DISTRIBUTED FUNCTIONAL CONNECTIVITY IMPAIRMENT IN SCHIZOPHRENIA: A MULTI-SITE STUDY

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Abstract

Schizophrenia has been considered as a dysconneciton syndrome, which means the disintegration, or over interaction between brain regions may underlie the pathophysiology of this disease. Noninvasive techniques like functional magnetic resonance imaging (fMRI) were utilized to test this hypothesis. However, there is no consensus on which brain areas and which functional network is related with it, mostly due to the small sample size of previous studies. Supervised machine learning techniques are able to examine fMRI connectivity data in a multivariate manner and extract features predictive of group membership. This technique requires large sample sizes and results from small sample study may not generalize well. By applying a multi-task classification framework to large size multi-site schizophrenia resting functional MRI (rsMRI) dataset, we were able to find consistent and robust features. We observed that schizophrenia patients had widespread deficits in the brain. The most informative and robustly selected functional connectivity (FC) features were between and within functional networks such as the default mode network (DMN), the fronto-parietal control network (FPN), the subcortical network, and the cingulo-opercular task control network (CON). Our finding validated the dysconnection hypothesis of schizophrenia and shed light on the details of the impaired functional connectivity.

1 Introduction

Supervised machine learning technique in combination with neuroimaging techniques has been used in disease research such as Schizophrenia. As a data driven framework, it not only provides the possibility of automatically recognizing the patients with high accuracy, but also gives knowledge of the features that we could use to do classification task. However, as with the traditional statistical tests, the data driven methods also suffer the small sample problem in this area [1]. The sample size in neuroimaging studies is rarely above 1000 while FC features extracted with a common brain atlas, for example, the Automated Anatomical Labeling template, are usually much more than 5000. Results may be biased in an experiment on a random selected small sample dataset that may not well represent the population. In particular, schizophrenia, as a complex and heterogynous psychiatry disease with distinct clinical subtypes and clinical states for the patients, may suffer this problem much more. Some other factors such as the scanner type and settings, subjective assessment of the clinical score, demographics also contribute

to the varied probability distribution of different samples. In such a case, the reliability of the studies and the reproducibility of the results should be reviewed carefully. In previous studies, the reported classification accuracy varies from ~60% to ~90% [2, 3]. One seldom noticed problem is that, different experiment may use different subset of features in their final classifier. The features and the classifier fit for one group of subjects may not work well for the other.

The multi-task feature learning framework has been successfully used to simultaneously model several related learning problems [4]. It captures the intrinsic relatedness among different tasks. Building classifiers on a multi-site data could be formed as a multi-task learning problem with feature selection for each site treated as a separate task. The introduced group sparsity regularization will ensures that a subset of features be selected for the classification models at all sites.

In this study, we fully used a multi-site collected data to train classifier to distinct the patients from the normal person. In addition to keeping an acceptable classification accuracy, we restricted the selected features to be consistent across the site. In other words, one feature may either be used in the classifiers from all the sites or not used by any one. Using such strategy, we can identify the FCs that were most discriminative between the schizophrenia and the normal. We assumed these impaired FCs were fundamentally related with the disease and shared by patients from different sources. Our findings indicate that schizophrenia is a dysconnection disease represented by abnormal interaction among large-scale functional networks.

2 Matierials and Methods

2.1 Subjects

The resting state fMRI data presented here was collected from six hospitals in China that participated in the Brainnetome Project for Schizophrenia. The six hospitals are Peking University Sixth Hospital (PKUH6), Beijing Huilongguan Hospital (HLG), Xijing Hospital (XJ), Henan Mental Hospital (HM), Renmin Hospital of Wuhan University (RWU), and Zhumadian Psychiatric Hospital (ZMD). Henan Mental Hospital provided images from two distinct MRI scanners: Siemens (HMS) and General Electric (HMG). The local ethical review board approved the study at each site. All the participants provided written informed consent. All schizophrenia patients (SZs) had a diagnosis of schizophrenia confirmed by trained psychiatrists using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P) [5]. Exclusion criteria were a current neurologic disorder, a history of serious medical illness, substance dependence, pregnancy, electroconvulsive therapy within the last six months, or a diagnosis of any other Axis I disorder. The Positive and Negative Syndrome Scale (PANSS) was used to assess positive, negative, and general psychopathology symptoms in the patients [6]. The healthy controls (HCs), who had no current axis I psychiatric disorders, were recruited from the local community near each site through advertisements. None of the HCs had any personal history of psychotic illness and any family history of psychosis in their first, second, or third degree relatives. All the participants were Han Chinese in origin, right-handed, and had no contraindications to MRI scanning. After extensive quality checking of the brain imaging data, 446 SZs and 451 HCs were included in the analysis. Patients and controls were matched for age and sex at each site.

2.2 Data acquisition and preprocessing

All the participating sites used 3T MRI scanners but produced by different manufacturers (four produced by Siemens, and three produced by General Electric). To ensure equivalent acquisition protocol and high quality imaging data, the scanning parameters at each of the six sites were set up by an experienced researcher before data acquisition. Briefly, the detailed functional scans were obtained by an echo planar imaging sequence with the following parameters: 30 axial slices, repetition time = 2000 ms, echo time = 30 ms, matrix = 64 × 64, flip angle = 90°, field of view = 220 × 220 mm^2, slice thickness = 4 mm, gap = 0.6 mm. 240 brain volumes were collected, resulting in a total scan time of 480s. To be noticed, the time point number of the images from ZMD is 180 and is different from the 240 of the other sites. We did not exclude this site in order to keep as much data and sites as possible, and to support the validation of the multi-site analysis.

The fMRI scans were preprocessed with Brainnetome fMRI Toolkit (http://www.brainnetome.org/en/brainnetometool/fmri-toolkit), which is based on functions in Statistical Parametric Mapping SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first ten images were discarded for the signal equilibration. The remaining images were corrected for slice timing and head motion movement. Subjects who had larger than 3.0 mm of head motion or 3.0° of angular rotation were eliminated. There were no differences with regard to the maximum displacement and maximum rotation between groups at all sites, except that at HMS the SZs had nominal higher maximum displacement (Wilcoxon rank sum test, $W = 2506.00$, $p < 0.02$). The fMRI images were then normalized to the standard Montreal Neurological Institute (MNI) template and resampled to the 3 mm isotropic voxels. Artefacts due to changes in global, ventricular and white matter signals, and residual motion were removed using voxel-wise regression. A temporal filter ($0.01\ Hz < f < 0.08\ Hz$) was used to reduce the low-frequency drift and physiological high frequency respiratory and cardiac noise. Finally, the data were smoothed with an isotropic Gaussian kernel of 6 mm full-width at half-maximum.

2.3 Regions of interest (ROIs)

We used 264 putative functional areas as the ROIs [7]. These ROIs are attributed to several predefined functional brain systems, which will facilitate our interpretation of the results. Five mm radius sphere ROIs centered at peak coordinates were created in MNI standard space. We averaged the time

series of all voxels within each ROI for each subject. Pearson correlation was then performed to estimate functional connectivity between each pair of ROIs. Fisher's Z transformation was applied to transform Pearson r to Z scores. We standardized the features within each site by removing the mean of each feature and dividing the standard deviation. Finally, we got 34761 (264×263/2) FC features for each subject.

2.4 Multi-task classification and feature selection

We assumed that the model for different sites share a common set of features that are informative for the classification tasks. The key strategy was introducing a group sparsity in the classification model. We used logistic regression as the base model. The model is formulated as:

$$\min_{W,c} \sum_{i=1}^{t} \sum_{j=1}^{n_i} \log(1+\exp(-Y_{i,j}(W_j^T X_{i,j} + c_i))) + \rho_1 \|W\|_{2,1} + \rho_{L2} \|W\|_F^2 \quad (1)$$

where $X_{i,j}$ denotes FC data of subject j from the i-th site, $Y_{i,j}$ denotes its corresponding label, W_i and c_i are the model parameters for task i, the regularization parameter ρ_{L2} penalizes the complexity of model and ρ_1 by incorporating sparsity will select subset of features and keep them consistent across sites. We adopted the multi-task learning via structural regularization (MALSAR) software to solve this model [8]. In the training period, we used a 10-fold cross validation to estimate the performance of the classifier. We finally calculated the classification accuracy, specificity, and sensitivity for each site to evaluate the performance of the model. These metrics were calculated at each level of sparsity respectively, by averaging across 10 folds.

3 Results

3.1 Demographics and clinical data

Sociodemographic and psychopathological data are presented by site (Table 1). No statistically significant differences in age and sex were noted between the SZs and HCs at each site. The patients had significantly fewer years of education than the HCs in five out of seven sites.

	HC	SZ	Statistics	*p*
HLG	n = 55	n = 65		
Age (Years)	24.89 (5.37)	26.06 (5.38)	T = -1.19	0.24
Gender (M/F)	26/29	26/39	$\chi2$ = 0.38	0.54
Education (Years)	13.33 (4.59)	13.33 (3.05)	T = 0.75	0.45
Illness duration (Months)	NA	60.79 (49.78)	NA	NA
PANSS total	NA	79.00 (6.71)	NA	NA
PANSS positive	NA	26.25 (2.94)	NA	NA
PANSS negative	NA	16.69 (3.37)	NA	NA
PANSS general	NA	36.06 (3.85)	NA	NA
PKUH6	n = 80	n = 80		
Age (Years)	25.83 (5.44)	27.32 (6.73)	T = -1.54	0.13
Gender (M/F)	46/34	50/30	$\chi2$ = 0.23	0.63
Education (Years)	13.61 (3.53)	13.26 (3.59)	T = 0.63	0.53
Illness duration (Months)	NA	45.88 (53.53)	NA	NA
PANSS total	NA	77.92 (9.31)	NA	NA
PANSS positive	NA	23.84 (4.10)	NA	NA
PANSS negative	NA	18.26 (5.72)	NA	NA
PANSS general	NA	35.83 (5.35)	NA	NA
RWU	n = 77	n = 67		
Age (Years)	24.89 (5.37)	26.06 (5.38)	T = -1.03	0.30
Gender (M/F)	37/40	28/39	$\chi2$ = 0.34	0.59
Education (Years)	14.60 (2.24)	11.76 (3.55)	T = 5.61	*p*<0.00*
Illness duration (Months)	NA	42.82 (37.09)	NA	NA
PANSS total	NA	88.04 (12.08)	NA	NA
PANSS positive	NA	23.69 (4.21)	NA	NA
PANSS negative	NA	21.18 (6.04)	NA	NA
PANSS general	NA	43.18 (7.65)	NA	NA
HMG	n = 66	n = 43		
Age (Years)	30.75 (7.28)	29.24 (7.81)	T = 1.01	0.31
Gender (M/F)	32/34	24/19	$\chi2$ = 0.30	0.58
Education (Years)	13.08 (4.51)	9.14 (3.42)	T = 5.17	0.00
Illness duration (Months)	NA	51.00 (62.52)	NA	NA
PANSS total	NA	88.70 (11.91)	NA	NA
PANSS positive	NA	24.44 (3.65)	NA	NA
PANSS negative	NA	23.60 (5.57)	NA	NA
PANSS general	NA	40.65 (6.55)	NA	NA
HMS	n = 80	n = 80		
Age (Years)	27.16 (5.70)	26.09 (5.36)	T = 1.23	0.22
Gender (M/F)	42/38	43/37	$\chi2$ = 0.00	1.00
Education (Years)	13.82 (2.85)	11.13 (2.83)	T = 5.96	*p*<0.00*
Illness duration (Months)	NA	39.92 (38.80)	NA	NA
PANSS total	NA	81.12 (8.52)	NA	NA
PANSS positive	NA	22.54 (2.80)	NA	NA
PANSS negative	NA	19.52 (5.33)	NA	NA
PANSS general	NA	39.06 (5.46)	NA	NA
XJ	n = 40	N = 58		
Age (Years)	29.74 (6.36)	27.54 (5.95)	T = 1.73	0.09
Gender (M/F)	21/19	30/28	$\chi2$ = 0.00	1.00
Education (Years)	13.00 (3.19)	10.05 (4.81)	T = 3.65	*p*<0.00*
Illness duration (Months)	NA	25.98 (29.78)	NA	NA
PANSS total	NA	88.95 (14.07)	NA	NA
PANSS positive	NA	22.34 (4.91)	NA	NA
PANSS negative	NA	22.31 (5.73)	NA	NA
PANSS general	NA	44.29 (8.02)	NA	NA
ZMD	n = 53	n = 53		
Age (Years)	33.29 (7.09)	31.03 (7.38)	T = 1.61	0.11
Gender (M/F)	24/29	26/27	$\chi2$ = 0.04	0.85
Education (Years)	12.87 (3.31)	8.71 (3.60)	T = 6.16	*p*<0.00*
Illness duration (Months)	NA	64.95 (64.14)	NA	NA
PANSS total	NA	87.47 (13.67)	NA	NA
PANSS positive	NA	25.43 (5.09)	NA	NA
PANSS negative	NA	21.04 (5.76)	NA	NA
PANSS general	NA	41.00 (6.40)	NA	NA

Continuous variables represented by Mean (SD).
M: male; F, female.
*: statistically significant at 0.05 level.

Table 1: Sociodemographic and psychopathological data.

3.2 Classification performance and feature selection

Classifier training and testing were performed using the 10-fold cross validation. We set the sparsity parameter ρ_1 in a range from 0.000 to 0.049 with a 0.001 step. At first, the number of selected features dropped sharply from 34761 to 539 when we added the sparsity penalty (ρ_1 = 0.001) and the accuracy showed an increase (Figure 1, 2). At this level, the classification accuracy of the seven sites varied from 60% to 86%. The selected features distributed across the whole brain. As the sparsity increased, accuracy all dropped. The number of selected features decreased as well.

Several ROIs in DMN, FPN, and the subcortical network showed up as the most discriminated patterns. We drew the selected features at six different levels of sparsity: ($\rho_1 \in [0.014, 0.019, 0.024, 0.029, 0.034, 0.039]$) with circos software (Figure 3) [9]. ROIs belong to different functional networks were displayed in different colors, and red lines indexed the FCs selected by the classifier. The selected FCs mainly included FCs from DMN to FPN, visual cortex, sensory somatomotor system, FCs within the subcortical

network and from the subcortical to CON, and FCs between the dorsal attention network and the cerebellar (ρ_1 = 0.029). The most robust FC was one within the subcortical and one between the subcortical and CON (ρ_1 = 0.034). The ROIs involved in the selected FCs were listed in Table 2.

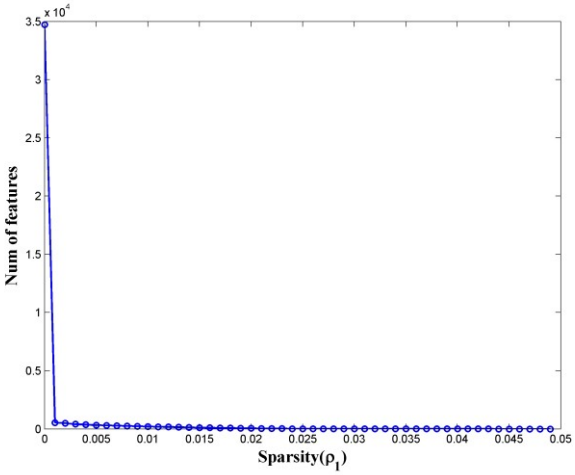

Figure 1: The number of selected features at different levels of sparsity (averaged over folds and sites).

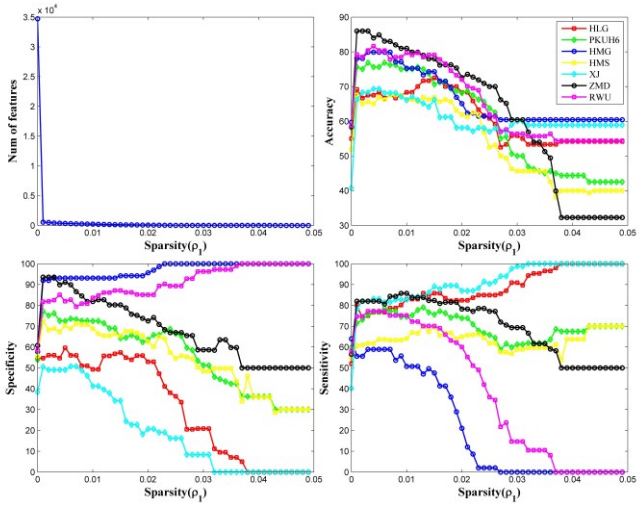

Figure 2: The classification accuracy on each site at different levels of sparsity.

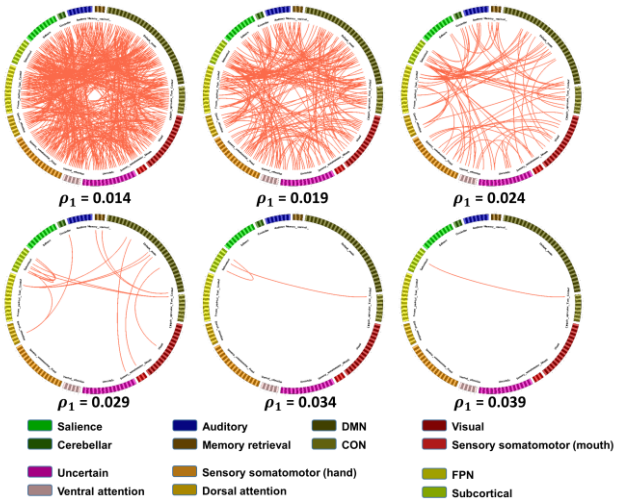

Figure 3: FCs used in the model at different levels of sparsity.

MNI coordinates			Modular	Brodman Area
X	Y	Z		
23.96	31.94	-17.78	Uncertain	Frontal_Mid_Orb_R
36.04	-9.44	13.95	Sensory/somatomotor Mouth	Insula_R
-2.88	2.38	53.21	CON	Supp_Motor_Area_L
5.91	-58.82	35.45	DMN	Precuneus_R
7.94	-48.37	30.57	DMN	Cingulum_Post_R
5.94	54.42	16.18	DMN	Frontal_Sup_Medial_R
-7.04	50.82	-1.29	DMN	Cingulum_Ant_L
-3.06	44.41	-9.46	DMN	Frontal_Med_Orb_L
-55.72	-12.96	-10.24	DMN	Temporal_Mid_L
-2.47	-34.8	31.07	Memory retrieval	Cingulum_Post_L
49.26	35.47	-12.2	DMN	Frontal_Inf_Orb_R
15.18	-76.68	31	Visual	Cuneus_R
-41.68	45.16	-2.31	FPN	Frontal_Mid_Orb_L
1.75	-24.25	30.36	Memory retrieval	UNDEFINED
-10.28	-18.48	7.04	Subcortical	Thalamus_L
11.75	-17.18	7.54	Subcortical	Thalamus_R
-21.97	7.48	-4.78	Subcortical	Putamen_L
-15.41	3.57	7.99	Subcortical	UNDEFINED
23.26	10.19	1.46	Subcortical	Putamen_R
14.98	4.94	7.24	Subcortical	UNDEFINED
8.62	-3.57	5.76	Subcortical	Thalamus_R
0.51	-61.91	-18.14	Cerebellar	Vermis_6
46.09	-58.93	3.93	Dorsal attention	Temporal_Mid_R

Table 2: ROIs contribute to the classifier (ρ_1 =0.029).

4 Discussion

In the present study, we applied a multi-task learning framework to classify the schizophrenia patients and healthy controls with multi-site imaging data. We found that, features contributed to our trained classifier were widely distributed in the whole brain. As we know, schizophrenia is a complex and heterogeneous disorder with many different symptoms observed. It affects all aspects of motivation, thinking, memory, decision-making, affect, emotional expression, and social communication. Thus, we suspect that schizophrenia may have diffuse impairment in brain while the effect is subtle in each local brain region. These wide spread deficits may underlie the complexity of the disease. In our study, the patients from different sites may varied in their causes, pathologies, symptoms and illness degrees of the disease. The more heterogeneous of the sample, the more independent features we need to achieve high accuracy, especially when most features had weak association with the disease. Thus, most of the features selected in the early stage may only play

a small role in classification but not well characterize the fundamental mechanism of this disease.

However, features selected at a high sparsity level are supposed to be robust to the heterogeneous of the disease. The DMN showed a dysconnection with FPN, the visual and the CON. This network has been proved to be closely associated with schizophrenia and correlated with cognitive task performance and clinical scores [10-14]. Functional connections within the subcortical network (including the thalamus and the putamen) and between the subcortical network and CON also showed a great discriminative power. This result was in line with previous studies [15]. Interestingly, functional connectivity between the visual cortex (Cuneus) and DMN (Mid temporal cortex) also showed itself having a non-negligible predictive power. Little evidence but a quantitative meta-analysis of functional imaging studies of episodic retrieval support impairments of the left middle temporal gyrus and the right cuneus [16].

One obvious advantage of our study is the large sample size. More importantly, the multi-task approach provides a good tool to make full use of such data. The most predictive features were selected as multi-site consistent functional connectivity deficits. However, the classification performance varied greatly among the sites and was not satisfying. Meanwhile, we noticed that the performance decreased as the selected features decreased. We suspect that, the impact of schizophrenia may widely spread in the whole brain. The composition of effects from all the deficits in the brain may cause the complex symptoms of this disease. While the effect is quite weak as we see from the results, future studies should pay more attention to the heterogeneity of the sample. Data sharing is necessary to further the research in this area. The limitation of this study is that the consistent features may be the result of shared cofounding factors across sites such as the antipsychotic meditation. One solution is that we could apply the multi-task strategy on different subtypes of the disease，which requires a well-designed sample collection strategy.

5 Conclusion

In this study, we applied a multi-task feature selection algorithm to the functional connectivity features constructed from multi-site rsfMRI data. We found that the algorithm could efficiently select common set of features. The most discriminative FCs selected were between and within the DMN, the subcortical, the CON and the FPN etc. We validated some of the previous findings. Based on the results, we validated that schizophrenia is a dysconnection disease that incorporates multiple functional systems. Most importantly, we were able to determine the most predictive functional connectivity pattern, which will inform future study in this area.

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