed a code for multiple calculations using Mx to estimate the heritability of gray matter thickness at 81,924 surface points across the cerebral cortex. Although FF and SEM provided similar results, SEM was inclined to yield lower heritability estimates and more conservative significance than FF. In considering the results, we propose that the correction for multiple comparisons should be carefully performed for the results from SEM.

1 Introduction

Heritability is a fundamental notion in genetics that summarizes how much of the variation in a trait among individuals is attributable to differences in genotype [3]. h^2 is used in reference to the proportion of total phenotypic variance due to genetic influence. There are two representative methods for estimation of heritability: Falconer's formula (FF) and structural equation modeling (SEM). FF is based on the difference between monozygotic (MZ) and dizygotic (DZ) twin correlations. In FF, heritability is defined as

$$h^2 = 2(r_{MZ} - r_{DZ}) . \quad (1)$$

where r_{MZ} is the MZ or identical twin correlation, and r_{DZ} is the DZ or fraternal twin correlation. SEM is based on decomposition of the phenotypic variance into the genetic and environmental components. SEM defines heritability as

$$h^2 = V_G / V_P . \quad (2)$$

where V_G is the genetic variance and V_P is the phenotypic variance.

Contrary to the simplicity of FF, the heritability estimation in SEM is a complex process. Variance decomposition for estimation of the genetic variance requires various sophisticated statistical methods such as a matrix algebra interpreter and a numerical optimizer (e.g. Mx, or LISREL). The optimizer is used to minimize the fitting function that denotes a discrepancy measure between the expected model and the observed data. The iterative process of model fitting continues until the fitting

function appears to reach the minimum. The SEM fit is so time-consuming that it is not easy to apply to large-scale data like brain images that consist of numerous voxels. Moreover, despite the increasing computational power of the modern computer, the SEM software packages did not provide sequential as well as parallel processing facilities that are necessary to manipulate numerous data together.

2 Methods

2.1 Approach

We decided to use the methodological heritage of genetic researchers as much as possible. This approach could save a software developer time and labor, and would enable a researcher to apply easily the methods in genetics to neuroimaging analysis. Moreover, it could produce the reliable results to use the methods and tools verified in the research field.

2.2 Software Development

Among the SEM software packages, Mx was chosen. The Mx developed by [9] is widely used in human genetics, particularly twin studies because it facilitates specification of complex models and mixture distributions and provides diverse model fitting functions. To apply the SEM software Mx to neuroimaging analysis, we write a MATLAB code for sequential processing of multiple data. The algorithm of simple version of the program is below:

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Array h [N] , p [N] ;
for vertex=1 to N
    read brain measures of all twins at the vertex;
    write data for Mx;
    execute Mx;
    parse the result in text from Mx;
    h[vertex] = the heritability value from the parsing;
    p[vertex] = the p value from the parsing
end for
write h;
write p;

```

2.3 Twin Subjects

To measure the heritability of the brain structure, we recruited twin volunteers. The study protocol was approved by the relevant institutional review boards (Seoul National University, Catholic University of Korea), and written informed consent was obtained from participants. A total of 40 healthy male twin volunteers aged 20.5 ± 1.9 (mean \pm SD), consisting of 10 MZ and 10 DZ same-sex twin pairs, were recruited from the community with advertisements. The MZ and DZ pairs were matched for age ($t = 0.23$, $P = 0.87$) and sex. Blood or hair samples were taken at the date of

scanning or cognitive testing. Zygosity was determined by DNA analysis using the 15 highly polymorphic markers.

2.4 Image Acquisition and Analysis

From the twins, contiguous 0.9 mm axial MPRAGE images were acquired with a 1.5T MR scanner (Magnetom Avanto, Siemens) with TR=1160 ms; TE=4.3 ms; flip=15; FOV=224 mm; matrix=512x512; number of slices=192; two images were acquired and averaged. Anatomical images were corrected for intensity non-uniformity [10], spatially registered to stereotaxic space [2], and masked to remove extra-cerebral voxels. We used INSECT [11] to classify gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF).

For measuring gray matter thickness, the inner and outer cortical surfaces are reconstructed [8]. These surfaces are automatically reconstructed by the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm [6]. The cortical thickness was measured using the t-link method of calculating the Euclidean distance between linked vertices on the white matter surface and the GM/CSF intersection surface [5]. To compare thickness across subjects, the thickness was spatially normalized. The vertices were transformed to the spherical model from which the cortical surfaces originated, and nonlinearly registered to an standard template on the sphere. A highly flexible deformation, in two dimensions, of a template cortex to an individual was used for cortical surface registration. This algorithm provided a transformation to match crowns of gyri between subjects using a geodesic distance map. With this transformation, thickness information on the vertices was transformed to the template. Then, diffusion smoothing, which generalizes Gaussian kernel smoothing, with 30 mm FWHM (full width half maximum) was used to increase the signal to noise ratio [1].

2.5 Statistical Analysis

To calculate the identical and fraternal twin correlations, we used the intraclass correlation coefficient (icc) function of package psy in a statistical programming environment R [4]. The statistical significance of the two twin correlations was computed using Fisher's z transformation.

For SEM, the conventional, univariate ACE model was adopted [9]. The ACE model decomposes the phenotypic variance into additive genetic (A), shared environmental (C), and non-shared environmental (E) variances. The statistical significance of the genetic variance or h^2 was derived from chi-square difference between ACE and CE models.

3 Results

To estimate heritability of a brain-based phenotype like gray matter thickness, both FF and SEM were adopted and compared.

3.1 Falconer's Formula

First, we applied FF to estimate the heritability of cortical thickness across the whole brain. The MZ and DZ intracorrelations were derived the icc function of R. By the equation 1 mentioned in the introduction, we computed and mapped heritability estimates at surface points of the cerebral cortex (Fig. 1A). The statistical significance of differences between the MZ and DZ intracorrelations were shown in Fig 1C.

3.2 Structural Equation Modeling

For SEM, the ACE structural equation model, a standard model for twin analysis, was employed to determine what proportion of variance in a brain-based phenotype is heritable (h^2), versus the proportions which are due to shared environment or non-shared environment. By fitting a univariate ACE model to each of 81,964 vertices over the cerebral cortex, we produced high-resolution surface maps of the heritability of brain structure in the twin sample (Fig. 1B). The statistical significances of the heritability estimates were based on chi-square difference between ACE and CE models (Fig. 1D).

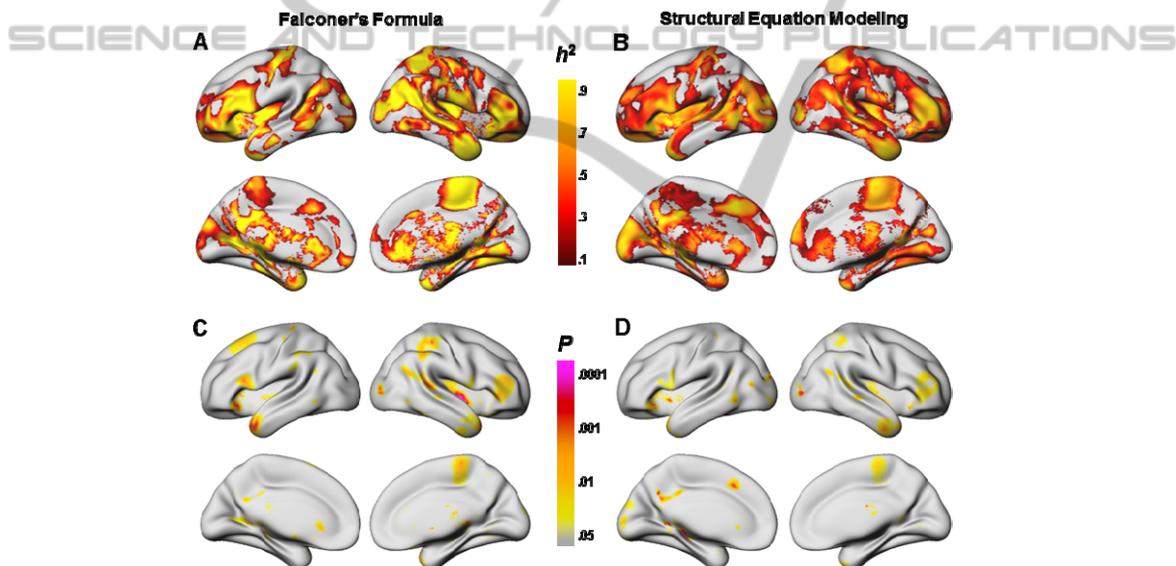


Fig. 1. Heritability of gray matter thickness from Falconer's formula (*left*) and from structural equation modeling (*right*). The brain maps illustrated the heritability estimates (*A* and *B*) and the statistical significance values (*C* and *D*) at eighty thousand or more vertices of the cerebral cortex. *P* values are the statistical difference in intracorrelations between monozygotic and dizygotic twins using Fisher's z transformation (*C*) or chi-square difference between ACE and CE models (*D*).

3.3 Comparison between Results from FF and from SEM

Genetic and environmental influences on gray matter thickness differed with cortical regions (Fig. 1). The topological patterns of inherited regions were very similar whether FF or SEM is employed. However, the results from SEM in Mx [9] tend to be smaller and statistically conservative than Falconer's estimation. The tendency also is found in a previous study [7]. Precisely, 34.9% of all the vertices showed FF heritability estimates larger than SEM ones by 0.1 or more, while only 18.9% did vice versa (Fig. 2). At the other vertices (46.2%), the heritability differences were very small (<0.1). In considering the results, the correction for multiple comparisons should be carefully performed for the results from SEM.

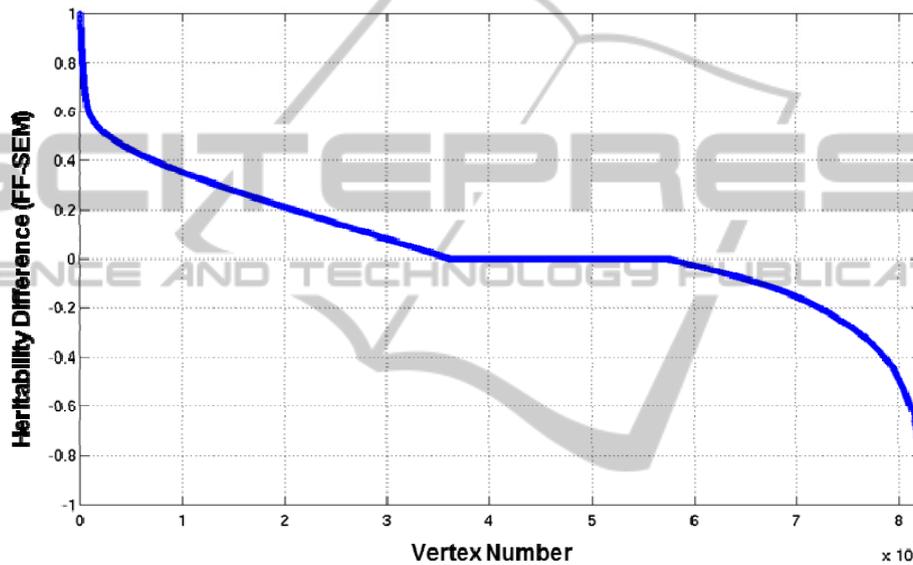


Fig. 2. The heritability estimate differences between FF and SEM. The vertices on the whole cortices are represented on the x axis and are numbered from 1 to 81,924. The y axis shows the subtraction of SEM heritability estimates from FF heritability estimates.

4 Conclusions and Future Works

We presented a simple method to apply genetic analyzing tools for neuroimaging researches. SEM analysis has many advantages over Falconer's approach. Falconer's method provides nothing but heritability estimates, whereas SEM provides the statistical significance as well as heritability estimates. Moreover, SEM can distinguish shared and random environmental effects. Now, the proposed method facilitates diverse and complex models that were used only in genetic research for neuroimaging analysis including anatomical and functional MRI. In future, we will apply multivariate SEM model for anatomical and functional neuroimaging analysis.

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