Image Genetic Analysis and Application Research Based on QRFPR and Other Neural Network-Related SNP Loci

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The development of neuroimaging technology and molecular genetics has produced a large amount of imaging genetics data, which has greatly promoted the study of complex mental diseases. However, because the feature dimension of the data is too high, the correlation measure assumes that the data obey Gaussian distribution, and traditional algorithms often cannot explain these two types of data well. This article mainly studies image genetics analysis and its application based on neural network. In this paper, based on the theory and application technology of neural network, the tree structure is established by prior knowledge, that is, each SNP site is used as a leaf node of the tree, and the LD block and genome formed by the linkage imbalance of multiple SNP sites are used as intermediate nodes. Then, the hierarchical relationship of features was introduced. On this basis, a sparse learning method based on tree structure guidance is used to select features from multiple features of multiple SNPs locus regression candidate brain regions. Finally, the identification of SNPs in feature selection is used to predict quantitative traits of brain regions. The distribution of the typical vector values obtained by the algorithm in the experimental data is basically consistent with the distribution of the median of the actual data, and the correlation coefficient obtained is closest to the actual correlation coefficient in the data set. The average correlation coefficient of the algorithm reaches 82.3%, which is about 4.2% higher than the control algorithm. Experimental results show that this method can not only significantly improve the regression performance but also detect the risk gene SNPs loci with spatial clustering features and functional interpretation significance. It is practical and effective to use it in clinical trials.

1. Introduction

In recent years, with the deepening of informatization in the medical field, the heterogeneous data in the biomedical industry has expanded rapidly. Therefore, integrating complex heterogeneous data, analyzing biological pathogenic mechanisms, and further applying it to personalized medicine have become the global scientific and technological community. The focus of the health and industry circles on the "big data revolution in the medical industry." The US government has launched the "brain activity atlas plan" and "precision medical plan." The Ministry of Science and Technology of my country has launched and deployed the “Precision Medical Plan” and “Brain Science and Brain-like Research” and included it in my country’s “13th Five-Year” major scientific and technological development and innovation projects. Therefore, the research of brain diseases and brain science has become one of the major needs for the future development of the country. It has very important research significance for the in-depth development of the medical treatment industry.

A research hotspot of brain diseases and brain sciences is the development of multimodal heterogeneous data analysis methods based on neural networks and pattern recognition technology. The knowledge automatically learned on the data will provide a reference for further scientific hypotheses on the disease, will deeply dig the association relationship and evolution law between the multimodal data and the disease, and establish the biomarkers of neuropsychiatric brain diseases. It provides a powerful tool to explain the
pathogenesis of complex diseases and realizes diagnosis and prediction and provides methodological support for “open neuroscience”.

The China Imaging Genetics (CHIMGEN) study established the largest Chinese neuroimaging genetics cohort, aimed at identifying genetic and environmental factors and their interactions with neuroimaging and behavioral phenotypes. Xu et al.’s study collected hundreds of quantitative macroenvironmental measurements from remote sensing and national survey databases based on each participant’s location from birth to the present, which will help to discover new environmental factors related to neuroimaging phenotypes. With cross-environmental measurements, they can also provide insights into the macroenvironmental exposure that affects the human brain and its time and mechanism of action [1]. The research only analyzed the factors that affect the human brain and did not solve the problems found in combination with the actual situation. Du et al. believes that brain imaging genetics is aimed at revealing the association between genetic markers and quantitative features of neuroimaging. Sparse canonical correlation analysis (SCCA) can find double multivariate associations and select relevant features and has become more and more popular in imaging genetics research. The L1-norm function is not only convex at the origin but also singular, which is a necessary condition for sparsity. Therefore, most SCCA methods will impose individual features or structural hierarchy of features in pursuit of corresponding sparsity [2]. The research was not objective, and the environmental factors in which the research occurred were not taken into account. Cognitive impairment and dementia are the most common non-motor changes in Parkinson’s disease. Berg and Postuma introduce the latest clinical and neurobiological findings of Parkinson’s disease dementia. They proposed a new consensus standard for clinical diagnosis of Parkinson’s disease dementia. In two independent long-term cohort studies, the cumulative prevalence of Parkinson’s disease dementia was high. Even in early Parkinson’s disease, mild cognitive impairment occurs and is accompanied by a shorter period of dementia. People’s awareness of the cognitive decline of Parkinson’s disease and the underlying mechanism of dementia has been enhanced. It is hoped that by affecting these mechanisms, new therapies for preventing or delaying the onset of dementia will be caused [3]. The research helps to understand the clinical and neurobiological aspects, but there are still problems for practical applications.

The innovative point of this paper was as follows: This paper adopts a method based on expectation to approximate negative entropy, with the goal of maximizing negative entropy, to maximize the overall correlation between the two data sets while ensuring that each type of feature is independent of each other. Finally, construct the final Lagrange equation, use alternating least squares to update the diagonal matrix continuously, and calculate the weight score of each feature. The results show that the combination of SNP location structure information and image location structure information can effectively improve the prediction of associated features. The research in this paper can provide new ideas for the in-depth study of image genetic analysis and application and can also expand new directions for the related research of the neural network algorithm.

2. Neural Networks and Imaging Genetics

2.1. Imaging Genetics. Imaging genetics (imaging genetics) is a genetic association analysis method, that is, the use of neurophysiological indicators obtained by structural and functional brain imaging technology as a phenotype to assess genetic variation and its impact on behavior [4]. It has a history of more than 20 years since it was mentioned in the early 21st century. It maps neural phenotypes to genotypes, trying to find the biological mechanism behind genetic factor-mediated variation [5]. Previous imaging genetic studies have confirmed that the risk genes involved in the emotional loop can cause differences in individual behavior, emotions, and cognition. Therefore, when the behavioral measurement of subjective evaluation lacks statistical significance, imaging genetics can explain the difference in neurobiology by evaluating the relationship between genes and brain function or morphology, thus building a bridge between genes and pathological behavior [6].

Imaging genetics integrates neuroimaging and genetics to study the effects of genetic variation on brain structure and function. In the study of psychiatric genetics, brain structure and function is the so-called “intermediate phenotype,” which is closer to related genes on biological pathways than mental disease itself [7]. The intermediate phenotype should be stable, heritable, and have good psychological attributes. In the general population, it is related to the disease and its clinical symptoms. The relatives of the patient who did not have the disease showed the corresponding characteristics (but did not reach the disease, degree); there is a universal genetic basis. This difference may be due to more fine-grained gene-level differences. There are two main ideas for imaging genetics research based on intermediate phenotypes: one is to use imaging genetics as a tool to discover risk genes for mental illness; the other is to use risk alleles to group intermediate phenotypes that characterize the nervous system. Quantitative and mechanistic research on the role of brain function in mental diseases. These two ideas have different hypotheses, but the method of verifying the hypothesis is the same, which is carried out by analyzing the correlation between neuroimaging data and genetic variation [8, 9].

Although imaging genetics studies based on candidate genes have found many clear and consistent results, there is still controversy about a better understanding of the mechanisms of mental illness. Because the candidate sites determined based on a priori hypothesis have inconsistent results in disease phenotype classification studies, GWAS is a data-driven method for studying disease-related loci [10]. It refers to conducting multicenter, large-sample, and repeatedly validated gene-disease association studies at the genome-wide level. With the development of gene
sequencing technology, early GWAS studies used image-related intermediate phenotypes and found many significant sites such as schizophrenia risk gene ZNF804A (encoding transcription factors involved in cell adhesion), TCF4 (encoding neurons transcription factor), and NRGN (encoding post-synaptic protein kinase substrates that bind calmodulin). However, it is impossible for GWAS to reach the strict statistical threshold setting of GWAS (\( p < 5 \times 10^{-8} \)), resulting in some studies failing to discover the risk of mental illness (genetic factors) [11, 12]. The reason for this phenomenon may be that these meaningful gene loci have too little effect and require large-scale cooperation to increase the sample size. The GWAS study, which includes the most normal people and schizophrenic patients, found 108 risk sites, 82 of which were new sites that have not been found before, and other sites include information on DRD2 and participation in glutamatergic nerves. In the genes transferred, these sites have biochemical molecular experiments to confirm that they are very related to schizophrenia. However, it is still necessary to consider the collection of large samples is time-consuming and labor-intensive work, and the heritability obtained through GWAS research. Therefore, in addition to increasing the sample size, new methods are needed to discover more genetic mechanisms behind mental illness [13].

2.2. BP Neural Network Algorithm

1. BP algorithm with variable learning rate

The BP algorithm is composed of two processes, the forward propagation of the signal and the back propagation of the error. During forward propagation, the input sample enters the network from the input layer and is passed to the output layer by layer through the hidden layer. If the actual output of the output layer is different from the expected output, it goes to the error back propagation. In the standard BP learning algorithm, the algorithm is very sensitive to the setting of the learning rate. In the initial stage of network learning, choosing a larger learning rate can significantly accelerate the convergence rate, but when the error is close to the minimum, the excessive learning rate will be obtained. As a result, the weight adjustment range is too large, causing oscillation or nonconvergence [14]. The effectiveness of the BP algorithm depends to some extent on the choice of the learning rate. Since the learning rate in the standard BP algorithm is fixed, its convergence speed is slow and it is easy to fall into a local minimum. Therefore, it is difficult to take into account the convergence of different error ranges within a single fixed learning rate in network training [15]. In the variable learning rate algorithm, the learning rate can be changed during the training process to ensure that the learning step size is sufficiently large and stable, which is essentially the extension of the gradient method in neural network training [16]. This method can ensure that the network is always trained at the maximum acceptable learning rate.

The adjustment formula for variable learning rate is

\[
\eta(k) = \begin{cases} 
1.05 \cdot \eta(k-1), & \text{When } \text{SSE} < \text{SSE}(k-1), \\
0.7 \cdot \eta(k-1), & \text{When } \text{SSE} > \text{SSE}(k-1) \cdot 1.04, \\
\eta(k-1), & \text{Other.}
\end{cases}
\]

(1)

SSE is the output error of the network. The selection of the initial learning rate \( \eta(0) \) of this method is very arbitrary.

The algorithm is a commonly used fast learning algorithm. It is proposed according to the advance and retreat method in the optimization theory and uses the following variable learning rate method:

\[
w(k + 1) = w(k) + \alpha \Delta w(k + 1) + \eta \Delta w(k),
\]

\[
\left\{ \begin{array}{l}
\alpha(k) = \alpha(k - 1) g \varphi, \quad \eta = \eta, \Delta E < 0, \\
\alpha(k) = \alpha(k - 1) g \beta, \quad \eta = 0, \Delta E > 0.
\end{array} \right.
\]

(2)

Among them, \( \Delta E = E(k) - E(k - 1) \) and \( \varphi \) and \( \beta \) are constants.

The main idea is to determine the learning rate according to the situation, that is, let \( \alpha \) be variable. In an ideal situation, \( E \) should continue to decrease, and \( \varphi \) is the forward learning factor, generally \( \varphi > 1 \); \( \beta \) is the reverse factor, generally \( \beta < 1 \). If the current error correction direction is correct, increase the learning rate and add the momentum term; otherwise, decrease the learning rate and discard the momentum term [17, 18].

In actual operation, the alternation of increase and decrease of \( \alpha \) is very frequent, whether \( \Delta E > 0 \) or \( \Delta E < 0 \), it must go through one iteration. Since the number of effective corrections of the weight value when \( \Delta E > 0 \) is reduced, the efficiency is reduced. There are also some improved methods of the Vogl algorithm, such as setting the upper and lower limits of \( \alpha \), so that the \( \alpha \) adjustment cannot exceed this range, to prevent \( \alpha \) from being adjusted too large or too small; or only after \( \Delta E < 0 \) several times before \( \alpha \) correction to prevent oscillations etc. corrected by \( \alpha \) [19].

2. BP algorithm with momentum added

In physics, momentum is a physical quantity related to the mass and velocity of an object. In classical mechanics, momentum is expressed as the product of an object’s mass and velocity. Content about more precise measures of momentum. Introducing momentum items in network training can use a higher learning rate while maintaining the stability of the algorithm, so that when the network corrects its weights and deviations, it not only considers the role of error on the gradient, but also considers the trend on the error surface impact. Without the effect of additional momentum, the network may fall into shallow local extrema, and the use of additional momentum may slip past these minimums [20].

The method is to add a value proportional to the previous weight change to each weight change on the basis of
back propagation and generate a new weight change according to the back propagation method, with addition of the weight adjustment formula of momentum factor, which is

$$\Delta w_{ij}(k + 1) = mc \Delta w_{ij}(k) + (1 - mc)\eta \delta_i(k) y_j(k),$$

$$\Delta b_i(k + 1) = mc \Delta b_i(k) + (1 - mc)\eta \delta_i(k).$$

(3)

Among them, $k$ is the training frequency, $mc$ is the momentum factor, and $0 < mc < 1$ generally takes about 0.9.

This method is based on back propagation, adding a value proportional to the previous weight change to each weight change, and determining the new weight change according to the back propagation method. The essence of adding momentum method is to transfer the influence of the last weight change through a momentum factor. When the momentum factor is 0, the weight change is only based on the gradient descent method; when the momentum factor is 1, the new weight change is set to the last weight change, which is generated according to the gradient method. The changes are ignored [21, 22]. In this way, when the momentum term is added, the adjustment of the weight is changed toward the average direction of the bottom of the error surface. When the network weight enters the flat area at the bottom of the error surface, $\delta_i(k)$ will become very small, so $\Delta w_{ij}(k + 1) \approx \Delta w_{ij}(k)$, thus preventing the appearance of $\Delta w_{ij}(k) = 0$ which helps to make the network jump out of the local minimum of the error surface.

When designing the training program of the additional momentum method, additional conditions must be added to correctly use its weight correction formula:

$$mc = \begin{cases} 0.95, & \text{When } SSE < SSE(k - 1), \\ 0, & \text{When } SSE > SSE(k - 1) \times 1.04, \\ mc, & \text{Other.} \end{cases}$$

(4)

SSE is the sum of the output errors of the network.

Thus, we can get the output response. In this experiment, we set the sparseness of the feature vector $\alpha$ to carry out three sets of tests, that is, the actual number of signals in the 45 elements in the nonall zero vector element group is 5, 15, and 25.

3.2. Experimental Setup. In the comparison of three different sets of simulated data, we use L1 regularized Lasso, L1/L2 norm group Lasso, and elastic net as our proposed TGSL control method for testing. In the experiment, different methods are used for feature selection, and then, the selected features are used to perform regression on the output response. According to the method of predefined group weighting coefficients in the study, we also define the parameters $w_i^f$ of the group Lasso and TGSL as the square root of the number of elements. The number of layers of the TGSL tree is 3 layers. The other regularization parameters of all models were selected using 5-fold cross-validation, and the parameter range was \{0, 0.001, 0.002, 0.005, 0.01, 0.02, 0.05 , 0.1, 0.2, 0.5, 1\}. For the performance evaluation of the method, we use some common standards in regression prediction analysis, for example, root mean squared error (RMSE), Pearson correlation coefficient (CC), and coefficient of determination (coefficient of determination, CD).
Finally, we performed the average calculation of the 50% cross-validation test on the regression performance of different methods.

3.3. Evaluation Index. In order to comprehensively evaluate the effectiveness and correctness of the algorithm, this study used 4 simulation data sets to test and compare the benchmark algorithm and the algorithm in this paper. The reference data of the simulation experiment data set generation method, the details of the data set are shown in Table 1, each data set. All contain the true weight coefficients \(u\) and \(v\), and correlation coefficients of \(X, Y, X, Y\), where \(n\) represents the number of samples, \(p\) represents the feature dimension of \(X\), and \(q\) represents the feature dimension of \(Y\).

The experiment used 5-fold cross-validation to test each data set, randomly selected 4 samples from all samples as the training set, and the remaining 1 sample was used as the test set. The evaluation criterion of the experiment is to find a group of \(u\) and \(v\) that are closest to the true correlation coefficient. In order to minimize the adverse effects on the results caused by the difference between the selection of the training set and the test set, we choose the training set in 5 experiments. The set of \(u, v\) with the smallest difference in correlation coefficient with the test set is used as the final result.

4. Image Genetics Analysis Based on Neural Network

4.1. Analysis of Gene Modules Divided by WGCNA. As shown in Figure 1, these 3,525 genes with high SES values were used to construct a coherent gene co-expression network of 6 donated brains. This gene coexpression network includes 15 modules, and each color module is marked as M1-M15. Among the subjects, M8 (including 191 genes) consistently showed the highest gene expression in the striatum.

Table 1: Details of the simulation data set.

| Data set | \(n\) | \(p\) | \(q\) | Correlation coefficient |
|---------|------|------|------|------------------------|
| Data1   | 100  | 250  | 600  | 0.6214                 |
| Data2   | 100  | 250  | 600  | 0.8384                 |
| Data3   | 100  | 250  | 600  | 0.7525                 |
| Data4   | 100  | 500  | 900  | 0.6542                 |

Use the top 50% SES genes to build a consistent network. Each colored block represents M1-M15. The spatial expression pattern of each donated brain M8 module gene. The axis represents the intrinsic gene value of M8 module. The dotted frame represents the sample of the striatum. Each point represents a sample in the brain area, and the error bar represents a standard error.

Figure 1: Spatial specific expression analysis of gene coexpression network and M8 module.

Table 2: Correlation results of correlations on simulated data sets under different methods.

| Attribute | SCCA | GSCCA | TGSCCA |
|-----------|------|-------|--------|
| BL        | 0.957| 0.959 | 0.963  |
| M06       | 0.938| 0.946 | 0.949  |
| M12       | 0.942| 0.951 | 0.956  |
| M24       | 0.924| 0.944 | 0.946  |
less noise is introduced in the simulation data set 1, GSCCA
and TSCCA have similar correlation performance; however,
when the noise increases, TGSCCA has stronger resistance
to noise on the simulation data set 2, and its performance
is better than GSCCA. For the estimation of the true values
of $u$ and $v$, SCCA’s feature detection at different time points
is scattered; although GSCCA can have the same result as
TGSCCA in the detection of $u$, the influence of noise in
the detection of $v$ cannot be reflected. This indicates that
the algorithm still has certain limitations in practical appli-
cation and progressive variability of adjacent features. The
experimental results show that TGSCCA can achieve the fea-
ture selection close to the real signal, so as to achieve higher
 correlation performance, and has significant advantages
compared with other methods.

4.2. Analysis of Cross-Validation Results. “NAN’ means that
this method fails to calculate the typical vector $u, v$. The
black value is the average of 5 experiments. It can be clearly
seen that for the training set, the SC-SCCA algorithm
obtained on Data2, Data3, and Data4. The average correla-
tion coefficient is significantly greater than the average cor-
relation coefficient obtained by the other two algorithms.
For the test set, the SC-SCCA algorithm is also significantly
better than the LI-SCCA and FL-SCCA algorithms. Generally
speaking, the test set results are better than the training set.
The results of this can better reflect the effectiveness of the
algorithm.

As shown in Table 3, in order to obtain the correlation
coefficient using a set of typical vectors $u, v$ with the smallest
difference between the correlation coefficients obtained from
the training set and the test set in 5 experiments, the black
value is the closest to the true correlation among the three
algorithms and the value of the coefficient. If we consider
the true correlation coefficient of the data set, the two algo-
rithms SC-SCCA and FL-SCCA have smaller average evalu-
ation errors and are closer to the true correlation coefficient.
In other words, SC-SCCA and FL-SCCA are more accurate
in training results than LI-SCCA. In addition, SC-SCCA
has the smallest evaluation error, and the correlation coeffi-
cient error obtained on Data3 and Data4 is 0. As shown in
Figure 3, the experimental results of the three algorithms
on different data sets are more intuitively displayed. The first
three columns represent three different methods, and the
fourth column represents the actual correlation coefficient
of the data set. SC-SCCA can be seen. The two methods with
FL-SCCA are significantly better than the LI-SCCA method,
especially on Data2-4. In addition, on Data2-3, the SC-
SCCA method is superior to the FL-SCCA method.

The process of the entire algorithm is concise and clear,
and the respective variances and covariances of the matrices
$X$ and $Y$ need to be calculated separately. Due to the high
dimensionality of the SNP and fMRI data, the output
variable changes linearly with the size of the input data set,
and the spatial complexity is $O(n)$; the larger the space
complexity, the larger the space it occupies, and the more
difficult the algorithm processing task is. The rest of the calculations are simple matrix addition, multiplication, and inversion. The algorithm in this paper can make the algorithm converge within a reasonable time. After convergence, the value does not increase with the increase of the number of iterations, but infinitely approaches a certain value, which is also the closest value between the predicted value and the real value. In addition, the algorithm in this paper regards each feature as a vertex in the graph, and the correlation coefficient between the features is used as the weight of the edge. The network graphs are constructed for the two types of data, so that the spatially related features will rely more. Recently, it is more conducive to the selection of related features.

4.3. Connectivity Analysis. As shown in Figure 4, according to the partial correlation analysis of the genetic working memory score, the PGRS memory has a significant negative correlation, but it does not reach a meaningful level, which indicates that the score can better reflect the changes in personal working memory. Partial correlation analysis of the nucleus and caudate nucleus on both sides of the dopamine gene PGRS showed that PGRS was positively correlated with the volume of the left nucleus, and age, gender, and total brain volume were excluded as covariates.

The brain network model is a simple representation of the brain system. The nodes in the figure are defined as brain regions, and the edges correspond to the connections between brain regions. The thickness represents the weight of the edge after feature selection (it can be understood that the edge is in regression, the importance of the question). Using the algorithm to deal with the staggered linear edge after segmentation can effectively eliminate the influence of burr points and obtain the real edge. The connection edges and the results show that not only the internal structure of the default network will seriously affect the identification of genotypes but also the connection between the default network and other ROIs and the genotype are importantly related, such as the caudate nucleus, dorsal lateral prefrontal lobe, and center in the table (wait back). In previous studies, it was proved that the local anomaly of the default network node area causes the topological network attributes of other network areas to change. The experimental results of this study also proved the default network as a key target for
Alzheimer’s disease. In addition, the results of this study also confirmed that the default network, as an important part of different networks, has a higher weight for the identification of Alzheimer’s disease genotypes. In addition, we also found that the sensorimotor area plays an important role in identifying the genotype of Alzheimer’s disease. The perceptual motion area (central anterior gyrus, central lobe, and auxiliary motion area) is mainly related to the movement and perception of the human body, and it mainly allocates and controls the movement and posture of the trunk and limbs. Our results to some extent confirm the source of motor and sensory disturbances in the clinical manifestations of Alzheimer’s disease patients. At the same time, the experimental results show that the functional connection between the anterior wedge and the central anterior gyrus has the largest weight in prediction, that is, for discrimination, this connection in the brain network is the most critical for the accuracy of genotype prediction.

5. Conclusions
In this paper, based on structural magnetic resonance and functional magnetic resonance imaging data, and based on imaging genetics research ideas, we studied the effects of genes related to the dopamine system on the brain network. First, the influence of single-gene SNP sites on cortical morphology and functional network was studied, and then, the interaction between the two gene SNPs on the prefrontal-striatal function loop was studied, and finally, all the spirit and spirit of the dopamine system were included. The effect of SNP sites related to schizophrenia risk on the dorsal striatum function network.

This article finds that human neuroticism is significantly related to striatum functional connections, but not to striatum volume. In addition, on the mesoscopic scale, neurotic-related functional connections are related to the specific expression of intermediate spinous neurons; on the time scale, especially in the middle and late childhood and adolescence, striatum-specific expression is involved. These findings may deepen our understanding of the genetics and neural mechanisms of human neuroticism.

This paper uses structural information such as the hierarchical relationship between the features of SNPs to detect the multivariable gene loci associated with the QT of a candidate brain region of neuroimaging. Specifically, first, establish a tree structure through prior knowledge, that is, each SNP site is used as a leaf node of the tree, and the LD blocks and genomes formed by the linkage imbalance of several SNP sites are used as intermediate nodes, and then, the characteristic hierarchical relationship. Further, for the problem of multi-SNP locus regression candidate brain image QT, a sparse learning method based on tree structure guidance is used for feature selection. Finally, the SNPs with recognition in feature selection are retained to predict QT of brain images. On the ADNI data set, the experimental results show that the proposed method can not only significantly improve the regression performance of the learning algorithm but also detect the risk gene SNPs loci with spatial clustering characteristics and functional interpretation significance. In this paper, a deep study of image genetics and its application has been carried out, but there are still many deficiencies. The experimental level of this paper is limited, and the research level and quality will be continuously improved in future research work.

Data Availability
This article does not cover data research. No data were used to support this study.

Conflicts of Interest
The authors declare that there are no conflicts of interest.

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