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Differences among first-episode schizophrenia patients, healthy siblings, and controls at the individual level

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1. Introduction

Schizophrenia is a disorder characterized by long duration, psychosis, negative symptoms, cognitive impairments and several affective symptoms (van Os and Kapur, 2009). The diagnosis of schizophrenia is currently dependent on the confirmation of key symptoms and elimination of the most probable differentials (van Os and Kapur, 2009). Several biological abnormalities (e.g., abnormally large ventricles and altered P300) have been reproduced, but these abnormalities are not sensitive or specific enough to be of diagnostic use (Allen et al., 2009). In the past 20 years, techniques of magnetic resonance imaging (MRI) especially brain anatomical imaging, have been extensively applied to research patients with mental disease, including schizophrenia, but the results of these studies presented minimal clinical effects. One of the reasons is that neuroimaging studies typically reported differences at group level. The other reason is that the abnormalities in brain of patients with schizophrenia were so subtle for group comparisons. The third reason is that, prior to clinical use, it is necessary to get the characteristic traits from complex genetic background. At present, the strategies of assuring these questions are taking the methods of multivariate analysis of pattern recognition, and, recruiting individuals with the genetic background as controls.

Methods of pattern recognition allow us to make decision at an individual level,and made it possible to use multivariate information and previously unseen data (Haller et al., 2014). In these methods, Support vector machine (SVM) was one of the most popular used one. It is a specific type of supervised machine learning analysis method, allows the categorization of an individual into a predefined group by a classification algorithm, which is developed on a training data set (Vapnik, 1995; Orru et al., 2012). In recent years, SVM has been applied to classify numerous neurological and psychiatric disorders, such as Alzheimer's disease (Liu et al., 2014), major depression (Liu et al., 2012), bipolar disorder (Schnack et al., 2014), and post-traumatic stress disorder (Gong et al., 2014). SVM has also been applied to classify schizophrenia (Fan et al., 2008; Ingalhalikar et al., 2010; Nieuwenhuis et al., 2012). In a study based on whole brain gray matter (GM) densities (voxel-based morphometry, VBM), authors constructed an SVM model from 239 subjects (128 schizophrenia patients and 111 healthy controls) and classified 71.4% correctly (leave-one-out). They then replicated and validated this result by testing the unaltered model on a completely independent sample of 277 subjects (155 schizophrenia patients and 122 healthy controls), and obtained a similar classification rate (70.4%) (Nieuwenhuis et al., 2012). In another study based on diffusion tensor imaging data, a clear distinction between schizophrenia patients and controls was achieved with 90.62% accuracy (Ingalhalikar et al., 2010).

In these studies, relatively high accuracies have been got in discriminating schizophrenia patients from controls. But it still has limitations in expanding its observations in clinical practices or in pathology. For it is necessary to take the characters of disease from genetic background. Fan et al. (Fan et al., 2008) built a high-dimensional pattern classifier, which is based on GM and white matter (WM) volume, from a group of 69 patients and 79 control subjects, and applied the classifier to examine the brain structure of 30 family members (FMs). In another study, Mandl et al. (Mandl et al., 2013) compared conventional classification methods (single subject model) with a new family-wise model, and demonstrated that the inclusion of heritable features can lead to an increase in classification accuracy from 0.54 to 0.72 using SVM.

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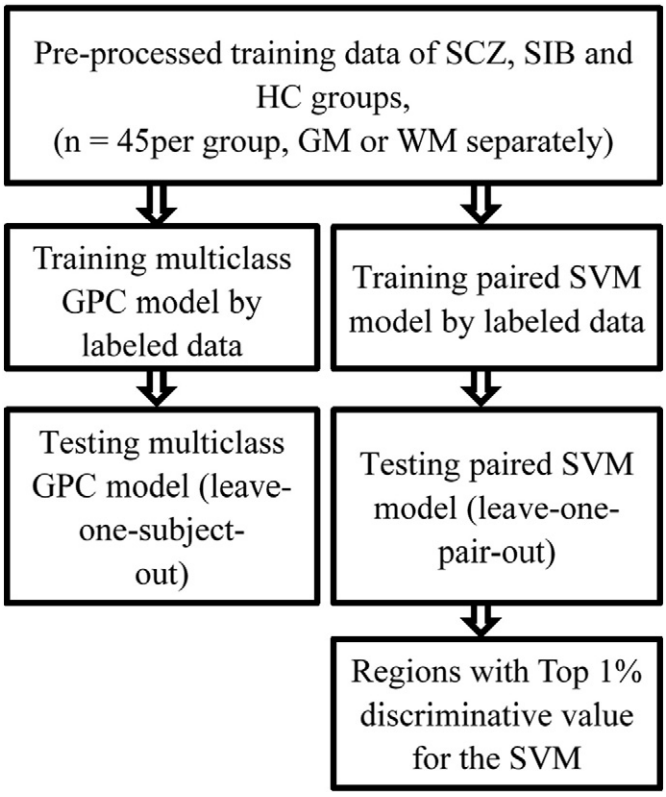

Fig. 1. Flowchart of classifications of schizophrenia patients (SCZ), siblings(SIB), and healthy controls (HC).

Their results showed that gene sharers present highly overlapping structural profiles with those of patients. Given the similarity of brain anatomical patterns between patients and FMs which was bring about by the same genetic background, confirming which structural profiles are directly associated with the pathology of schizophrenia is important. These two studies emphasized similarity between patients and their gene sharers, and take genetic background into classification for improving the performance of classifier. However gene sharers don't have the characteristic symptoms of schizophrenia. And so we hypothesized that patients with schizophrenia could be directly discriminated from siblings and healthy controls with their specific spatially distributed anatomical patterns that are associated with schizophrenia. It was considered that it is more important in discriminating patients from their gene sharers than in improving performance of discriminating patients from healthy controls.

For examining this hypothesis, we recruited schizophrenia patients, their healthy siblings and healthy controls to do the classification. Despite the robust performance in binary classification, SVM do have limitations in multiclass pattern recognition. For this reason, we used the "Multiclass Gaussian Process Classification" (MGPC) machine (Rasmussen and CKI, 2006) (http://www.gaussianprocess.org/gpml/code/matlab/doc/) to do the multiclass classification. It is a Bayesian approach to non-parametric multiclass classification with the advantage of producing probabilistic outputs that measure uncertainty in the predictions (Rasmussen and CKI, 2006). This study also aimed to identify certain brain regions that contribute significantly to classification. By this purpose, we using paired SVM to finding differences in anatomical patterns between the three groups with each other. Several previous studies suggested that antipsychotic medication affects structural neuroimaging (Ho et al., 2011), although the reported effects are inconsistent (Shepherd et al., 2012). Given that we recruited first-episode patients who never received any antipsychotics, antidepressants, mood stabilizers, or stimulants in this study, the potential effect of medication for structural neuroimaging can be discounted. We expected that schizophrenia patients can be discriminated from unaffected siblings and healthy controls with statistically significant accuracy. We also expected that certain regions or spatially distributed pattern of anatomical changes are potential biomarkers for schizophrenia.

2. Methods

2.1. Participants

The present study was approved by the ethics committee of the Second Xiangya Hospital and complied with the Declaration of Helsinki. The study was conducted between January 2009 and December 2012. All participants provided written informed consent before enrollment.

Schizophrenia patients were recruited in first-visit outpatients of the Second Xiangya Hospital if they met the following criteria: 1) aged 18–30 years, right-handed, Han Chinese ethnicity, and received a minimum of nine years of formal education; 2) a diagnosis of schizophrenia, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000), was confirmed by a senior psychiatrist through an outpatient interview; 3) the diagnosis of schizophrenia was confirmed using the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (SCID) (First et al., 1997); 4) the observed duration of illness, which was identified as the time interval from the first reported abnormality by relatives/others to recruitment, was less than two years; 5) never received any antipsychotics, antidepressants, mood stabilizers, or stimulants before recruitment; and 6) the total score of Positive and Negative Syndrome Scale (PANSS) ≥ 60. To mitigate the effect of combined diseases, patients with other psychiatric illnesses, which were verified by SCID, were excluded. Patients with severe physical diseases (e.g., neurological illness, traumatic brain injury, hematological system diseases, autoimmune disorders, malignant tumor, and visual or auditory disability) were also excluded from the present study.

Unaffected siblings of schizophrenia patients were also recruited in the outpatient department. These unaffected siblings were unrelated to the patients recruited in this study, and the diagnosis of their relatives was confirmed by SCID. Healthy controls were also recruited from the

Table 1
Demographic and clinical characteristics of the study sample.

Characteristic	Patients ($n = 45$)	Siblings ($n = 45$)	Controls ($n = 45$)	Test		p
				F	χ^2	
Age, years:mean (s.d.)	23.24 (4.63)	22.60 (3.92)	23.64 (2.74)	0.43		0.65
Gender (male/female)	27/18	31/14	25/20		1.75	0.42
Education, years:mean (s.d.)	11.65 (2.57)	11.84 (2.39)	12.13 (2.42)	0.83		0.43
Disease duration, months: mean (s.d.)	12.85 (6.30)					
PANSS: mean (s.d.)						
Positive score	22.23 (5.56)					
Negative score	22.10 (6.43)					
Total score	90.19 (10.94)					

PANSS, the Positive and Negative Syndrome Scale.