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Prediction of General Fluid Intelligence Using Cortical Measurements and Underlying Genetic Mechanisms

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Abstract. General fluid intelligence, the important component of human cognitive ability, has been reported under genetic control. Moreover, the correlation between general fluid intelligence and cortical structural measures has been identified. However, the biological mechanism behind it is still unclear. To answer these questions, we performed the general fluid intelligence prediction by using 3 cortical measurements through the SVR (support vector regression) machine learning algorithm; then quantifying genetic and environmental contributions to individual variability in 3 cortical measures by using the SOLAR software. We found that the cortical measures are concerned with the general fluid intelligence; the heritability difference was observed in cortical sulc, it may due to the fact that the cortical sulc contain the more information about the genetic factor.

1. **Introduction**

General fluid intelligence (gf), the ability to reason in novel situations. Specifically, general fluid intelligence comprise the set of ability involved in coping with novel environment and specially in abstract reasoning. The general fluid intelligence is correlated with the human high cognitive ability, such as emotion understanding [1] and working memory [2]. Moreover, the general fluid intelligence is concerned with some pathophysiology of psychiatric and neurological diseases, such as Alzheimer's disease (AD) [3].

Researchers have investigate the neural foundation of general fluid intelligence. Numerous lines of evidence implicated that the general fluid intelligence is correlated with many cortical structural measures, such as cortical thickness [4], cortical curvature and cortical sulc [5]. There are no studies to predict the individual general fluid intelligence from the overall level yet.

Though the correlation between cortical thickness, cortical sulc, cortical curvature and general fluid intelligence have been identified, and it showed that the different cortical measures have different level correlation with general fluid intelligence. Moreover, the biological mechanism behind it is still unclear. In the meantime, recent genome-wide association study (GWAS) found that 51% of the phenotypic variability in general fluid intelligence [6], it showed that the general fluid intelligence is under strong genetic control. It reasonable to assumed that the inter-region variability of heritability in cortical measure may be the origin of it.

Here, we used cortical measure content maps based on the Human Connectome Project's [HCP] to predict the individual general fluid intelligence by applying the machine learning algorithm SVR (support vector regression); then quantifying genetic and environmental contributions to individual variability in 3 cortical measures by using the SOLAR software; Finally, we test the significant heritability difference of selected and unselected feature sets by t test. We hypothesized that: (1) the

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cortical measures have the ability to predict the individual general fluid intelligence; (2) there are significant heritability difference in cortical measure of selected features and unselected features.

2. Material and method

2.1. Subjects

All the subjects in this paper came from the S900 dataset released by Human Connectome Project (HCP) in December 2015 (humanconnectome.org). The S900 dataset included 897 subjects with structural imaging were taken into account in the study. And to acquire a more accurate estimate of effects on the mean and variance on the genetic parameters, unpaired individuals were considered in this study [7]. 26 subjects were excluded because of missing population information about race/ethnicity (labeled "Unknown or Not Reported"). Finally, 873 subjects (28.8 ± 3.7 years, range 22-36years) were included for the estimation of heritability in cortical thickness, cortical curvature and cortical sulc. As for the predication of subject's general fluid intelligence, there are 184 subjects were not tested, only 713 subjects in S900 dataset were included.

2.2. MRI Data acquisition and processing

All the HCP subjects were scanned in a customized Siemens Magnetom Connectome 3T scanner with a 32 channel head coil. The T1 images were collected by using 3D magnetization-prepared rapid gradient echo (3D-MPRAGE) sequence: echo time (TE) = 2.14 ms, repetition time (TR) = 2400 ms, flip angle = 8°, file of view (FOV) = 224◊224 mm^2, and resolution = 0.7 mm isotropic. The T2 images were acquired with a 3D-T2SPACE sequence: echo time (TE) = 565 ms, repetition time (TR) = 3200 ms, variable flip angle, file of view (FOV) = 224◊224 mm^2, and resolution = 0.7 mm isotropic. Details on the scanner, image acquisition, and reconstruction are available in the HCP reference manual (https://www.humanconnectome.org/storage/app/media/documentation/s900/HCP_S900_Release_Reference_Manual.pdf).

Structural images were preprocessed by the WU-Minn HCP consortium using the HCP pipelines in the website: https://github.com/Washington-University/Pipelines. We applied the Brainnetome Atlas [8] in this study, which is registered to the surface space of FreeSurfer's fsaverage subject (available at http://surfer.nmr.mgh.harvard.edu/). Given that the brain structural maps (cortical thickness, cortical curvature and cortical sulc) offered by HCP were registered to 'fs_LR' surface space, a surface registration was performed. The brain structural maps for each individual were transformed from 'fs_LR' mesh to fsaverage mesh by applying the command metric-resample in the workbench software (http://www.humanconnectome.org/software/get-connectome-workbench.html). Then the average structural content values for all areas of the Brainnetome Atlas were computed by averaging the structural value of all the vertexs in the particular area. In the end, for each of the cortical measure, we got the matrix data in the size of 713 ◊ 210, which the 713 and 210 represents the total subjects which participate the Raven's Progressive Matrices test and 210 ROI (region of interest) in left and right hemisphere based on the Brainnetome Atlas respectively.

2.3. General fluid intelligence

The most commonly used measure of general fluid intelligence is Raven's Progressive Matrices. HCP used Form of an abbreviated version of the Raven's developed by Gur and colleagues. Participants are presented with patterns made up of 2 x 2, 3 x 3 or 1 x 5 arrangements of squares, with one of the squares missing. The participant must pick one of five response choices that best fits the missing square on the pattern. The task has 24 items and 3 bonus items, arranged in order of increasing difficulty. However, the task discontinues if the participant makes 5 incorrect responses in a row. HCP provided the data about the result of Raven's Progressive Matrices test in which the "PMAT24_A_CR" data represent for the Number of Correct Responses. Here, we chose it to represent the individual general fluid intelligence.

2.4. Heritability estimation

For the heritability estimates, the variance components method was applied in the sequential oligogenic linkage analysis routines (SOLAR) software package [9]. SOLAR uses maximum likelihood variance

decomposition methods derived from the strategy proposed by Amos[10]. The proportion of the variance in a phenotype is ascribed either to additive shared genetics (A) or to measurement error and other known sources of variance (E). In this model, the covariance matrix Ω for a pedigree of individuals is given by:

$$\Omega = 2 \cdot \Phi \cdot \sigma_g^2 + I \cdot \sigma_e^2 \quad (1)$$

σ_e^2 is the genetic variance due to the additive genetic factors, Φ represents the kinship matrix representing the pair-wise kinship coefficients between all the individuals, σ_e^2 is the variance due to individual-specific environmental effects, and I represents the identity matrix (here environmental effects are supposed to be uncorrelated among family members) [11]. The model used to fit the variability observed in the brain structural maps (cortical thickness, cortical curvature and cortical sulc) in our study is the same as previously published ones [12]. Narrow sense heritability is defined as the additive genetic factors divided by the phenotypic variance σ_p^2 as follows: $h^2 = \sigma_g^2 / \sigma_p^2$. The variance parameters are calculated by comparing the phenotypic covariance matrix with the covariance matrix due to kinship. Before testing the significance of heritability, we adjusted the phenotype values by taking the covariates sex, age, age^2, age◊sex interaction and age^2◊sex interaction into consideration. In addition, to ensure the normality of the measurements, an inverse Gaussian transformation was applied. The outputs from SOLAR included the heritability estimate (h^2), the significance value (*p*), and the standard error for each phenotype (SE).

2.5. General fluid intelligence prediction

We performed the general fluid intelligence prediction by using the machine learning algorithm SVR (support vector regression). Considering the sample size (713) and the data dimension (210) in our data are not big both, the SVR algorithm is suitable for this situation. We did the general fluid intelligence prediction as follow steps. First, we performed the feature selection by calculating the pearson correlation between each feature and the individual general fluid intelligence in 3 cortical measures. All the feature which the pearson correlation less than 0.05 were selected; second, we performed the 10-fold cross validation to predict the all the individual general fluid intelligence; we splited all the subjects into 10 folds, then we chose one fold for testing, the rest of subjects for training, in each cross validation, we perform the normalization in training data to reduce the noise. Third, by using the training data as the input of the SVR model, the predication of general fluid intelligence in the test fold are available, eventually, we combined all the prediction result of 10 folds to represent the prediction of general fluid intelligence.

2.6. Heritability significance test

In the feature selection process, all the features were splited into two parts. One part was selected for the model training the fluid intelligence prediction by the criterion of the pearson correlation result; one part was not selected. After performing the heritability estimation in all ROIs. We did the heritability result t test in the two parts to find whether there are significant different between them.

3. Result

After the feature selection of 210 ROI (region of interest), we performed the prediction of general fluid intelligence in 10 folds cross validation. We found that significant correlations emerged between the model-prediction and tested general fluid intelligence in the cortical measure of cortical thickness (r=0.26, p = 1.9◊10^{-12}) and cortical sulc(r=0.22, p = 4.6◊10^{-9}) (Fig1 a, b). As for the cortical curvature, we found that there are no significant correlated features in it. And for the t test of heritability in selected and unselected features, we found that in cortical sulc measure, the heritability of the selected set is significantly different with these unselected features (Fig 2); while in in cortical thickness, no significant heritability difference was observed.

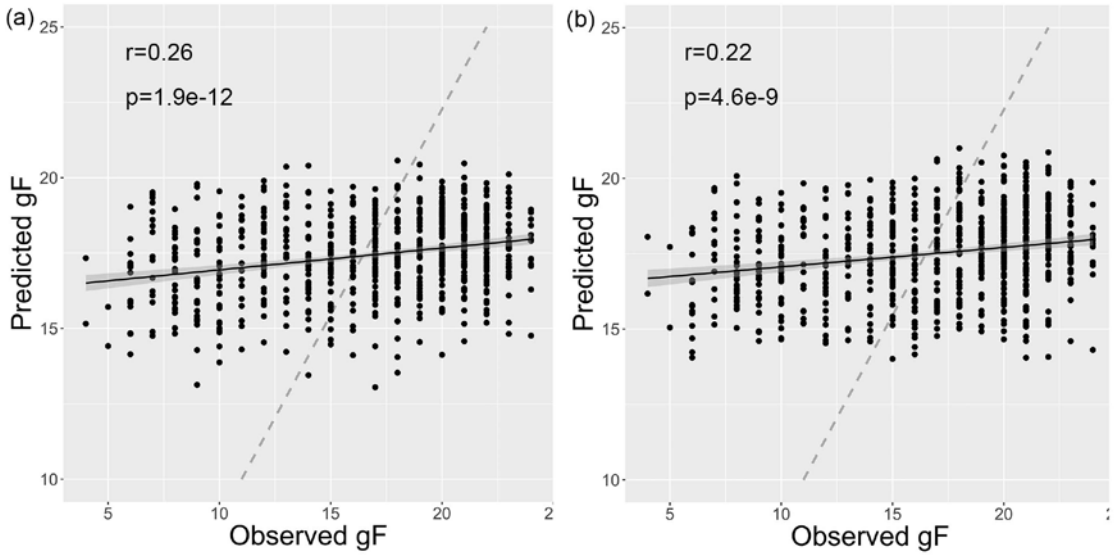


Figure 1. (a) The correlation of prediction general fluid intelligence and observed general fluid intelligence in cortical thickness. (b) The correlation of prediction general fluid intelligence and observed general fluid intelligence in cortical sulc.

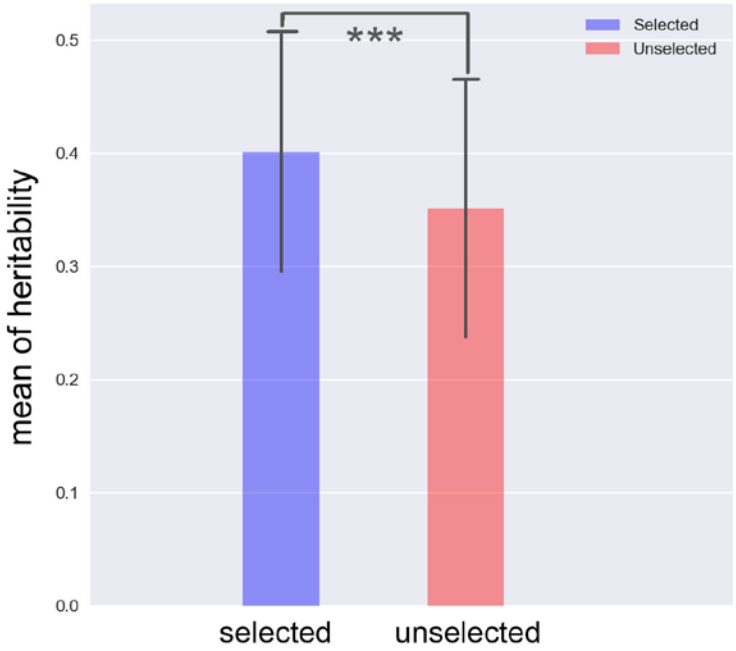


Figure 2. The mean and stand error of heritability in selected and unselected ROIs, *** $p < 0.05$ for t test.

4. Discussion

In this study, first, we used the cortical thickness, cortical curvature and cortical sulc content maps for 873 subjects from HCP dataset to predict the individual general fluid intelligence; second, we did the t test of heritability of selected features set and unselected features set in 3 cortical measures. We found that the cortical thickness and cortical sulc except the cortical curvature can predict the general fluid intelligence by applying the machine algorithm SVR. Moreover, we found that only the cortical sulc have the significant heritability difference in the result of t test of selected and unselected features.

The facts of cortical measure of thickness and cortical sulc can predict the general fluid intelligence and the significant heritability difference in cortical sulc implied that the genetic factor may be the biological

mechanism for the individual general fluid intelligence difference. According to the literatures, both cortical thickness [13] and cortical sulc [7] are both heritable; additionally, the general fluid intelligence are concerned with the genetic factor both in twin study and GWAS study. It showed that there may exist the connection between them. The prediction result ($ps < 0.05$) echoed our assumption.

As for heritability difference result observed in cortical sulc, a longitudinal study has demonstrated that the spatial distribution of the sulcal pits already exists at term birth and becomes more pronounced during the first 2 years of life along with the rapid brain volume increase [14], it showed that the cortical sulc was under stronger genetic control comparing with the cortical thickness; and the cortical sulc may the foundation of human general fluid intelligence development.

5. Conclusion and Limitation

In this study, we found that the cortical measures are concerned with the general fluid intelligence. In the prediction experiment, we found that the cortical thickness and cortical sulc have the ability to predict general fluid intelligence; On the other hand, the heritability difference was observed in cortical sulc, it may due to the fact that the cortical sulc contain the more information about the genetic factor as mentioned in the discussion. It showed that the general fluid intelligence was strongly concerned with the genetic factor.

However, we did not investigate the relationship between the gene expressions with the general fluid intelligence. We still did not know whether the fluid intelligence is influenced by the gene. Moreover, we did not investigate the relationship between cortical measures of subcortex region and general fluid intelligence and did not try other machine learning algorithm in this study, all this attempt may help us to get a better prediction result [15].

6. References

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