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Overlapping but Asymmetrical Relationships Between Schizophrenia and Autism Revealed by Brain Connectivity

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Although the relationship between schizophrenia spectrum disorder (SSD) and autism spectrum disorder (ASD) has long been debated, it has not yet been fully elucidated. The authors quantified and visualized the relationship between ASD and SSD using dual classifiers that discriminate patients from healthy controls (HCs) based on resting-state functional connectivity magnetic resonance imaging. To develop a reliable SSD classifier, sophisticated machine-learning algorithms that automatically selected SSD-specific functional connections were applied to Japanese datasets from Kyoto University Hospital (N = 170) including patients with chronic-stage SSD. The generalizability of the SSD classifier was tested by 2 independent validation cohorts, and 1 cohort including first-episode schizophrenia. The specificity of the SSD classifier was tested by 2 Japanese cohorts of ASD and major depressive disorder. The weighted linear summation of the classifier's functional connections constituted the biological dimensions representing neural classification certainty for the disorders. Our previously developed ASD classifier was used as ASD dimension. Distributions of individuals with SSD, ASD, and HCs s were examined on the SSD and ASD biological dimensions. We found that the SSD and ASD populations exhibited overlapping but asymmetrical patterns in the 2 biological dimensions. That is, the SSD population showed increased classification certainty for the ASD dimension but not vice versa. Furthermore, the 2 dimensions were correlated within the ASD population but not the SSD population. In conclusion, using the 2 biological dimensions based on resting-state functional connectivity enabled us to discover the quantified relationships between SSD and ASD.

Key words: schizophrenia/autism/resting state/machine learning/classifier/fMRI

Introduction

The relationship between schizophrenia and autism is a matter of historical and long-lasting debate. No clear distinction between schizophrenia and autism had been described by the presentation of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-II in 1968. From the mid-1960s to the 1970s, epidemiological studies concluded that these 2 conditions were distinct and unrelated. The neurodevelopmental histories and age at onset are quite different between schizophrenia and autism. However, recent biological studies showed overlapping relationships and commonalities between the 2 disorders.[1,2] Genetic studies demonstrated common loci and pathways, suggesting that the neurodevelopmental pathway of autism spectrum disorder (ASD) is similar to that of schizophrenia spectrum disorder (SSD).[3,4] Brain structural magnetic resonance imaging (MRI) and functional MRI studies also reported common abnormalities in gray matter volumes[5] and brain activations.[6,7] Nevertheless, the relationship between SSD and ASD remains controversial.[1]

The fundamental problems behind this issue are that we lack a reliable biological identification for these disorders and that the diagnosis is based mostly on a symptomatological and categorical approach as represented by DSM. DSM criteria are mainly based on the patient's behavioral signs and symptoms,[8] although the symptoms in patients with SSD and ASD, respectively, are heterogeneous and vary erratically over time.[9,10] Hence, there is an explanatory gap between phenomenological entities and neurobiological underpinnings. To bridge this gap,[11] researchers have begun to use a dimensional approach.[12] It was necessary to develop the biological dimensions in order to unravel the relationship between SSD and ASD.

Then, we developed the 2 independent ASD and SSD classifiers on strictly defined clinical and categorical diagnoses that excluded the other disorder for biological dimensions using sophisticated machine-learning algorithms from brain functional connectivity (FC) measured by resting-state functional connectivity magnetic resonance imaging (rs-fMRI) on the basis of the reports that ASD[13–17] and SSD[18–25] exhibited FC abnormalities in rs-fMRI. The classifiers for biological dimensions must be robust enough to have generalizability to independent cohorts with different ethnicities or MRI machine vendors. We have already developed an ASD classifier that has generalizability to independent validation cohorts,[26] and here we developed a generalizable SSD classifier using the same machine-learning methods and 6 independent cohorts. Furthermore, we determined each biological dimension from the weighted linear summation (WLS) of functional connections of SSD and ASD classifiers, and we plotted individuals with ASD, SSD, and healthy controls (HCs) on the SSD-ASD dimensions. Finally, visualizing and quantifying each individual in a relative manner, we could verify the relationship between SSD and ASD populations. We hypothesized that SSD and ASD on the 2 biological dimensions that provide each classification certainty are not distinct, but rather overlapping.

Methods and Materials

Participants and MRI Data Acquisition

Kyoto. A total of 68 adult patients with SSD, including 64 patients with schizophrenia and 4 patients with schizoaffective disorder, and 102 HCs were recruited at the Department of Psychiatry, Kyoto University. Patients met the DSM-IV criteria for schizophrenia and schizoaffective disorder, based on the consensus of 2 trained psychiatrists. In addition, we confirmed the diagnosis by the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). No patients had any comorbid psychiatric disorders including ASD, based on diagnosis according to the DSM-IV-TR diagnostic criteria for the pervasive developmental disorder. The Positive and Negative Syndrome Scale (PANSS) was used to assess clinical symptoms. We recruited 2 groups: Kyoto A and Kyoto B (supplemental Methods and table S1). All patients were receiving antipsychotic medications. T1-structural and rs-fMRI images at Kyoto A and B were scanned on 3T Siemens TimTrio and 3T Siemens Trio, respectively (supplemental table S2).

Preprocessing of MR Images

MRI datasets (68 SSD and 102 HC) for training of the SSD/HC classifier in Kyoto were preprocessed, and calculation of a correlation matrix was performed using Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, University College London) software running on MATLAB (R2014a, Mathworks) in the same manner as in our previous study[26] (supplemental Methods and tables S3 and S4).

Selecting FCs as SSD Classifier

To develop an SSD classifier from the correlation matrices, we adopted a cascade of L_1-norm regularized sparse canonical correlation analysis[27] and sparse logistic regression (SLR)[28] to select SSD-specific FCs while minimizing the effects of over-fitting and nuisance variables. The selection of SSD-specific FCs and classification performance evaluation were carried out through a sequential process of 9 × 9 nested feature-selection and leave-one-out cross-validation (LOOCV) (supplemental Methods and figure S1). The machine-learning algorithms automatically selected 10–20 FCs as the SSD classifier from about 10 000 FCs of whole-brain rs-fMRI. The WLS of the selected FCs, transformed by

sigmoid function, predicted the categorical diagnostic label for each individual. The untransformed continuous values of WLS provide a degree of classification certainty, which can be interpreted as neural classification certainty for ASD and SSD. Then, we utilized neural classification certainty as a biological dimension (see supplemental Methods).

The performance of the classifier was expressed in terms of area under the curve (AUC), accuracy, sensitivity, and specificity. The statistical significance of classification was assessed by the permutation test.[29]

In addition, we confirmed that the selected FCs of the classifier did not reflect variation in duration of illness (DUI), amount of antipsychotic medication, DUI × amount of antipsychotic medication, and age of participants. Therefore, we paradoxically predicted them from the selected FCs using the same methods (cross-validated linear regression) and evaluated them by Pearson correlation coefficient.

Generalizability of the Kyoto Classifier

We tested the generalizability of the Kyoto classifier to 3 independent cohorts, COBRE of the Mind Research Network (Center for Biomedical Research Excellence, University of New Mexico, USA), UMCU-TOPFIT (The Outcome of Psychosis and Fitness Therapy, University Medical Centre Utrecht, the Netherlands), and a first episode schizophrenia cohort JHU-FES (Johns Hopkins University, USA) (supplemental table S5, figure S2, and supplemental Methods). The patients with SSD of Kyoto, COBRE, and UMCU-TOPFIT were mainly in a chronic stage of the disease, while JHU-FES was in an early stage. The MR images were scanned on 3T Siemens TimTrio (COBRE) and Philips Achieva (UMCU-TOPFIT and JHU-FES) (supplemental table S6). The external datasets (COBRE, UMCU-TOPFIT, and JHU-FES) were preprocessed in the same manner as the Kyoto dataset (supplemental tables S3 and S4, and supplemental Methods).

COBRE. COBRE is the dataset publicly available at http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html. A total of 46 patients with SSD, including 41 patients with schizophrenia and 5 patients with schizoaffective disorder, and 61 HCs were recruited.

UMCU-TOPFIT. A total of 47 patients with SSD, including 35 patients with schizophrenia and 12 patients with schizoaffective disorder, and 43 HCs were recruited. About four-fifths of the participants were born in the Netherlands.

JHU-FES. A total of 30 patients with FES, including 21 patients with schizophrenia, 7 with schizoaffective disorder, 1 with schizophreniform, and 1 with psychotic disorder not otherwise specified, and 71 HCs were recruited at Johns Hopkins University Hospital and incorporated into the present analysis.

Specificity of the Kyoto Classifier

We tested the specificity of the Kyoto classifier, applying the classifier to 2 additional Japanese cohorts of ASD and major depressive disorder (MDD), respectively (supplemental figure S2). The datasets of ASD and MDD were scanned on a 3T or 1.5T MRI system. Details of their demographic information and MRI parameters are shown in the referred study[26] (see supplemental Methods). The other disorders' datasets (ASD and MDD) were preprocessed in the same manner as the Kyoto dataset. The WLS distributions between each disorder population (ASD and MDD) and the corresponding HCs were compared via AUC and Kolmogorov-Smirnov test (see supplemental Methods).

ASD. A total of 74 adults with ASD and 107 age-, sex-, handedness-, and IQ-matched typically developed individuals as HCs were examined. All ASD individuals were diagnosed with pervasive developmental disorder based on the DSM-IV-TR criteria. The Japanese version of mini-international neuropsychiatric interview (M.I.N.I.) was used to evaluate psychiatric comorbidity. No individuals satisfied the diagnostic criteria for SSD.

MDD. A total of 104 patients with MDD and 143 age-matched HC were examined.

Relationships Between SSD and ASD on the Two Biological Dimensions

We plotted the SSD and HC participants in the Kyoto dataset and the ASD and HC participants on the SSD-ASD dimensional plane. The SSD and ASD dimensional scores are the WLS using the SSD and ASD classifiers, respectively. The ASD classifier was taken from our previous study.[26] The WLS distributions between each disorder population (ASD and SSD) and the corresponding HCs were compared via AUC and Kolmogorov-Smirnov test. Categorical ellipses of SSD, ASD, and HC were calculated using multivariate Gaussian distribution (see supplemental Methods). To understand the impact of individual FCs on the ASD-SSD relationship, we analyzed the contribution to WLS of the other disorder's population (eg, SSD) for each FC selected by the classifier of 1 disorder (eg, ASD). Furthermore, separately for each population, we analyzed the correlation coefficients between the most relevant FCs (top 5 each; 25 correlations) selected by the ASD and SSD classifiers and the cumulative sum across correlation coefficients in order to find the general trend of correlation (see supplemental Methods).

Results

Accurate SSD classifier for Kyoto Discovery Cohort

The 16 FCs incorporated in our final classifier were selected by the SLR using the whole Kyoto datasets. The identified FCs showed robustness and stability

across the cross-validation procedure (supplemental figure S3). The classifier differentiated SSD from HC populations with an accuracy of 76% and an AUC of 0.83 (permutation test, $P = .006$; see table 1 and supplemental figure S4). We calculated the WLS of each participant from the 16 FCs. The 2 WLS distributions of the SSD and HC populations were clearly separated by a threshold of WLS = 0 (figure 1A). We found that high classification accuracy was not only achieved for the entire datasets, but also for the 2 sites separately (the accuracies of Kyoto A and B were 74% and 77%, respectively) (table 1 and supplemental figure S5). When tested on the COBRE dataset, the Kyoto classifier achieved high performance, with an accuracy of 70% (AUC = 0.75) (table 1 and figure 1B). The probability of obtaining this high performance by chance is as small as $P = .001$ (permutation test, see supplemental figure S4). For UMCU-TOPFIT (figure 1C), the classifier also achieved accuracy of 61% (AUC = 0.66) ($P = .031$, permutation test), although this classification performance for UMCU-TOPFIT was lower than for COBRE. For JHU-FES (figure 1D), AUC (0.42) was below the chance level (table 1), and thus generalization was not observed.

Characteristics of 16 identified FCs in the SSD Classifier

The 16 FCs as SSD classifier were distributed as inter-hemispheric (44%), left intra-hemispheric (25%), and

Table 1. Performance of the SSD Classifier for the Kyoto, COBRE, UMCU-TOPFIT, and JHU-FES Datasets

Dataset	AUC	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy Kyoto A	Accuracy Kyoto B
Kyoto ($N = 170$)	0.83	76	72	79	74	77
COBRE ($N = 107$)	0.75	70	65	74		
UMCU-TOPFIT ($N = 90$)	0.66	61	64	58		
JHU-FES ($N = 101$)	0.42	45	40	47		

Note: AUC, area under the curve.

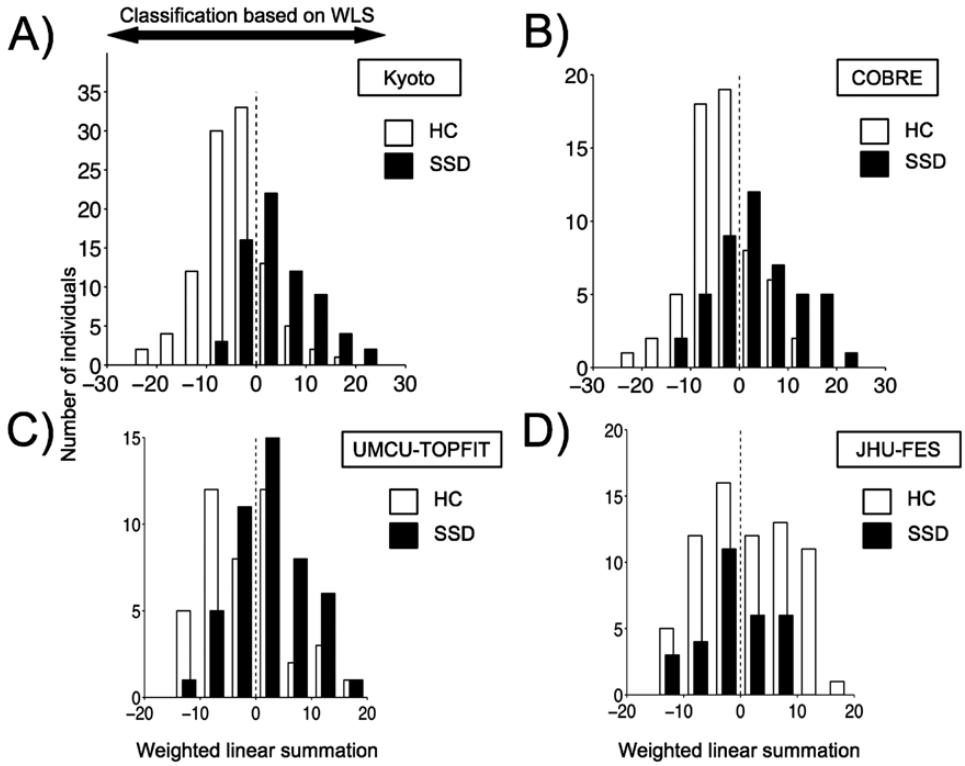

Fig. 1. Distribution of weighted linear summation (WLS) of the SSD classifier. (A) The number of HC and SSD individuals in the Kyoto datasets included in a specific WLS interval of width 5 is shown as a histogram (B, C, D). WLS for the COBRE, UMCU-TOPFIT, and JHU-FES datasets is shown in the same formats as in (A). For this classifier, WLS (or linear discriminant function) of the correlation values of the identified FC predicted the diagnostic label of each individual. A participant with positive or negative WLS was classified as SSD or HC, respectively.

right intra-hemispheric connections (31%) (figure 2A and 2B, and supplemental table S7). The 16 FCs as SSD classifier were different from the 16 FCs as ASD classifier that we previously developed[26] (figure 2C and supplemental figure S6).

In the paradoxical prediction from the 16 FCs, no significant correlations were found between the clinically measured scores of DUI, amount of antipsychotic medication, DUI × amount of antipsychotic medication, and age and their predicted scores. Pearson correlation coefficients were 0.04, −0.07, 0.003, and 0.015, respectively. This result means that the 16 FCs of the SSD classifier did not reflect DUI, antipsychotic medication, or age.

Specificity of the Classifier to SSD Regarding Other Psychiatric Disorders

Separation of WLS distribution was the largest between SSD and HC (figure 3A) as already shown (figure 1A). In ASD and MDD, the distribution was not distinguishable from HC (AUC = 0.50, Kolmogorov-Smirnov test, P = .57 for ASD; AUC = 0.55, P = .15 for MDD) (figure 3B and 3C). These results suggest that, on the biological dimension defined by the SSD classifier, ASD and MDD were not close to SSD.

Individuals With SSD, ASD, and HC on the SSD-ASD Dimension Plane

There were 2 main asymmetry findings of relationships between SSD and ASD (figure 4 and supplemental Results). First, the center of the SSD population on the ASD dimension was elevated to close to 0.5 with respect to the center of its HC population, while the center of the ASD population on the SSD dimension remained at zero, the same as the center of its HC population. Second, the SSD and ASD dimensional scores were significantly correlated in the ASD population (r = 0.28, P = .040, permutation test corrected for multiple comparisons), while there was no correlation in the SSD population. The first asymmetry finding was interpreted by the differences of contribution results (supplemental Results and figure S7). Most of the ASD classifier's FCs consistently contributed to the SSD-HC classification, but the FCs selected by the SSD classifier made inconsistent contributions to the ASD-HC classification, resulting in a cumulative WLS close to zero. The second

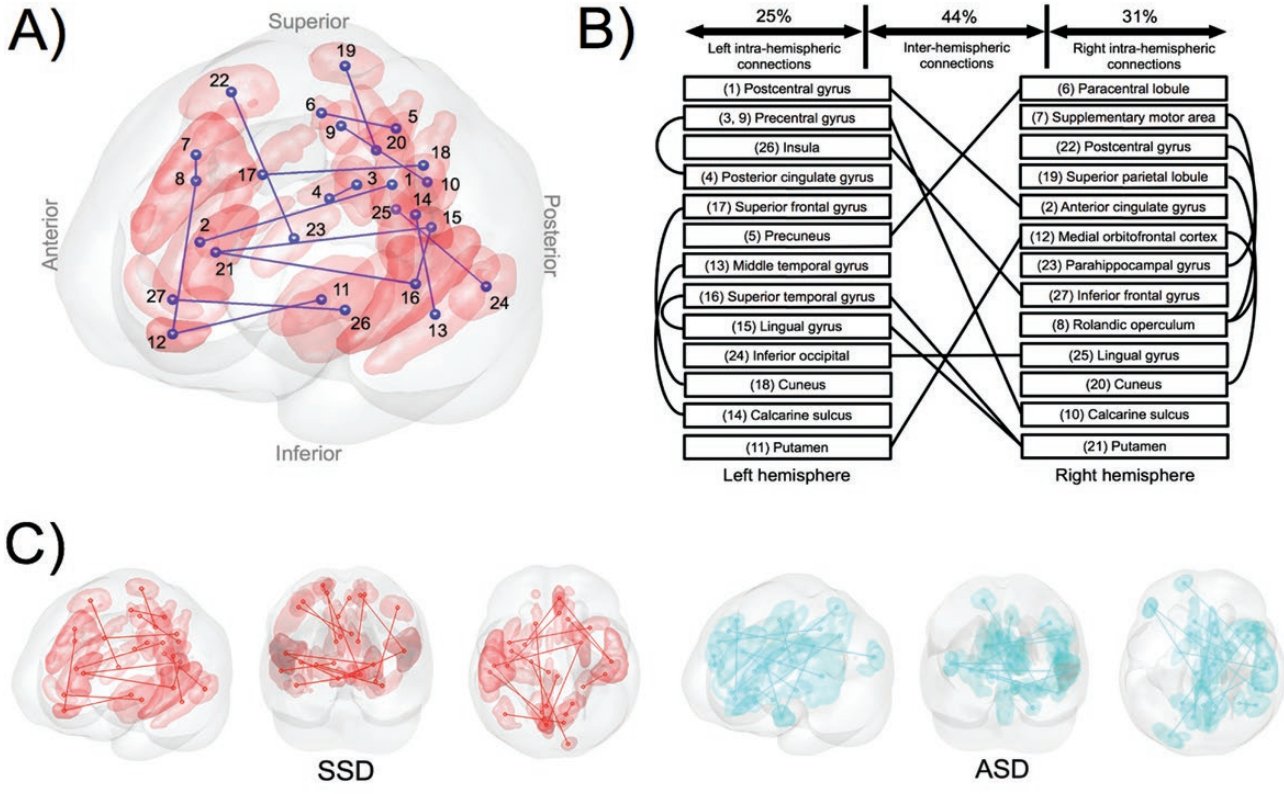

Fig. 2. The 16 functional connectivities (FCs) of the SSD classifier. (A) The 16 FCs viewed from anterior-left. The properties of the 16 FCs were noted in supplemental table S7. (B) The 16 FCs (solid lines) and their terminal regions (names in boxes) are presented. The left and right halves of the figure correspond to the left and right brain hemispheres, respectively. The FCs were classified into 3 hemispherical categories: left intra-hemispheric, right intra-hemispheric, and inter-hemispheric. The terminal regions were defined by anatomical automatic labeling. (**C**) The 16 FCs as SSD classifier were entirely different from the 16 FCs as ASD classifier.

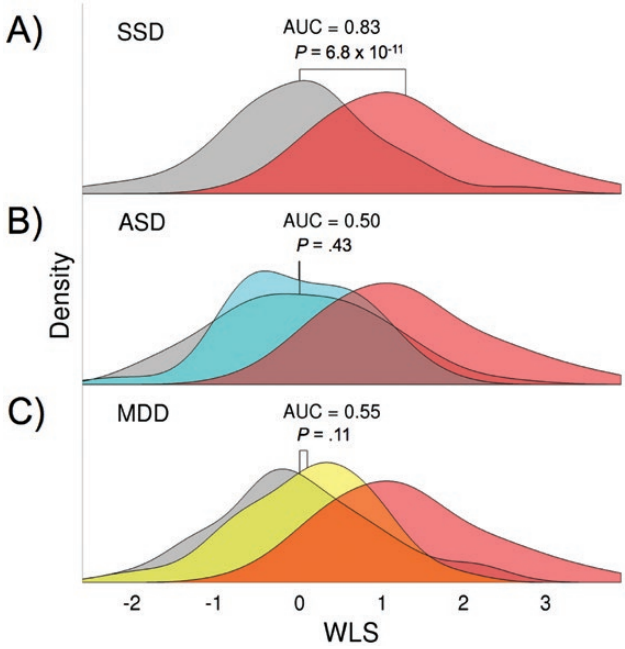

Fig. 3. Application of the SSD classifier to other psychiatric disorders (ASD and MDD). The density distribution of the weighted linear summation (WLS) was obtained by applying the SSD classifier to (A) SSD, (B) ASD, (C) MDD datasets. In each panel, patient distribution and HC distribution are plotted separately. For reference, the WLS distribution of the SSD patients in A is duplicated across the panels (B, C). For each patient and control pair in (A–C), statistical significance was tested by Benjamini-Hochberg-corrected Kolmogorov-Smirnov.

asymmetry finding was explained by these correlation coefficient analyses (supplemental figure S8). The sum of the correlation coefficients within the SSD population was close to zero, due to contradicting correlation coefficients. On the other hand, the cumulative sum of the correlation coefficients within the ASD population indicated a general positive trend, which was the same direction as the largest correlation.

Frequency of Selection Within LOOCV

The number of features selected across the ASD LOOCV was 34, while that of SSD was 73.

In addition, the FC with the largest absolute weight in the ASD classifier (FC_1ASD) was always selected, while that in the SSD classifier (FC_1SSD) was selected in only 15% of the total LOOCV folds.

Discussion

To our knowledge, this is the first study to quantify overlapping, but asymmetrical relationships between SSD and ASD on the 2 independent dimensions providing classification certainty for each categorical diagnosis. The sophisticated machine-learning algorithms using categorical diagnostic labels and whole-brain rs-fMRI produced a classifier that could discriminate patients from HCs. At the same time, the classifier generated a probabilistic degree of classification certainties for SSD and ASD based on whole-brain FC from WLS distributions. The neural classification certainty was so continuous that we could regard it as a biological dimension. Moreover, the biological dimension needs to be robust enough to have generalizability to independent cohorts, as the biological dimension should be compatible with diagnoses that are common in different cohorts. Here, we developed the SSD classifier by a similar method to that described for our previous ASD classifier.[26] The SSD classifier had generalizability to 2 independent cohorts in different countries and MRI machine vendors, not to other psychiatric disorders, and had specificity to chronic patients. Using these 2 classifiers, we could visualize individuals with ASD and SSD with their relative classification certainty and determine the overlapping, but asymmetrical relationships between SSD and ASD populations on the 2 biological dimensions. The relationships were more complicated than previously discussed in conceptual frameworks.[1]

The ASD classifier was developed in our previous study,[26] and here we focused on generating the SSD classifier. Various machine-learning algorithms have been applied previously to develop SSD classifiers that could discriminate patients with SSD from HCs.[30–35] However, none of the previous studies using only rs-fMRI tested whether the classifiers could present generalizability across different countries and MRI machine vendors. It was reported that there was a significant effect of MRI machine vendors[36] and ethnicities on MRI signals.[37] A robust universal classifier should have generalizability to cohorts in a range of different countries under varying scanning protocols and imaging apparatus. Our classifier achieved high AUC (generalizability) to COBRE and UMCU-TOPFIT over the differences of various countries and MRI machine vendors. In contrast to COBRE and UMCU-TOPFIT, the SSD classifier achieved lower AUC (0.42) for a JHU-FES dataset. This can be attributed to differences in patients' disease stage. Indeed, previous studies reported consistent differences in FC patterns between chronic SSD and FES.[38,39] Consequently, the finding that the SSD classifier did not generalize to FES might indicate that the classifier was specific to patients at a chronic stage of the disease. In addition, we confirmed the specificity of the SSD classifier by demonstrating that it did not discriminate other psychiatric disorders from their respective control populations.

By using mathematical and machine-learning methods, we succeeded in developing the ASD and SSD classifiers from categorical labels and rs-fMRI connectivity. At the same time, the classifiers produced the ASD and SSD dimensions, which were composed of continuous probabilistic neural classification certainties. Plotting individuals

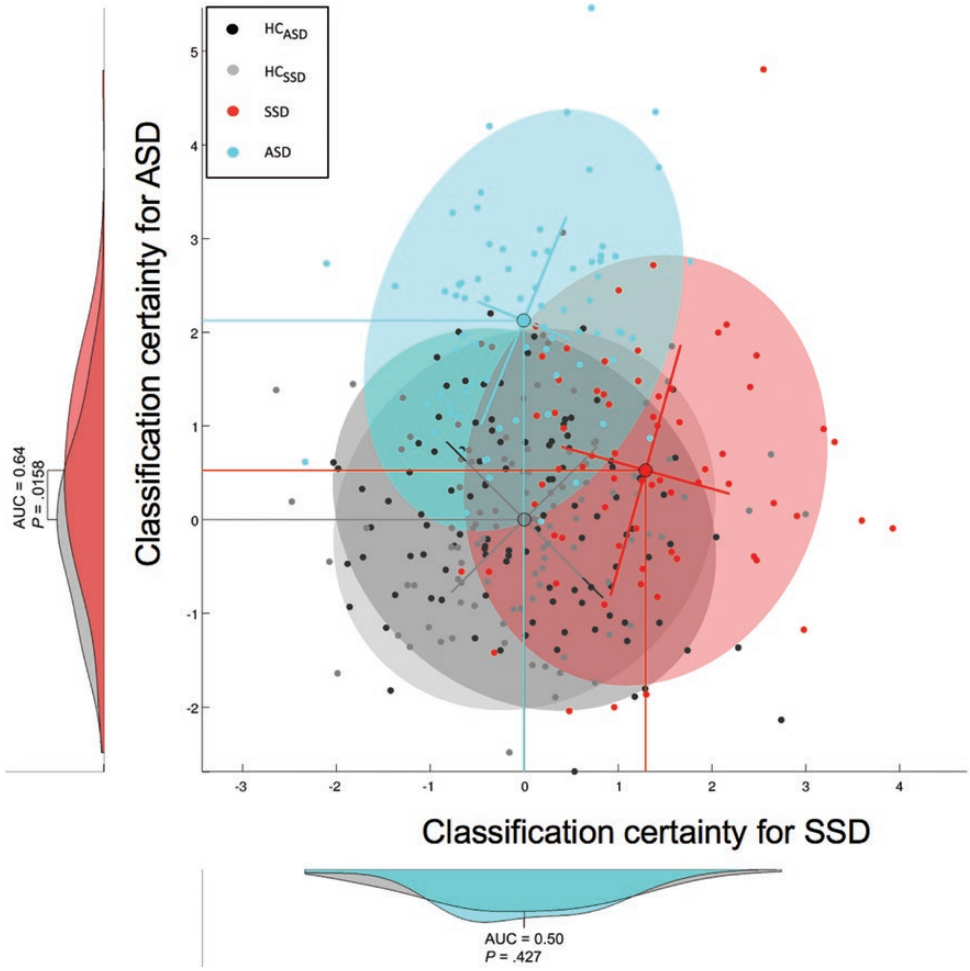

Fig. 4. Relationships between SSD and ASD on the 2 biological dimensions. Individuals with SSD, ASD, and HC on the SSD-ASD dimension plane. On the abscissa, the SSD dimension is the weighted linear summation (WLS) computed using the SSD classifier. On the ordinate, the ASD dimension is the WLS computed using the ASD classifier. WLS of each dataset was normalized so that controls have zero mean and unit variance (statistical analysis was not affected by this normalization).

with ASD, SSD, and HC on the dimensions along with DSM could show their heterogeneity based on functional neural circuits.

Several alternate models about the relationship between ASD and SSD have been proposed.[1] While these models were within conceptual frameworks, some studies that applied biological methods actually showed commonalities[3,6] or diametric conditions[40,41] between the 2 disorders. We took advantage of the 2 biological dimensions of ASD and SSD and revealed an overlapping, but asymmetrical relationships, which cannot be attained by a single dimension. The asymmetries here have dual meanings. First, the SSD population showed increased classification certainty for the ASD dimension, while the ASD population did not for the SSD dimension. Second, the 2 dimensions were correlated within the ASD population but not in the SSD population. Considering the asymmetries, we suggested a schema of the relationship between ASD and SSD (supplemental figure S9).

Taken together, the results from the frequency of selection within LOOCV underlying these asymmetries suggested that the network SSD is characterized by a larger diversity and that it partially shares information with the smaller network of ASD. This is in agreement with recent genetic evidence that ASD shares a significant degree of polygenic risk with SSD,[3] and that common genetic variations explain nearly 50% of total liability to ASD[42] and 25%–33% of total liability to SSD,[43] suggesting that environmental factors play a significant role in the heterogeneous etiopathogenesis of schizophrenia.[44]

Limitations

First, we developed the classifiers from the categorical diagnoses, not from symptoms across SSD and ASD. Thus, we did not assess relationships on a psychopathological dimensional level between the 2 nosological entities. Second, we did not directly classify the patients with SSD and ASD, because the SSD and ASD

rs-fMRI datasets were scanned from different MRI machines and sequence parameters. Third, the AUC of UMCU-TOPFIT (0.66) was lower than the AUC of COBRE (0.75). There was a difference between 3-dimensional (3D) scan in UMCU-TOPFIT and 2-dimensional (2D) scan in the other cohorts (Kyoto, COBRE, JHU-FES, ASD, and MDD).[45] The classifier was developed from Kyoto datasets in the 2D scan, and this might be related to the AUC difference. Fourth, almost all patients were on antipsychotic medication. Previous studies reported that antipsychotics altered the FC in frontal and striatal circuits.[46,47] Although we found no significant correlation between the SSD classifier and antipsychotic medication, the potential effects of antipsychotics on the SSD classifier cannot be entirely ruled out. Fifth, we did not recruit comorbid patients (ASD with psychosis) and we did not discuss comorbidity.

Conclusion

We succeeded in visualizing individuals with ASD, SSD, and HCs quantitatively on the SSD-ASD dimensions and in verifying the relationship between SSD and ASD populations. Consequently, using the two dimensions led us to discovering the overlapping but asymmetrical relationships and the complicated associations of neural classification certainties for SSD and ASD.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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