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Shared atypical default mode and salience network functional connectivity between autism and schizophrenia

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Abstract

Schizophrenia and autism spectrum disorder (ASD) are two prevalent neurodevelopmental disorders sharing some similar genetic basis and clinical features. The extent to which they share common neural substrates remains unclear. Resting-state fMRI data were collected from 35 drug-naïve adolescent participants with first-episode schizophrenia (15.6 ± 1.8 years old) and 31 healthy controls (15.4 ± 1.6 years old). Data from 22 participants with ASD (13.1 ± 3.1 years old) and 21 healthy controls (12.9 ± 2.9 years old) were downloaded from the Autism Brain Imaging Data Exchange. Resting-state functional networks were constructed using predefined regions of interest. Multivariate pattern analysis combined with multi-task regression feature selection method was conducted in two datasets separately. Classification between individuals with disorders and controls was achieved with high accuracy (schizophrenia dataset: accuracy=83%; ASD dataset: accuracy=80%). Shared atypical brain connections contributing to classification were mostly present in the default mode network and salience network. These functional connections were further related to severity of social deficits in ASD ($p=0.002$). Distinct atypical connections were also more related to the default mode network and salience network, but showed different atypical connectivity patterns between the two disorders. These results suggest some common neural

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Author Contributions

HC, LQU, XJD, JJZ, ZLL and HFC contributed to the analysis design, HC, YXZ and XNG contributed to the ASD dataset downloading and all data analysis. YZ and JPZ contributed to the SZ dataset acquisition.

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mechanisms contributing to schizophrenia and ASD, and may aid in understanding the pathology of these two neurodevelopmental disorders.

Lay summary—Autism spectrum disorder and schizophrenia are two common neurodevelopmental disorders which shared several genetic and behavioral features. The presenting study suggested some common neural mechanisms contributing ASD and schizophrenia using the functional connectivity method based on the resting-state functional fMRI data. The results may help to understanding the pathology of these two neurodevelopmental disorder.

Keywords

schizophrenia; autism spectrum disorder; functional connectivity; multivariate pattern analysis; default mode network; salience network

Introduction

Schizophrenia and autism spectrum disorder (ASD) are two prevalent neurodevelopmental disorders affecting around 1% of the population (American Psychiatric Association 2013). At one point historically, schizophrenia and ASD were regarded as the same disorder that occurred in different developmental periods (American Psychiatric Association 1952, 1968). Although they are regarded as separate disorders in the current DSM, they share some clinical and etiological features, and numerous studies have shown some shared mechanisms between them (Stone WS et al. 2011). Shared genetic mutations mostly related to atypical synaptic development have been documented in both schizophrenia and ASD (Mitchell KJ 2011). At the behavioral level, schizophrenia and ASD showed some common deficits, especially in the area of social cognition (Couture SM et al. 2010). Despite these commonalities in genetics and symptomatology, very few studies have investigated shared neural substrates between the two disorders (Cheung C et al. 2010; Ciaramidaro A et al. 2015). The extent to which these two disorders share some common neural basis remains unclear.

Functional connectivity (FC), or temporal correlations between remote neurophysiological events (Friston KJ et al. 1993), has become a common tool to study the intrinsic organization of the human brain (Greicius M 2008). Numerous FC studies have shown atypical connections between default mode network (DMN) regions in ASD, which are thought to play a major role in the social deficits characteristic of the disorder (Assaf M et al. 2010; Gotts SJ et al. 2012; Lynch CJ et al. 2013; von dem Hagen EA et al. 2013; Burrows CA et al. 2016). Abnormal salience network (SN) connectivity in ASD has also been reported in previous studies of children. Uddin et al. suggested that SN hyperconnectivity has the potential to be used as a biomarker for objectively identifying children with ASD (Uddin LQ et al. 2013). Our previous multivariate pattern analysis (MVPA) study also showed that the DMN and SN are the most informative in classifying ASD and healthy controls (HC) (Chen H et al. 2015). The DMN is also an important brain network implicated in the psychopathology of schizophrenia. Camchong et al. found lower FC of the medial frontal cortex (MPFC) in participants with schizophrenia (Camchong J et al. 2011). Rotarska-Jagiela et al. reported decreased connectivity in the posterior cingulate of individuals with

schizophrenia (Rotarska-Jagiela A et al. 2010). Dodel-feder et al. found that reduced FC of the dorsal MPFC subsystem of the DMN may be related to social dysfunction in individuals at familial high risk for schizophrenia (Dodell-Feder D et al. 2014). Pelletier-Baldelli reported that DMN and SN connectivity contributed to aberrant social processing in youth at high risk for psychosis (Pelletier-Baldelli A et al. 2015). A MVPA study reported that SN hyperconnectivity could successfully predict the severity of positive symptoms, while DMN hyperconnectivity could forecast negative symptoms in paranoid schizophrenia (Krishnadas R et al. 2014).

In the present study, we aimed to explore the shared neural basis of ASD and schizophrenia using a MVPA method based on resting-state FC data. In line with above prior evidence, we hypothesized that: 1) a significant overlap of atypical FC between ASD and schizophrenia would be observed; 2) the shared atypical FC would mostly be located in the DMN or SN.

Methods

Participants

Schizophrenia dataset—Thirty-five drug-naïve adolescent participants (age range 12 – 18 years; 20 males and 15 females) with first-episode schizophrenia were recruited from The Second Affiliated Hospital of XinXiang Medical University. All subjects met the DSM-IV-TR criteria for schizophrenia (American Psychiatric Association 2013) and had no co-morbid Axis I diagnosis. The duration of illness was less than 2 years. Schizophrenia was independently diagnosed by research psychiatrists based on the Structured Clinical Interview for DSM-IV-TR, Patient Version (SCID-I/P). Psychopathology was assessed in patients using the Positive and Negative Syndrome Scale (PANSS). Thirty-one age-, gender-, education- and IQ-matched HCs were recruited (age range 13 – 17 years, 13 males and 18 females). All HCs had no (1) past or current neurological disorders, or family history of hereditary neurological disorders; (2) history of head injury resulting in loss of consciousness; (3) alcohol or substance abuse; (4) claustrophobia. No subject was excluded due to maximum head motion greater than 3mm or 3 degrees rotation or more than 50% censored frames, see Preprocessing for details.

ASD dataset—Resting-state fMRI data were downloaded from the Autism Brain Imaging Data Exchange (ABIDE) database (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino A et al. 2014). Data from the Yale site (ASD: age range 7 – 17.17 years; 15 males and 7 females; HC: age range 7.66 – 17.83 years, 17 males and 7 females) were included in the current study to match the age range from the schizophrenia dataset. After exclusion due to excessive head motion (7 participants were excluded due to maximum head motion greater than 3mm or 3 degrees rotation. 3 participants were excluded as more than 50% frames were censored, see Preprocessing for details), 22 participants with ASD and 24 HCs were included. The subject IDs of the participants were listed in table. S2 (see in SI).

Ethic Statement

The Schizophrenia dataset was approved by the Ethics Committee of The Second Affiliated Hospital of Xinxiang Medical University. The study was conducted under relevant

guidelines between February 2012 and January 2013. The methods were carried out in accordance with the approved guidelines. We obtained written informed consent from each participant. All experimental protocol were approved by the Ethics Committee of The Second Affiliated Hospital of Xinxiang Medical University.

The ASD dataset was from the open-access ABIDE database. Please found the ethic statement at the official website of ABIDE database (http://fcon_1000.projects.nitrc.org/indi/abide/)

Demographic details for the two datasets are listed in Table 1.

Imaging parameters

Resting-state fMRI data for the schizophrenia dataset were acquired on a Siemens 3.0 T Trio scanner (Siemens Medical Systems, Erlangen, Germany), using an echo-planar imaging sequence with the following parameters: TR/TE = 2000/30 ms, flip angle = 90 degrees, 33 slices, acquire matrix = 64×64, field of view = 220×220 mm², gap = 0.6 mm, voxel size = 3.4×3.4×4 mm³. 240 volumes resulting in 8 minutes of data were obtained.

Resting-state fMRI data for the ASD dataset were acquired on a Siemens 3.0 T Trio scanner (Siemens Medical Systems, Erlangen, Germany), using an echo-planar imaging sequence with the following parameters: TR/TE= 2000/25 ms, flip angle = 60 degrees, 34 slices, acquire matrix = 64×64, field of view = 220×220 mm², no gap, voxel size = 3.4×3.4×4 mm³. 200 volumes resulting in 6.7 minutes of data were obtained.

Resting-state fMRI data preprocessing

All resting-state fMRI data were preprocessed using the Statistical Parameter Mapping 8 toolbox (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) and the Data Processing Assistant for Resting-State fMRI toolbox (DPARSF, <http://rfmri.org/DPARSF>). To ensure steady-state longitudinal magnetization, the first 10 images of each subject were excluded. Slice timing correction was applied to correct the difference between slices and rigid head motion correction was utilized to correct the difference between volumes caused by head motion. Subjects with head motion greater than 3.0mm in the x, y, or z direction or greater than 3 degrees rotation in each axis were excluded. The corrected images were then warped into standard Montreal Neurological Institute (MNI) space. All normalized images were smoothed using an 8mm FWHM Gaussian kernel. The smoothed images were detrended and filtered (0.01–0.1Hz). A CompCor method was applied to regress the signals from white matter and cerebrospinal fluid (Behzadi Y et al. 2007). Five components of white matter and cerebrospinal fluid and 24 head motion parameters were regressed out of the data (Friston KJ et al. 1996). Global signal regression was not used in this study. Volumes whose framewise displacement (FD) was larger than 0.5mm with prior 1 and later 2 volumes were excluded (Power JD et al. 2012). Subjects with censored frames > 50% were excluded from further analyses. FD was defined as:

$$FD_i = |\Delta d_{ix}| + |\Delta d_{iy}| + |\Delta d_{iz}| + r|\Delta \alpha_i| + r|\Delta \beta_i| + r|\Delta \gamma_i|$$

Where the d_{ix} represents the displacement of x axis at timepoint i and is similar with other parameters of d_{iy} , d_{iz} , α_i , β_i and γ_i . The r is the radius of 50 mm, which is the approximate mean distance from the center of the head to the cortex. No significant difference in mean FD between ASD and corresponding HCs ($p = 0.11$, t -test), and between subjects with schizophrenia and corresponding HCs ($p = 0.51$, t -test) were found.

Functional connectivity network construction

160 MNI coordinates across the brain defined in a previous study were used to define regions of interest (ROIs) for the current study (Dosenbach NU et al. 2010). The coordinates were expanded to create 5-mm radius spherical ROIs, and ROIs in the cerebellum were excluded, resulting in 142 ROIs. Mean timeseries of the ROIs were extracted, and Pearson correlation coefficients were calculated between pairwise ROIs. To ensure normality, a Fisher Z-transformation was applied and the transformed FC values were used as classification features in subsequent analyses. For the classification analysis, the Z values were normalized (range from -1 to 1).

Multi-task feature selection

To assess shared atypical FC between ASD and schizophrenia we utilized a multi-task logistic regression feature selection method (Liu J et al. 2010; Nie F et al. 2010). Here we treated the schizophrenia-HC classification and ASD-HC classification as two independent tasks. This method utilized an l_1/l_q -norm regularization to regularize feature selection between the two tasks. The objective function is listed below:

$$\min_x \sum_{l=1}^k \sum_{i=1}^{m_l} w_{il} \log \left(1 + \exp \left(-y_{il} (x_l^T a_{il} + c_l) \right) \right) + \beta \|x\|_{l_1/l_q} \quad (1)$$

where a_{il} represents the i-th sample for the l-th task, for example, in our study, a_{1l} represents the i-th sample in the schizophrenia dataset and a_{2l} represents the i-th sample in the ASD dataset; w_{il} is the weight of a_{il} ; y_{il} is the label of a_{il} ; c_l is the intercept of the l-th task; β is the l_1/l_q norm regularization parameter. The larger the w_{il} , the more the feature contributed in the regression model. We included the features with greater weight and constructed a classification model using these features on a training dataset. As the best number of features is unknown, we selected a range of numbers from 10 to 500.

Support vector machine classification

In the present study, we adopted a support vector machine (SVM) method as a classifier. SVM is one type of supervised learning that is appropriate for use in cases where there is a large number of features but a small sample (Vapnik V 2000). Here we used a linear kernel SVM to reduce the risk of overfitting (Pereira F et al. 2009). The LIBLINEAR toolbox was utilized with default parameters (Fan R-E et al. 2008).

Classification estimation

A leave-one-out cross-validation (LOOCV) was implemented to estimate the classification accuracy. In each trial of LOOCV, one subject was picked up for testing and the remaining

ones were used for training. The procedure was repeated n trials (n equals to the total number of subjects). The feature selection is embedded in the LOOCV and was only applied on the training set of each trial. In each trial of LOOCV in each dataset, we obtained the multi-task regression weight of all features and we selected features with greater weight as classification features. Since the optimal number of features is unknown, we chose a range of numbers from 10 to 500. A flowchart of the classification procedure is presented in Fig. 1.

Consensus features

In each trial of LOOCV, the features used in classification were not uniform, as different feature ranking occurred based on different subsets of the training dataset. We adopted a consensus feature method in the current study. We regard the features selected in every trial of LOOCV as the stable features which affect the classification (Liu F et al. 2013). Classification weights of the consensus features were calculated by the mean weights of each trial of LOOCV and the classification weights of the non-consensus features were set to 0. Classification weights of the regions were calculated by summing up the half of the classification weights of the connections linked to this region.

Atypical nature of the shared atypical connections in ASD and schizophrenia

The shared atypical connections in ASD and schizophrenia were defined as the connections in the consensus features of both ASD and schizophrenia classifications. Then the FC strength of the shared atypical connections were extracted in two datasets.

To assess whether the number of shared atypical connections is significantly larger than random cases, we did a random simulation analysis. According the consensus feature analysis, we found 9 shared atypical connections, 23 ASD atypical connections (including the 9 shared atypical connections) and 23 schizophrenia atypical connections (including the 9 shared atypical connections). For each random simulation trial, we treat ASD atypical connections and schizophrenia atypical connections are independent. We first randomly picked 23 out of the total 4005 connections, labeled them as ASD atypical connections and then put them back. Then we randomly picked 23 out of the total 4005 connections, labeled them as schizophrenia atypical connections and put them back. Finally we calculated the number of connections which are labeled both ASD and schizophrenia atypical connections. This random simulation trials are repeated 10000 times to construct the distribution of the number of shared atypical connections at random case. Based on the constructed distribution, we calculated the p value as the times whose shared atypical connection number are larger than the actual case divide 10000.

Distribution of the distinct atypical connections in ASD and schizophrenia

For the distinct atypical connections, we extracted the classification weight for each connection. Then we define the classification weight between and within 5 networks as the sum of the weights of all corresponding connections. To assess whether the weight between or within specific networks is significant larger than the averaged weights, we did a random simulation analysis to construct the distributions of classification weight at random cases. For ASD, we first summed the classification weights of all distinct atypical connections of ASD, and then randomly divided the total weight into 15 parts corresponding to the possible

connections between and within 5 networks. This trial was repeated 10000 times. For each connection between or within 5 networks, the p value was calculated as the times whose classification weight is larger than the actual case divide 10000.

Multivariate linear regression analysis

According to the consensus feature analysis, we found shared atypical connectivity in schizophrenia and ASD concentrated in DMN and SN regions (see Fig. 2). We next extracted the shared atypical DMN-DMN, DMN-SN and SN-SN connections of the schizophrenia and ASD groups and utilized a multivariate linear regression to assess the relationship between these connections and symptoms of ASD (ADOS scores including ADOS total score, ADOS social score, ADOS communication score and ADOS restrict behavior score) and schizophrenia (PANSS score including PANSS positive score, PANSS negative score, PANSS general score and PANSS total score) using SPSS19. Here we also included age and gender as independent variables. Full-scale IQ was also included in the model for the ASD dataset. The regression model was defined as below:

$$y = \beta_1 f_1 + \cdots \beta_n f_n + \beta_{n+1} cov_1 + \cdots \beta_{m+n} cov_m + \varepsilon \quad (2)$$

Where y represents the scores of symptoms, f represents the shared atypical DMN and SN FC values, cov represents the covariants such as age, gender etc. An ANOVA was used to determine the significance of the models using SPSS19.

Reproducibility analysis

To assert the reproducibility of the shared abnormalities between ASD and schizophrenia. We repeated the analysis based on the original schizophrenia dataset and a new ASD dataset from the USM site in ABIDE. Details are shown in SI.

Results

Classification accuracy

A classification accuracy of 80.43% was achieved in the ASD dataset (sensitivity = 77.27%, specificity = 83.33%, AUC = 0.76, permutation $p = 0.001$, 1000 loops) when using the 60 features with the greatest weight in each trial of LOOCV, while an accuracy of 83.33% was achieved in the schizophrenia dataset (sensitivity = 80%, specificity = 87.1%, AUC = 0.83, permutation $p = 0.005$, 1000 loops) when using the 58 features with the greatest weight in each trial of LOOCV.

Shared atypical FC in schizophrenia and ASD

As shown in Fig. 2A, the nodes connected shared atypical FCs in schizophrenia and ASD are mainly located in DMN and SN. A ROI located in aPFC showed the greatest classification weight both in schizophrenia and ASD classification (see in Fig. 2B). Meanwhile, we found the shared atypical FCs in schizophrenia and ASD are between DMN and SN (4 out of 9 shared atypical connections, see in Fig. 3A, the black lines). According to

the random simulation analysis, we found the number of shared atypical connections is significant larger than random cases ($p < 0.0001$, 10000 loops).

Distinct atypical connections in schizophrenia and ASD

As shown in Fig. 3, classification weights of the distinct atypical connections were mostly in the DMN and SN. Based on the random simulation analysis, we found that in ASD classification, the classification weights of the distinct atypical connectivity was more linked with intra-SN connections ($p = 0.0412$, 10000 loops), while in schizophrenia classification the classification weights were more concentrated in connections between the DMN and SN ($p = 0.0196$, 10000 loops). Intra-SMN connectivity also contributed to the schizophrenia classification ($p = 0.0182$, 10000 loops).

Relationship between the shared atypical DMN and SN connections with social deficits of ASD

Multivariate linear regression results showed a significant relationship between the shared atypical DMN and SN connections and the ADOS social score (ANOVA test, F value = 7.723, $p = 0.002$) in ASD. No significant relationship between the connections and the PANSS scores in schizophrenia group was found.

Reproducibility analysis

To assert the reproducibility of the shared abnormalities between ASD and schizophrenia. We repeated the analysis based on the original schizophrenia and USM ASD datasets and found the shared atypical ROIs are mainly located in DMN and SN (see in Fig. S1).

Discussion

Analytic Overview

In the current study, we explored shared and distinct atypical FC patterns in schizophrenia and ASD using a MVPA method. Combining a multi-task feature selection method and a SVM classifier, we achieved relatively high classification accuracies (80% in the ASD dataset and 83% in the schizophrenia dataset). According to the classification weight analysis, we found that the DMN and SN play a critical role in both schizophrenia and ASD. Shared atypical FCs in schizophrenia and ASD were concentrated in regions of the DMN and SN. The distinct atypical FC of schizophrenia and ASD also mainly connected to DMN and SN, but the connectivity patterns were different between schizophrenia and ASD. In schizophrenia, the atypical connections were mainly inter DMN-SN connections while in ASD, the atypical connections were mainly intra-SN connections. These results imply that schizophrenia and ASD share some neuronal basis of pathology, especially within the DMN and SN. The different atypical connectivity patterns of the DMN and SN between schizophrenia and ASD may help us to understand the different phenotypic characteristics of schizophrenia and ASD.

Shared atypical FCs between Schizophrenia and ASD

Schizophrenia and ASD are two prevalent genetic neurodevelopmental disorders. Some hypotheses hold the view that the mutation of genes which lead to altered neurodevelopment can result in schizophrenia and ASD (Mitchell KJ 2011). Large-scale epidemiological studies have shown individual and familial comorbidity between schizophrenia and ASD. The risk of ASD in individuals who have a sibling with schizophrenia is several-fold more than the typical population (Daniels JL et al. 2008; Steinhausen HC et al. 2009; Mitchell KJ 2011). Several previous studies showed shared synaptic-related genetic deficits in these two disorders, such as the gene APBA2 which regulates synaptic adaptor proteins (Consortium ISR 2008; Guilmatre A et al. 2009), gene ASTN2 which regulates neural recognition molecules (Glessner JT et al. 2009; Need AC et al. 2009), gene DLG1, DLG2, DLGAP2, LRFN5, NRXN1, PCDH19, SHANK3 and TSPAN7 which regulate synaptic scaffolding, organization and formation (Marshall CR et al. 2008; Walsh T et al. 2008; Guilmatre A *et al.* 2009; Pinto D et al. 2010; Mitchell KJ 2011). These shared genetic deficits may contribute to shared atypical brain FC in schizophrenia and ASD.

The DMN is a major brain network with major nodes located in mPFC, posterior cingulate cortex, precuneus and bilateral inferior parietal lobules, often active when participants are not engaged in any specific task and deactive during effortful cognitive tasks (Buckner RL et al. 2008). Several studies have shown that the brain regions within the DMN also activate during certain types of tasks, especially social cognition tasks (Uddin LQ et al. 2007; Corbetta M et al. 2008). A recent study using the online BrainMap database (www.brainmap.org) found significant overlap between DMN and the activation map of social cognition and theory of mind (Mars RB et al. 2012).

The SN is a task-positive brain network comprised of anterior insula, dorsal anterior cingulate cortex, the anterior prefrontal cortex and the thalamus (Dosenbach NU et al. 2006). The SN is thought to be related to redirecting attention to unexpected but salient stimuli and play some role in the brain's "switching" between internal, bodily or self-perspective and external, environmental or other's viewpoint (Corbetta M *et al.* 2008; Menon V et al. 2010; Uddin LQ 2015). Studies found regions within SN activate during a variety of psychological tasks such as empathy (Fan Y et al. 2011), language and executive function (Nelson SM et al. 2010), and attention allocation (Corbetta M *et al.* 2008). The anatomical and functional connectivity within SN is thought to be related to social cognition, emotion, as well as non-social cognition (Barrett LF et al. 2013).

Schizophrenia and ASD are both characterized by significant impairment of social cognition and social function, especially higher level social cognitive skills (American Psychiatric Association 2013). Behavioral studies have suggested common social cognition deficits between schizophrenia and ASD (Couture SM *et al.* 2010). Atypical brain activation during social cognition has been observed both in schizophrenia and ASD (Pinkham AE et al. 2003; Pelphrey K et al. 2004). A meta-analysis also indicates some common neural basis contributing to atypical social cognition in schizophrenia and ASD (Chung YS et al. 2014). Several studies have reported abnormal connectivity patterns within the DMN and SN, and implied that these atypical connections were related to social deficits in ASD (Gotts SJ *et al.* 2012; Supekar K et al. 2013). Our multivariate regression analysis also showed a significant

relationship between the connections in DMN and SN and the social deficits of ASD. For schizophrenia, atypical social cognition is also thought to be related to the DMN (Dodell-Feder D *et al.* 2014). Social reward salience as a negative symptom in schizophrenia is thought to contribute to social cognitive dysfunction in schizophrenia (Sergi MJ *et al.* 2007). We speculated that the shared atypical connections in DMN and SN might be a factor of the shared social deficits between ASD and schizophrenia. However, due to the missing of measures of the social deficits in schizophrenia dataset, the relationship between the social deficits in schizophrenia and the shared atypical connections could not be determined. Further studies should be made to determine the shared social deficits between ASD and schizophrenia and the shared atypical DMN-SN connections.

Previous meta-analysis comparing grey matter deficits in ASD and schizophrenia reported common deficits in right posterior cingulate and regions in limbic-striato-thalamic circuitry (Cheung C *et al.* 2010). Study investigate the grey matter of ASDs with and without psychosis reported that ASDs with and without psychosis both exhibited abnormalities in regions of temporal lobe, cerebellum and striatum (Toal F *et al.* 2009). Our study only found part of these common atypical regions, such as regions in post cingulate and temporal lobe. This difference may be due to the different data modal. Our study explored the functional connectivity between these two disorders while these previous studies are based on structural dataset.

Distinct atypical FCs between Schizophrenia and ASD

Similar to the shared atypical connectivity observed in schizophrenia and ASD, distinct atypical connectivity was also more concentrated in the DMN and SN. We found different patterns of distinct atypical DMN and SN connectivity in these two disorders. In schizophrenia, the distinct atypical connections comprised connections between the DMN and SN while in ASD, intra-SN connectivity occupied greater classification weight. We hypothesize that these different patterns may be related to the different syndromes between ASD and schizophrenia. Although ASD and schizophrenia have several shared synaptic-related genetic deficits (Mitchell KJ 2011) and these two disorders were regarded as same disorder in history (American Psychiatric Association 1952, 1968), the current version of DSM has classified ASD and schizophrenia as two disorders (American Psychiatric Association 2013). The shared behavior deficits between these two disorders are more concentrated in social cognition aspect and previous studies have reported more convergent social cognitive functioning deficits than divergent (Couture SM *et al.* 2010). Meanwhile, some differences in atypical social cognition in these two disorders have also been reported. For example, Sasson *et al.* compared eye movement patterns when assessing emotion content between participants with ASD and schizophrenia. They found that individuals with ASD and schizophrenia shared deficits in using facial information to assess emotional content, but differed in the ability to seek out social cues from complex stimuli (Sasson N *et al.* 2007). Abu-Akel suggested that individuals with ASD and schizophrenia exhibit different forms of theory of mind impairment (Abu-Akel A *et al.* 2000). Our results of the different patterns of atypical connections showed the difference between these two disorders at neural level, supported the notion that ASD and schizophrenia are two different disorders although some common genetic, neural and behavior deficits exist.

In addition to the DMN and SN, intra-SMN connectivity also plays an important part in discriminating schizophrenia from HCs. As reported in a recent study, intra-SMN connectivity is related to the severity of the positive symptoms of schizophrenia (Berman RA et al. 2016).

Conclusion

Schizophrenia and ASD are two prevalent neurodevelopmental disorders sharing genetic and clinical features. In the current study, we found shared atypical DMN and SN FC in these two disorders. Our results suggest some shared neural mechanisms in these two disorders, and may help us understand more about their etiology and pathology.

Limitation

In the present study, we explored the shared atypical functional connectivity in schizophrenia and ASD. However, the two datasets were from two different imaging platforms. To overcome this deficit, the classifications were done in these two datasets separately. In the multi-task feature selection procedure of one dataset, we only included the group-difference information of the other dataset to regulate the feature selection, the site information was not included. We thought the effect of the difference of sites could be minimized after these analysis steps.

The scan parameters of two datasets are different, especially the flip angle and voxel size which would affect the signal-to-noise ratio (SNR) of the fMRI data. As subcortical regions are often of lower SNR, the difference of SNR might be a factor that we have found few shared atypical subcortical connections while evidence exists that subcortical regions are important nodes of ASD and schizophrenia (Woodward ND et al. 2012; Cerliani L et al. 2015).

The atypical DMN and SN FC were found to be related to the ADOS social score. However, the PANSS just measured the positive and negative syndromes in schizophrenia, not the pure social deficits in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Flowchart of ASD classification procedure

Fig. 2. Atypical ROIs in schizophrenia and ASD
A: Shared and distinct atypical ROIs in schizophrenia and ASD: left: distinct ASD atypical nodes; middle: shared atypical nodes; right: distinct schizophrenia atypical nodes; *SZ means schizophrenia. **B:** the classification weights of the regions in schizophrenia and ASD classification, red represents shared regions in schizophrenia and ASD classification. The MNI coordinates of the regions were listed in table. S1 (see in SI).

Fig. 3. Atypical connections in schizophrenia and ASD

A: Atypical connections in schizophrenia and ASD: black lines represent the connections contributing both in schizophrenia classification and ASD classification; blue lines represent the connections only contributing in schizophrenia classification; red lines represent the connections only contributing in ASD classification. **B:** the distribution of the distinct atypical connections in schizophrenia and ASD classification.

*: The classification weight is significant larger than random cases.

Table 1

Characteristics of the groups

schizophrenia dataset	schizophrenia	HC	p value	ASD dataset	ASD	HC	P value
Count	35	31	-		22	24	-
Age [†] (mean±S.D.)	15.6±1.8	15.4±1.6	0.56		13.1±3.1	12.9±2.9	0.79
Gender(male/female) [‡]	20/15	13/18	0.22		15/7	17/7	0.85
meanFD [‡] (mean±S.D.)	0.1±0.05	0.1±0.03	0.51		0.18±0.07	0.14±0.06	0.11
fIQ [‡] (mean±S.D.)	-	-	-		95.2±22.1	104±18.3	0.15
PANSS				ADOS_GOTHAM			
Positive syndrome (mean±S.D.)	20.4±5.7	-	-	SocialAffect (mean±S.D.)	9.6±2.9	-	-
Negative syndrome (mean±S.D.)	20.9±8.4	-	-	RRB (mean±S.D.)	2.7±1.2	-	-
General scale (mean±S.D.)	33.3±6.7	-	-	Severity (mean±S.D.)	7.3±1.6	-	-
Total (mean±S.D.)	74.6±10.6	-	-	Total (mean±S.D.)	12.3±3.3	-	-

[†]T-test

[‡]chi-square test

fIQ: full-scale IQ

PANSS: Positive And Negative Syndrome Scale

ADOS_GOTHAM: Standardized scores of Autism Diagnostic Observation Schedule using Gotham algorithm, which has an improved prediction capacity for ASD (Gotham K et al. 2007).

RRB: Restricted and Repetitive Behavior

* one subject's ADOS_GOTHAM score is missing.