Diagnosing schizophrenia with network analysis and a machine learning method

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Abstract

Objective: Schizophrenia is a chronic and debilitating neuropsychiatric disorder. It has been suggested that impaired brain connectivity underlies the pathophysiology of schizophrenia. Network analysis has thus recently emerged in the field of schizophrenia research.

Methods: We investigated 48 schizophrenia patients and 24 healthy controls using network analysis and a machine learning method. A number of global and nodal network properties were estimated from graphs that were reconstructed using probabilistic brain tractography. These network properties were then compared between groups and used for machine learning to classify schizophrenia patients and healthy controls.

Results: In classifying schizophrenia patients and healthy controls via network properties, the support vector machine, random forest, naïve Bayes, and gradient boosting machine learning models showed an encouraging level of performance. The overall connectivity was revealed as the most significant contributing feature to this classification among the global network properties. Among the nodal network properties, although the relative importance of each region of interest was not identical, there were still some patterns.

Conclusion: In conclusion, the possibility exists to classify schizophrenia patients and healthy controls using network properties, and we have found that there is a provisional pattern of involved brain regions among patients with schizophrenia.

KEYWORDS
brain imaging, machine learning, network analysis, schizophrenia

1 | INTRODUCTION

Schizophrenia is a chronic and debilitating mental disorder with a considerable disease burden (Rossler, Salize, van Os, & Riecher-Rossler, 2005). Following on from previous postmortem studies (Bogerts, 1993), there have been efforts to identify anatomical alterations in brains with schizophrenia, particularly in light of advancements in brain imaging techniques (Dietsche, Kircher, & Falkenberg, 2017; Hajima et al., 2013; Shepherd, Laurens, Matheson, Carr, & Green, 2012; van Erp et al., 2018). Although there have been some significant findings to date on the anatomical alterations in the brains of schizophrenia patients, the pathophysiology of this disorder has not yet
been comprehensively explained by these findings. It has been recently suggested that it is not alterations in individual anatomical regions but the connectivity between multiple brain regions that underlies the core pathophysiology of schizophrenia (Cui et al., 2019; Fitzsimmons, Kubicki, & Shenton, 2013; Nelson, Bassett, Camchong, Bullmore, & Lim, 2017).

In terms of connectivity, network analysis based on the graph theory has recently emerged in the area of schizophrenia research (Bullmore & Sporns, 2009; van den Heuvel, Mandl, Stam, Kahn, & Hulshoff Pol, 2010) since its first application with the electroencephalogram and magnetoencephalogram methods (Stam, 2004). Graph theory is a branch of mathematics that describes a complex system, such as the brain, as a graph with nodes and edges (Deo, 2017). Brain networks can also be presented in this way as graphs, with nodes and edges representing neural elements and synaptic connections. Although each graph can only represent topological relationships between brain regions, it is known that topological distances are related to physical distances in the brain (Laughlin & Sejnowski, 2003), which indicates that network analysis with a structural brain image is possible.

It is possible to analyze the brain network after reconstructing it as a conceptual graph. Such analysis is based on multiple graph features or network properties (Bullmore & Sporns, 2009). Some prior studies that have investigated network properties within conceptualized brain networks in schizophrenia (Fornito & Bullmore, 2015; Jallili & Knyazeva, 2011; Lord et al., 2011; Nelson et al., 2017) have reported significant differences between patients and healthy controls. We have also previously compared brain structural networks between patients with schizophrenia and healthy controls and found significant difference in network properties (Shon et al., 2018). Notably, however, most prior studies have focused only on group differences in network properties, which has limited their clinical utility in terms of assessing individual patients or healthy controls.

We have here evaluated machine learning as a method of enhancing the clinical utility of network properties in individual patients with schizophrenia and healthy controls. Machine learning is a field of computer science that assesses the use of algorithms to perform a specific task without specified human instructions (Mohri, Rostamizadeh, & Talwalkar, 2018). It has seen recent widespread application in various fields including biology and neuroscience. Various machine learning techniques have shown great efficacy in this regard, particularly in classifying items by multiple features. These have also now been applied also to schizophrenia research (Rozycki et al., 2017; Winterburn et al., 2017) and have shown high disease classification accuracy from various nonpathognomonic features.

In our present analyses of a schizophrenia and normal cohort, we applied the machine learning method to the results of structural brain network analysis in these subjects, on the basis of graph theory. By conceptualizing hypothetical graphs with the brain tractography, the brain networks of both schizophrenia patients and healthy controls were reconstructed for network analysis. Both the global and nodal network properties of the brain were then compared between schizophrenia patients and healthy controls. Through the use of machine learning methods, we attempted to create a possible disease classification model of schizophrenia based on these network properties, which would have significant future clinical implications. Also, the relative importance of each network property or region of interest (ROI) in the machine learning model was evaluated for further insight.

2 | METHODS

2.1 | Study participants

Study participants were recruited from Asan Medical Center, Seoul, Korea. This included 48 patients diagnosed with schizophrenia using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2011), who had presented with psychotic symptoms within 5 years. We also enrolled 24 healthy controls without an Axis I psychiatric diagnosis or any first-degree relative with an Axis I psychiatric diagnosis. All subjects were between the ages of 20 and 40 years, were right-handed, and had no previously known organic disease that could affect the brain structure or function. Written informed consent was obtained from all study participants. This study was approved by the Institutional Review Board of Asan Medical Center (2012-0485).

2.2 | Clinical assessments

Full Scale Intelligence Quotient scores obtained using the short form of the Wechsler Adult Intelligence Scale—III were used to measure overall intelligence in all study participants. The Wisconsin Card Sorting Test: Computer Version 2 (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) was additionally applied to measure executive function in each study participant. In addition, the Korean version of the Positive and Negative Syndrome Scale (Yi et al., 2001) was used to evaluate psychiatric symptom severity in the patients with schizophrenia.

2.3 | Image acquisition

Imaging was conducted on a 3T scanner with an 8-channel SENSE head coil (Achieva; Philips Healthcare, Best, The Netherlands). T1-weighted images were acquired using a turbo field echo sequence (TR [repetition time]/TE [echo time], 4.9/4.6 ms; field of view, 240 × 240 × 170 mm; and voxel size, 1 mm³). Diffusion-weighted echo planar imaging was conducted (TR [repetition time]/TE [echo time], 5,422/70 ms; flip angle, 90°; field of view, 224 × 224 × 135 mm; and voxel size, 2 × 2 × 3 mm) for one baseline (b value, 0 s/mm²) and 32 gradient directions (b value, 1,000 s/mm²). All acquired images were then visually inspected again to exclude inappropriate images from further analysis. The data for one patient were therefore replaced with those for a newly enrolled patient in comparison with our previous study findings (Shon et al., 2018). This did not alter the results of either study.
2.4 | Image processing

Because anisotropic voxels can cause undesirable problems such as low signal intensity-to-noise ratio and a directional error with the fiber tracking algorithm, the importance of making each voxel isotropic for analysis has been stressed (P. Mukherjee, Chung, Berman, Hess, & Henry, 2008). Hence, diffusion-weighted images in this current study were upsampled and converted to an isotropic voxel size of 2 mm using Slicer Version 4.4 (Fedorov et al., 2012). Corrections for motion and eddy current distortions were then conducted through the affine transformation of all gradient volumes to the b = 0 baseline using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Jenkinson & Smith, 2003). T1-weighted images were parcellated into discrete anatomical ROIs using the Desikan–Killiany Atlas of FreeSurfer Version 5.3 (Fischl, 2012; Fischl et al., 2002). For each anatomical structure, white and grey matter ROIs were combined into a single ROI, which resulted in a total of 87 ROIs across the brain. These T1-weighted images were then registered into diffusion-weighted images with six degrees of freedom using FLIRT. Table S1 presents the list of 87 ROIs.

2.5 | Network reconstruction

FMRIB's Diffusion Toolbox (Behrens et al., 2003; Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) was used for analyzing processed diffusion-weighted images. By using BEDPOSTX, the distribution of the diffusion parameters at each voxel was modeled through the Metropolis–Hastings Markov chain Monte Carlo method. Probabilistic tractography was then employed by PROBTRACKX, with resampling conducted 5,000 times from the distribution for each ROI. As a result, a set of passing "probabilistic" streamlines was generated for each ROI. The degree of connectivity was estimated as the number of streamlines from one ROI to another, divided by the total number of generated streamlines. The nondirectional connectivity was the average of both unidirectional connectivities. The brain network of each study subject was then reconstructed from the ROIs and estimated connectivities and represented as a graph with nodes representing ROIs and edges representing connectivities. The threshold for the 10th percentile among the total connections was applied to remove weak or false positive connections in each brain network.

2.6 | Network examination

After reconstructing brain networks, a number of network properties were calculated via the MATLAB-based Brain Connectivity Toolbox (Rubinov & Sporns, 2010), on the basis of nondirectional weighted matrices. Considering the regional differences of general topology in the brain, both global and nodal network properties were separately calculated.

As global network properties, global and local efficiency, clustering coefficient, mean betweenness centrality, small coefficient, and overall connectivity were measured to represent the topological characteristic of each brain network. In the first instance, the efficiency (Latora & Marchiori, 2001, 2003) of a network is a measure of how efficiently it transports information across itself. Global efficiency quantifies the integrity of the whole network, whereas local efficiency represents the communication between neighbors. The clustering coefficient (Watts & Strogatz, 1998) comes from transitivity and is a measure of how closely a network clusters together. The betweenness centrality (Barthélemy, 2004), the fraction of shortest paths passing through each node, is a general measure of centrality. The mean betweenness centrality, calculated as the average of all betweenness centralities for each node, is a global property representing the whole network characteristic in general. Moreover, the small coefficient (Humphries & Gurney, 2008) is a measure of "small-worldliness,” which means the characteristic of a network with a short mean path length and clusters of tightly interconnected nodes. This coefficient is calculated by dividing the ratio of the clustering coefficient by that of the path length clustering among a given network to a random network. Lastly, overall connectivity (Beineke, Oellermann, & Pippert, 2002) is the average of all connection probabilities across the network, representing the overall strength of the network itself.

As nodal properties, local efficiency, degree, and betweenness centrality were measured for each specific brain region. Local efficiency, which represents the regional efficiency of information transfer by the shortest path length between neighbors, quantifies how much the network is segregated (Latora & Marchiori, 2001). The degree, which denotes the number of connections to a single given node, and betweenness centrality both represent the importance of the individual node (Freeman, 1977; Rubinov & Sporns, 2010).

2.7 | Statistical analysis

For demographics, clinical characteristics, and network properties, group differences were analyzed by the Statistical Package for the Social Sciences Version 21.0 (IBM Corporation, Armonk, New York). After the normality of each variable was determined by the Kolmogorov–Smirnov test, the independent t test or the Mann–Whitney U test was applied for comparisons. A p value <.05 was considered statistically significant, and the false discovery rate method was used for correcting multiple comparisons of nodal network properties.

2.8 | Machine learning model

We built several machine learning models based on the aforementioned brain network properties. The models were first built on the basis of global network properties. Other models were then built on the basis of nodal network properties, in which case each model was separately built according to the single nodal network property to prevent overcomplexity. We used various algorithms including support vector machine (SVM), multinomial naïve Bayes (NB), random forest (RF), and gradient boosting. SVM (Vapnik, 2000) is a classical supervised machine learning method that can classify different classes via the optimal "hyperplane" in a multidimensional space created with multiple
trained features. It has been used in a number of schizophrenia studies (Lu et al., 2016; Pina-Camacho et al., 2015; Xiao et al., 2017). NB classifier, which is based on a simple theorem of probability known as Bayes’ rule, is one of the classic machine learning methods but still shows significant performance in classification problems (Lewis, 1998; Zhou et al., 2015). RF (Breiman, 2001) is one of the ensemble learning methods composed of numerous decision trees. It is a popular machine learning method and shows strong predictive power in classification problems (Dahinden, 2011; Lee et al., 2016). Gradient boosting (Friedman, 2002) is also an alternative ensemble learning method with decision trees, which achieved noticeable outcomes in recent Kaggle competitions (Ben Taieb & Hyndman, 2014; Hoch, 2015).

Python 3.7.1 (https://www.python.org/) on CentOS 7 (https://www.centos.org) was used for machine learning in this present study. Previously developed python modules from Scikit-learn 0.20.1 (Pedregosa et al., 2011; http://scikit-learn.org/) were applied for model building and testing. XGBoost 0.82 (Chen & Guestrin, 2016; https://xgboost.readthedocs.io/) was additionally used as a gradient boosting algorithm. The hyperparameters of each model were optimized using a grid search method. Because the patient and healthy control sample sizes were imbalanced, the "class_weight" hyperparameter was set as "balanced" in all algorithms.

Cross-validation was used to test the model and assess its predictive performance with stratified k-fold (k = 10; Purushotham & Tripathy, 2011). The accuracy of each model was measured, as was the area under curve (AUC), which represents the area under the receiver operating characteristic curve, because this is considered to be a more appropriate performance measure in classification problems compared with accuracy (Bradley, 1997). Cross-validation was independently done 1,000 times, and the mean and standard deviation of the accuracy and AUC measures were calculated. After testing the model and performance assessment, the importance of each network property within a single machine learning model was estimated. The mean and standard deviation of each network property’s importance were calculated with 1,000 independent estimations. This was done only in the decision tree-based models.

### RESULTS

#### 3.1 Demographics and clinical characteristics

There was no significant difference between the age and sex of the schizophrenia patients and healthy controls. The mean Full Scale Intelligence Quotient of the schizophrenia patients was 97.6 ± 15.8, which was significantly lower than that for the healthy controls (120.1 ± 9.2; p < .001). In the Wisconsin Card Sorting Test, our patients achieved lower scores than the healthy controls, although the t score of the perseverative responses did not reach statistical significance (p = .201). Table 1 presents the demographics and clinical characteristics of our current study patients in detail.

#### 3.2 Comparisons of global network properties

The global and local efficiency, clustering coefficient, and overall connectivity of the network were all significantly lower in the schizophrenia group than among the healthy controls. The mean betweenness centrality and small-coefficient measures were both higher in the schizophrenia patients, although this difference did not reach statistical significance in the case of the small coefficient (1.06 ± 4.43E − 2, 1.04 ± 5.90E − 2, Mann–Whitney U = 420.0, p = .062). Table S2 presents the group differences in the global network properties.

#### 3.3 Comparisons of nodal network properties

Among the schizophrenia patients in our current study cohort, a number of the ROIs across the fronto–temporo–parietal brain area showed a lower nodal local efficiency compared with the healthy controls. Furthermore, a few ROIs at the cingulate cortex and diencephalon also showed a lower nodal local efficiency in these cases. For the nodal degree, however, the tendency was inconsistent. Although schizophrenia patients showed a decreased nodal degree value in the

| Variable             | Schizophrenia | Healthy  | t or Mann–Whitney U | p value |
|----------------------|---------------|---------|---------------------|---------|
| Age (year)           | 28.9 [6.3]    | 30.0 [5.3] | 495.0               | .444    |
| Sex (male/female)    | 18/30         | 9/15    |                     |         |
| PANSS                | 61.3 [14.8]   |         |                     |         |
| FSIQ                 | 97.6 [15.8]   | 120.1 [9.2] | 110.5               | <.001*  |
| WCST (t score)       |               |         |                     |         |
| Total errors         | 42.2 [15.4]   | 53.5 [4.9] | 236.0               | .001*   |
| Perseverative responses | 48.3 [16.7] | 53.9 [7.7] | 343.5               | .201    |
| Perseverative errors | 47.6 [14.7]   | 54.8 [7.1] | 306.0               | .037*   |
| Nonperseverative errors | 45.9 [11.9] | 52.3 [4.0] | 248.0               | .003*   |
| Conceptual-level responses | 45.5 [11.4] | 53.7 [4.5] | 4,179               | .001*   |

Note: Values are presented as a mean [standard deviation]; independent t test or Mann–Whitney U test. Abbreviations: FSIQ, Full Scale Intelligence Quotient; PANSS, Positive and Negative Syndrome Scale; WCST, Wisconsin Card Sorting Test.

*Statistical significance was set at p < .05.
right transverse temporal gyrus, right supramarginal gyrus, and right nucleus accumbens, they also showed an increased nodal degree value in the left pars orbitalis, right lateral orbitofrontal cortex, right hippocampus, and right ventral diencephalon. Nodal betweenness centrality in the right entorhinal cortex was higher among schizophrenia patients compared with the healthy controls. However, none of these results were maintained following a false discovery rate correction. Table S3 lists all of the significant (uncorrected) group differences in the nodal network properties.

### 3.4 | Machine learning model: Global

The SVM model showed a 58.2% mean accuracy and a mean AUC of 0.631, whereas the multinomial NB model showed a 66.9% mean accuracy and mean AUC of 0.638. The RF model on the other hand showed a 68.6% mean accuracy and a mean AUC of 0.680. Moreover, the gradient boosting (XGBoost) model showed a 66.3% mean accuracy and a mean AUC of 0.633. Among all of the tested models, the RF model achieved the highest performance (Table 2). Furthermore, among the six network properties that were evaluated, overall connectivity was revealed as the most important feature in classifying schizophrenia patients and healthy controls. Figure 1 shows the relative importance of each network property in each machine learning model.

### Table 2 | Performance of the machine learning models: Global

| Model       | Accuracy (%) | AUC          |
|-------------|--------------|--------------|
| SVM         | 58.2 [17.5]  | 0.631 [0.202]|
| Multinomial NB | 66.9 [4.0]  | 0.638 [0.233]|
| RF          | 66.1 [16.0]  | 0.680 [0.229]|
| XGBoost     | 66.3 [14.5]  | 0.633 [0.232]|

Note: Values shown are the mean [standard deviation].
Abbreviations: AUC, area under curve; NB, naive Bayes; RF, random forest; SVM, support vector machine.

### 3.5 | Machine learning model: Nodal

All 12 machine learning models, four per nodal network property, showed a maximum accuracy of around 66% and an AUC of approximately 0.66. Considering both of these values, the XGBoost model based on the nodal degree showed the highest performance with a 66.3% accuracy and an AUC of 0.656. All models showed relatively weaker performances comparing with those based on global network properties. Table 3 indicates the performance of all machine learning models tested. Furthermore, for all machine learning models, the importance of each ROI was investigated. Due to the characteristics of the gradient boosting model that uses a rather smaller number of features, there were differences in the relative importance of each

### Table 3 | Performance of machine learning models: Nodal

| Model        | Accuracy | AUC          |
|--------------|----------|--------------|
| SVM          | 66.0 [13.7] | 0.665 [0.239]|
| Multinomial NB | 66.9 [4.0]  | 0.347 [0.240]|
| RF           | 66.1 [14.9] | 0.619 [0.249]|
| XGBoost      | 63.0 [11.2]  | 0.540 [0.237]|
| SVM          | 66.7 [4.4]   | 0.518 [0.055]|
| Multinomial NB | 54.8 [16.7]  | 0.538 [0.225]|
| RF           | 56.9 [17.2]   | 0.545 [0.228]|
| XGBoost      | 63.5 [9.8]    | 0.656 [0.219]|

Note: Values shown are a mean [standard deviation].
Abbreviations: AUC, area under curve; NB, naive Bayes; RF, random forest; SVM, support vector machine.
ROI between the RF and XGBoost models. However, there were still a few regions contributing to both RF and XGBoost models at the same time, indicating patterns of involved brain regions. Also, ROIs in right hemisphere showed more contribution to the model than ROIs in left hemisphere (right: 37; left: 16). Figure 2 shows the relative importance of each network property ROI in each machine learning model.

4 | DISCUSSION

Our study has revealed some significant group differences in the brain network properties between schizophrenia patients and healthy controls. We first found that the global network properties, global and local efficiency, clustering coefficient, and overall connectivity of the networks were significantly lower in the schizophrenia patients than in the healthy controls. Considering the definition of each network property (Beineke et al., 2002; Latora & Marchiori, 2001, 2003; Watts & Strogatz, 1998), these results suggested that there is an impaired transformation of information across the network of a brain with schizophrenia, which is poorly clustered and has weak overall strength. These observations were also strongly consistent with the findings of many previous studies indicating brain network alterations in schizophrenia (Cui et al., 2019; Griffa et al., 2015; Micheloyannis, 2012; Nelson et al., 2017; Shon et al., 2018; van den Heuvel et al., 2013).

In contrast, the betweenness centrality was revealed to be higher in a brain with schizophrenia than in a healthy brain. This is not
consistent with the current literature (Rubinov & Bullmore, 2013; van den Heuvel et al., 2013), which has indicated that schizophrenia may be associated with a deterioration in network hub organization. According to Cheng et al. (2015), however, the mean betweenness centrality value may not properly reflect regional impairment in a brain network because only a small fraction of the nodes in a network show a high value for this parameter. It has been suggested in fact that the global properties of the brain are not sensitive enough to regional abnormalities (Tomasi & Volkow, 2014). Thus, the observed higher mean betweenness centrality in the brain networks of patients with schizophrenia in this study may be due to the increased betweenness centrality among less significant regions and decreased betweenness centrality among network hubs.

We further observed that in terms of nodal network properties, schizophrenia patients showed a lower nodal efficiency in a number of brain regions across the fronto–temporo–parietal area, cingulate cortex, and diencephalon, when compared with healthy controls. These results were consistent with the data from previous studies that indicated impaired connectivity in the frontal and temporal lobe (van den Heuvel et al., 2010), parietal lobe (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Peters et al., 2016), thalamus (Anticevic et al., 2014), and cingulate (Cui et al., 2015; Wang et al., 2015). Also, schizophrenia patients showed higher nodal betweenness centrality in the right entorhinal cortex in our study.

Furthermore, we attempted to generate a disease prediction model of schizophrenia using the machine learning method, which would have significant clinical applications. We thus built a number of models based on either global or nodal network properties, all of which showed a noticeable level of performance in classifying and distinguishing schizophrenia patients and healthy controls, with encouraging accuracy and AUC scores. Although previous studies (Greenstein, Weisinger, Malley, Clasen, & Gogtay, 2012; Lee et al., 2018; Schnack et al., 2014) have reported an even higher accuracy from 70% to 80% in classifying schizophrenia, the lower accuracy we obtained in our present study may have been due to our small sample size, considering sufficient sample size is required to reach a target performance (Figueroa, Zeng-Treitler, Kandula, & Ngo, 2012; S. Mukherjee et al., 2003; Tam, Kabbara, Yeh, & Leary, 2006). In addition, most of the previously reported models were based on features directly related to structural measures such as grey matter density (Schnack et al., 2014; D. Sun et al., 2009) or cortical thickness (Greenstein et al., 2012). The models we used in our present study were based on the features of conceptually reconstructed brain networks. Despite the large number of reports to date on the modern network analysis of the brain with schizophrenia (Micheloyannis, 2012), most have only focused on group comparisons of network properties between schizophrenia patients and healthy controls. Therefore, the possibility is noticeable that schizophrenia patients and healthy controls can actually be classified on the basis of these network properties.

By investigating the importance of each feature of each machine learning model, the overall connectivity was revealed as the most important feature in classifying schizophrenia. This was not unexpected because the disconnection of the brain has been considered to play a significant role in the underlying pathophysiology of schizophrenia (Friston, 2002). Moreover, as multiple regions were reported to show altered connectivity in brains with schizophrenia (Fitzsimmons et al., 2013; Lynall et al., 2010), the overall brain connectivity must also be altered. Of note in this regard, the global connectivity measure was previously revealed to be decreased in brains with schizophrenia (Skudlarski et al., 2010).

We observed a noticeable contributing pattern of ROIs in our machine learning models based on nodal network properties. Moreover, a number of the ROIs that were revealed to be significant in classifying schizophrenia patients and healthy controls in our current analysis were previously well-studied brain regions among schizophrenia patients. In terms of nodal local efficiency, the rostral anterior cingulate cortex, pericalcine cortex, superior parietal cortex, inferior temporal cortex, and superior frontal cortex were revealed as significant by our present analyses. The rostral anterior cingulate cortex, located in the frontal part of the cingulate cortex, has been considered to be the error-checking system of brain (Kiehl, Liddle, & Hopfinger, 2000). Notably in this regard, patients with schizophrenia have been reported to show dysfunction of the rostral anterior cingulate cortex during error processing (Laurens, Nga, Bates, Kiehl, & Liddle, 2003; Polli et al., 2008) and even a decreased volume of the rostral anterior cingulate cortex (Baiano et al., 2007). Impaired connectivity in the parietal lobe (Kahn et al., 2008; Peters et al., 2016) and frontal lobe (van den Heuvel et al., 2010) have also been described previously. Furthermore, the inferior temporal gyrus, which is known to be involved in visual processes (Papadelis et al., 2016; Zhang, Mlymaryk, Ahmed, Japee, & Ungerleider, 2018), has shown significant anatomical connectivity abnormalities in schizophrenia patients (Jeong, Wible, Hashimoto, & Kubicki, 2009).

With respect to the nodal degree, the lateral orbitofrontal cortex was also revealed by our analysis to be significant in classifying schizophrenia patients and healthy controls. The lateral orbitofrontal cortex, one of the prefrontal cortex regions, is known to be involved in the decision-making process (Domenech & Koechlin, 2015). According to a previous study, the sulcogyrical pattern of orbitofrontal cortex is altered in schizophrenia patients (Isomura et al., 2017), and even the grey matter volume is decreased (Nakamura et al., 2008). Lastly, in terms of nodal betweenness centrality, the middle anterior corpus callosum, entorhinal cortex, posterior cingulate cortex, lateral occipital cortex, and pars opercularis were revealed by our current data to be important regions in classifying schizophrenia patients and healthy controls. Most of these regions have shown anatomical or functional brain alterations in previous studies of schizophrenia. A significant reduction of the corpus callosum in the brain with schizophrenia has also been reported (del Re et al., 2016), and reduced fractional anisotropy was revealed in a prior meta-analysis study (Zhao, Liu, Wang, Tian, & Tang, 2016). In another prior study of the posterior cingulated cortex, although no brain connectivity was found to be altered, alterations of muscarinic and GABA receptors were observed among schizophrenia patients (Newell, Zavitsanou, Jew, & Huang, 2007). Postmortem studies have revealed a limbic pathology in
schizophrenia patients, represented by a volume reduction of the entorhinal cortex (Falkai, Bogerts, & Rozumek, 1988). Another study similarly reported cytoarchitectural abnormalities in the entorhinal cortex of the brain with schizophrenia (Arnold, Hyman, Vanhoesen, & Damasio, 1991). The lateral occipital complex, which is known to process visual perception, has also shown impairment in the brain with schizophrenia, as reflected by an altered connectivity measured using functional magnetic resonance imaging (Harvey et al., 2011).

Interestingly, it has been revealed that contributing ROIs in the machine learning models were located more commonly in the right hemisphere of the brain. Because it is known that the normal brain asymmetry may be attenuated in schizophrenia (Ribolzi, Daskalakis, Siracusano, & Koch, 2014), an asymmetrical hemispheric contribution could be expected in the machine learning model. Notably in this regard, alteration of the hemispheric asymmetry has long been recognized in the brain with schizophrenia (Newlin, Carpenter, & Golden, 1981) and was recently advocated also in a number of brain imaging studies (Joo et al., 2018; Okada et al., 2016; Y. Sun, Chen, Collinson, Bezerianos, & Sim, 2015). Although the current literature generally supports mainly left hemisphere anomalies in schizophrenia (Ribolzi et al., 2009), there have been a number of studies suggesting a relationship between the right cerebral hemisphere and psychiatric disorders (Cutting, 1990), including schizophrenia (Cutting, 1994).

Our present study had some limitations of note. In the first instance, the network properties chosen for our machine learning models were intercorrelated. There are various different network properties representing the characteristics of each network. Some attributes are correlated, and some even can be derived from others. Because machine learning models such as SVM can be affected significantly by feature selection (Nguyen & de la Torre, 2010), overall model performance and feature importance could be altered. Hence, we attempted to choose the most frequently studied network properties from previous studies (Alexander-Bloch et al., 2010; Lynall et al., 2010; Zalesky et al., 2011). In addition, the RF and Gradient Boosting models, which were based on a decision tree algorithm, were not significantly affected by correlated features because the decision tree discarded redundant features (Hall, 1999). Another limitation of our present analysis was that a relatively small number of study participants was included. A small sample size makes it hard to correctly evaluate the model in machine learning (Raudys & Jain, 1991). It can also cause a large deviation in prediction (Lemm, Blankertz, Dickhaus, & Muller, 2011). In addition, it is known that a classification model based on a small sample size is more unstable, particularly because of the overfitting problem (Arbabshirani, Plis, Sui, & Calhoun, 2017). We thus used a cross-validation method to minimize overfitting and also inspected the accuracy and AUC in both the training and test sets among each fold. The scores from the training and test sets showed similar values in every fold, which suggested the absence of overfitting. However, considering the statistical power issues with our small patient population, further studies with larger sample sizes are recommended.

In conclusion, we have here found significant differences in the network properties of a brain with schizophrenia compared with a healthy brain and also found that schizophrenia patients and healthy controls can be properly classified by these properties based on machine learning models. Because there have already been a number of studies on machine learning and network analysis in schizophrenia, it is meaningful to evaluate the possibility of integrating both methods. Further investigations with large sample sizes and extensive network properties are warranted.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest in relation to this study.

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