A Structural Equation Modeling Approach for the Estimation of Genetic and Environmental Effects from Twin fMRI Data

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Abstract—Structural equation modeling (SEM) is a statistical technique widely used in quantitative genetics to measure genetic and environmental variances of human traits. Using SEM, the proportions of genetic and environmental influences can be separated from the phenotypic variance. However, the SEM softwares like Mx or LISREL were not designed for a big data analysis. They can hardly be applied for brain images that comprise hundreds of thousands of voxels. Here, to introduce SEM in the field of neuroimaging, we developed a simple code in MATLAB for multiple computations of Mx. Our method could estimate genetic and environmental variances of neural activations at 153,594 voxels of the whole brain, to be converted to brain images.

Index Terms—fMRI, genetics, structural equation modeling, twin.

I. INTRODUCTION

In the field of human behavioral genetics, twin research is an indispensable tool to understand nature versus nurture. Twin studies use structural equation modeling (SEM) as a standard analysis method to reveal the relative importance of genetic and environmental influences on human traits and behaviors. SEM is a statistical technique that is based on decomposition of the phenotypic variance into the genetic and environmental components. The genetic component is called heritability, which is a fundamental notion in quantitative genetics that summarizes how much of the variation in a trait among individuals is attributable to differences in genotype [1]. Heritability can also be translated as the standardized genetic variance, which means the proportion of total phenotypic variance due to genetic influence.

In SEM, the standardized genetic variance (\(a^2\)) is defined as

\[
a^2 = \frac{V_G}{V_P} \tag{1}
\]

where \(V_G\) is the genetic variance and \(V_P\) is the phenotypic variance. The standardized environmental variance (\(e^2\)) is defined as

\[
e^2 = \frac{V_E}{V_P} \tag{2}
\]

where \(V_E\) is the environmental variance.

The estimation of genetic and environmental variances using SEM is a complex process. Variance decomposition for estimation of the genetic variance requires various sophisticated statistical software tools 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.

We made a simple software tool for neuroimaging. Using our software tool, researchers can apply the SEM technique for neuroimaging analysis to distinguish genetic and environmental influences on the brain function as well as the structure. Additionally, because our tool is coded in MATLAB (http://www.mathworks.com/), the parallel computing toolbox can be used to enhance the performance. The voxels of a brain image are independent of one another in terms of the fitting process. Thus, even a multicore desktop can shorten the total processing time of all voxels of the whole brain.

II. METHOD

A. Twin Subjects

To measure genetic and environmental variances of the brain activations, 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 26 healthy twin volunteers aged 20.3 ± 1.7 (mean ± SD), consisting of 16 MZ and 10 DZ male twins, were recruited from the community with advertisements. The MZ and DZ pairs were matched for 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.

B. Image Acquisition and Analysis

The functional MRI (fMRI) tasks requiring fluid reasoning ability and the fMRI protocol were as described in our previous paper [2]. The statistical parameters for cortical activation such as t scores were acquired using the statistical parametric mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm/).

To determine genetic and environmental variances, the conventional, univariate ACE model was adopted [3]. 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 was derived from chi-square difference between ACE and CE models. Genetic and environmental variances mentioned in this paper mean A and E, respectively.

C. Software Development

We decided to use the methodological heritage of genetic researchers as much as possible. This “Do not re-invent the wheel” 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 because the methods and tools were verified in the research field.

Among the SEM software packages, Mx was chosen for analysis. The Mx software is widely used in human genetics, particularly in twin studies because it facilitates specification of complex models and mixture distributions and provides diverse model fitting functions [3]. To apply the SEM software Mx to neuroimaging analysis, we write a MATLAB code for sequential processing of multiple data. A simple version of the algorithm of our program is below:

```
for voxel = 1 to N
    read t-scores of all twins at the voxel;
    write data for Mx;
    execute Mx;
    parse the result_in_text from Mx;
    A[voxel] = the genetic variance from the parsing;
    E[voxel] = the environmental variance from the parsing
end for
write A, E;
convert the A text file to the images in SPM2;
convert the E text file to the images in SPM2;
```

D. Software Development

- Programming language: MATLAB 7.7
- SEM software: Mx 1.52b
- fMRI analysis: SPM2
- Brain image viewer: MRICRO 1.39

III. Results

The univariate ACE structural equation model, a standard model for twin analysis, was employed to determine what proportion of variance in a brain-based phenotype (e.g., brain activation) is heritable ($a^2$), versus the proportions which are due to shared environment or non-shared environment ($e^2$). The brain images for t scores (activation maps) had the dimensions of $53 \times 63 \times 46$. By fitting the ACE model to t scores at each voxel of the whole brain, we obtained the standardized genetic and environmental variances of the brain activations at 153,594 voxels. All the standardized genetic and environmental variances were overlaid on the standard template using MRICRO. Finally, we produced 3-dimensional maps of the genetic and environmental variances of the brain activation during fluid reasoning tasks (Fig. 1 and Fig. 2).

A. Genetic Components of the Variance of Brain Activation

Using our tool, we determined the genetic influence on the
cortical activation during reasoning. As shown in Fig. 1, the genetic variances were scattered all over the cerebral cortex. Compared to other regions, the inferior frontal and superior temporal regions in the right hemisphere showed relatively strong heritability.

B. Environmental Components of the Variance of Brain Activation

The environmental influence on the cortical activation was also determined. As shown in Fig. 2, compared to the genetic variances in Fig. 1, the environmental variances were very high in most regions of the cerebral cortex. The prefrontal, and right temporal regions showed relatively low environmental variances compared to other regions.

IV. CONCLUSION

We provided a simple software tool to apply genetic analyzing methods for functional neuroimaging studies. This tool is an upgraded version of our previous tool that was applied for anatomical MRI only [4]. Now, this simple tool enables us to perform SEM analysis of functional and anatomical brain images. SEM is a statistical method with many advantages. 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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REFERENCES


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