Schizophrenia Research 214 (2019) 11–17

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Support vector machine-based classification of first episode drug-naïve schizophrenia patients and healthy controls using structural MRI

Yuan Xiao [a], Zhihan Yan [b], Youjin Zhao [a], Bo Tao [a], Huaiqiang Sun [a], Fei Li [a], Li Yao [a], Wenjing Zhang [a], Shah Chandan [a], Jieke Liu [a], Qiyong Gong [a], John A. Sweeney [a,c], Su Lui [a,*]

[a] Department of Radiology, the Center for Medical Imaging, West China Hospital of Sichuan University, China
[b] Department of Radiology, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, China
[c] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, USA

ARTICLE INFO

Article history:
Received 14 August 2017
Received in revised form 19 November 2017
Accepted 27 November 2017
Available online 6 December 2017

Keywords:
Schizophrenia
Support vector machine (SVM)
Surface area
Cortical thickness
Classification

ABSTRACT

Although regional brain deficits have been demonstrated in schizophrenia patients by structural MRI studies, one important question that remains largely unanswered is whether the complex and subtle deficits revealed by MRI could be used as objective biomarkers to discriminate patients from healthy controls individually. To address this question, a total of 326 right-handed participants were recruited, including 163 drug-naïve first-episode schizophrenia (FES) patients and 163 demographically matched healthy controls. High-resolution anatomic data were acquired from all subjects and processed via Freesurfer software to obtain cortical thickness and surface area measurements. Subsequently, the Support Vector Machine (SVM) was used to explore the potential utility for cortical thickness and surface area measurements in the differentiation of individual patients and healthy controls. The accuracy of correct classification of patients and controls was 85.0% (specificity 87.0%, sensitivity 83.0%) for surface area and 81.8% (specificity 85.0%, sensitivity 76.9%) for cortical thickness ($p < 0.001$ after permutation testing). Regions contributing to classification accuracy mainly included the gray matter in default mode, central executive, salience, and visual networks. Current findings, in a sample of never-treated FES patients, suggest that the patterns of illness-related gray matter changes has potential as a biomarker for identifying structural brain alterations in individuals with schizophrenia. Future prospective studies are needed to evaluate the utility of imaging biomarkers for research and potentially for clinical purpose.

1. Introduction

The current diagnostic systems (DSM 5 and ICD-10) for establishing psychiatric diagnoses are based on psychological and behavioral criteria. For example, the diagnosis of schizophrenia is based on observed behaviors and examination of psychiatric signs and symptoms rather than objective biological markers. The lack of quantitative objective measures may be one reason that the causative factors in schizophrenia remain obscure (Agarwal et al., 2010). First-episode schizophrenia (FES) patients are of particular interest, by way of providing more information about illness-associated brain abnormalities independent of antipsychotic treatment and long course of illness effects.

Imaging studies have reported widespread anatomical and functional alterations in FES patients relative to healthy controls, especially in frontal and temporal cortex (Asmal et al., 2016; Gutierrez-Galve et al., 2010; Lui et al., 2009; Ren et al., 2013; Xiao et al., 2015). However, most previous imaging findings have limited value for clinical application for two reasons. First, most previous studies typically measured average group-level differences rather than classify individual patients, thus they do not allow for evaluation of individual patients (Zarogianni et al., 2013). Second, most prior studies considered brain regions of interest in isolation rather than as a pattern of illness-related alterations.

Addressing these challenges can be accomplished using pattern recognition approaches to identify biologically similar discrete patient subgroups, such as cluster analysis and machine learning approaches with support vector machine (SVM) (Noble, 2006; Pereira et al., 2009). Using SVM in FES and healthy controls, studies have demonstrated cortical thickness or blood flow reduction in prefrontal and temporal regions, as well as white matter alterations in uncinate fasciculus and cingulum, which connect frontal and temporal lobe regions. These studies report an accuracy in the range of 70%–90% for differentiating FES patients from controls (Peruzzo et al., 2015; Squarcina et al., 2017; Squarcina et al., 2015). Functional connectivity or activity in salience

Abbreviations: SVM, support vector machine; AUC, area under curve; ROC, receiver operating characteristic.

* Corresponding author at: Department of Radiology, West China Hospital, #37 Guo Xue Xiang, Chengdu 610041, China.
E-mail address: lusuwcums@tom.com (S. Lui).

https://doi.org/10.1016/j.schres.2017.11.037

network and default mode network were also reported to have potential for diagnostic classification between FES and controls (Guo et al., 2017; Mikolas et al., 2016).

Though these findings are encouraging, the interpretation of the results is to some extent hindered by potential medication effects and small sample sizes. In machine learning studies, small sample size can cause model overfitting and introduce a bias to the classification, which result in poor generalization of the method to independent data sets (Zarogianni et al., 2013). In some studies, larger samples were used but including data from scanners from multiple centers. Findings from animal and human studies indicate significant anatomic and functional alterations even after short-term antipsychotic treatment (Emsley et al., 2017; Goghari et al., 2013; Hu et al., 2016; Lui et al., 2010; Reis Marques et al., 2014; Yue et al., 2016). To our knowledge, no study has yet applied machine learning approaches in a large cohort of never treated first episode patients from a single center and scanner.

Brain surface area and cortical thickness are widely used Magnetic Resonance Imaging (MRI) parameters in schizophrenia research. During early development of the human brain, the process of gyrification and surface expansion accompanies the significant increase in brain surface area (Armstrong et al., 1995), making this parameter of particular interest in relation to early neurodevelopmental models of schizophrenia (Palaniyappan et al., 2011).

In the present study, we acquired high-resolution T1WI data from a large cohort of subjects, including 163 drug-naïve FES patients and 163 demographically matched healthy controls. We in this study examined cortical thickness and surface area rather than the gray matter volume because cortical thickness and surface area are influenced by different genetic factors (Panizzon et al., 2009). Surface area mainly represents the number of columns of neurons within a cortical region (Rakic, 1988), while cortical thickness reflects the size, density and arrangement of neurons, neuroglia and nerve fibres (Narr et al., 2005) in cortical columns.

Two hypotheses were addressed. First, we predicted that both cortical thickness and surface area would show high sensitivity and specificity in differentiating individual FES patients from controls separately. Second, the regions contributing to the difference between FES patients and controls would be primarily within the prefrontal and temporal cortex.

2. Materials and methods

2.1. Subjects

The study included 163 treatment-naïve FES patients and 163 healthy controls (Table 1). The study was approved by the local research ethics committee and written informed consent was obtained from all subjects. Diagnoses of schizophrenia were determined using the Structured Interview for the DSM-IV (SCID-P). Psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS). Psychiatric evaluations were performed by two experienced clinical psychiatrists prior to treatment and MR examinations.

Healthy controls were recruited by poster advertisement, and did not differ significantly from the schizophrenia group on age, sex, and years of education. All controls were screened using the SCID-NP to confirm the lifetime absence of psychiatric illnesses. Control subjects reported no history of psychiatric illness in first-degree relatives. The following exclusion criteria applied to all of the above groups: any neurological disorder, lifetime drug or alcohol abuse or dependency, pregnancy or significant systemic illness, such as hepatitis or cardiovascular disease. Brain MR images (i.e., T1-weighted and T2-weighted images) were inspected by an experienced neuroradiologist to check image quality and exclude patients with visible cerebral abnormalities of neuroradiological significance.

Table 1
Demographic and clinical characteristics for antipsychotic-naive first-episode schizophrenia patients and healthy controls.

Characteristic	Antipsychotic-naïve FES (N = 163)	HC (N = 163)	*P*
	Mean ± SD	Mean ± SD	
Age (years)	23.54 ± 7.63	23.61 ± 5.94	0.92
Education (years)	12.03 ± 3.17	13.15 ± 2.45	0.10
Illness duration (months)	12.21 ± 20.08	–	–
GAF scores	30.10 ± 11.13	–	–
PANSS scores			
Total	95.58 ± 19.33	–	–
Negative symptoms	24.71 ± 6.36	–	–
Positive symptoms	18.73 ± 7.97	–	–
General psychopathology symptoms	45.89 ± 9.82	–	–
	N	N	*P*
Gender(M/F)	74/89	86/77	0.18

FES: first-episode schizophrenia; HC: healthy controls.

2.2. Data acquisition

All subjects were scanned on a 3.0 T MR scanner (EXCITE, General Electric, Milwaukee, USA). High-resolution T1-weighted volumetric 3D images were obtained using a spoiled gradient recall (SPGR) sequence (TR = 8.5 ms, TE = 3.4 ms, Flip angle = 12°, slice thickness = 1 mm) and an 8-channel phase-array head coil. A Field of View of 240 × 240 mm^2 was used with an acquisition matrix comprising 256 readings of 128 phase encoding steps, producing 156 contiguous coronal slices with slice thickness of 1.0 mm. The final matrix of T1-weighted images was automatically interpolated in plane to 512 × 512 to yield an in-plane resolution of 0.47 × 0.47 mm^2. Foam padding and ear-plugs were used to reduce head motion and scanner noise.

2.3. Data analysis

Structural MRI data were processed using the FreeSurfer image analysis package (version 5.3.0, http://surfer.nmr.mgh.harvard.edu/).We used the default parcellation and the Desikan atlas. Briefly, processing included motion correction and removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation, intensity normalization, tessellation of gray matter and white matter boundaries, automated topology correction, and surface deformation following intensity gradients to optimally place the gray matter–white matter and gray matter–cerebrospinal fluid borders at the location where the greatest shift in intensity defined transition to other tissue class (Dale et al., 1999).

The above procedure generated average cortical thickness and surface area for 68 frontal, temporal, parietal, and occipital lobe regions. We used them as features in the machine learning analysis (below). Before the variables were used to classify, they were each residualized using a general linear model with gender, age, and intracranial volume as independent variables.

2.4. Multivariate pattern classification analysis

We used a specific multivariate pattern classification analysis approach known as SVM from the LIBSVM machine learning library (www.csie.ntu.edu.tw/~cjlin/libsvm), which is a frequently used classifier in neuroimaging research. The cortical thickness and surface area features of 68 cortical regions from the Desikan atlas were extracted.

Table 2
Classification performance.

	Specificity	Sensitivity	Accuracy	AUC
Surface area	87.0%	83.0%	85.0%	0.85
Cortical thickness	85.0%	76.9%	81.8%	0.78

Table 3
Regions contributing to discrimination between first episode schizophrenia and healthy control groups based on surface area.

Regions	Weight	Network
lh_fusiform_area	0.037163317	visual network
lh_lingual_area	0.394043481	visual network
lh_posterior_cingulate_area	0.373321496	default mode network
lh_supramarginal_area	0.002481527	language network
lh_insula_area	0.044973661	salience network
rh_isthmus_cingulate_area	0.016799451	default mode network
rh_lateral_occipital_area	0.256421248	visual network
rh_lingual_area	0.076792878	visual network
rh_frontal_pole_area	0.010835031	default mode network

LH = left hemisphere; RH = right hemisphere.

We analyzed these features separately to advance understanding of the utility of both feature sets for classification purposes. We first normalized the surface area features. Then we reduced the number of features using a two-sample *t*-test between the FES and healthy controls, thresholded to include parameters with group differences above $p < 0.05$ corrected for multiple comparisons. This step was used to improve and stabilize classification performance (Dosenbach et al., 2010). A linear decision boundary in this high dimensional space was defined by a hyperplane that separated individual cortical thickness or surface area values according to a class label (i.e., FES vs. healthy controls). The optimal hyperplane was computed based on the whole multivariate pattern of anatomical features across all subjects in the training set. A similar procedure was implemented for a separate analysis of cortical thickness data.

To obtain a stable and reliable performance of the proposed model and to avoid the possibility of over fitting the model, we used 10-fold cross validation technique (Kohavi, 1995). In 10-fold cross validation the dataset was segmented into 10 random subsets from both patients and controls. One subset was selected as the testing subset to test the model in the first iteration, and the remaining 9 subsets were used for training. In the subsequent 9 iterations, the process continues through selecting, one by one each of the 9 subsets as a testing subset. After 10 iterations (folds), the performance measures were averaged. We repeated this procedure for the cortical thickness and surface area data separately to assess the predictive power of each morphometric parameter. Statistical significance of the overall accuracy, sensitivity, and specificity for cortical thickness or surface area were determined by permutation testing, randomly permuted the data (1000 times) to obtain two types of randomized versions of the data. The first version is a standard labels permutation test (Good, 2000), and the second uses a data columns per class permutation test (Ojala and Garriga, 2010). To evaluate the performance of the classification in different features, receiver operating characteristic (ROC) curves were obtained by using the SVM classifier.

3. Results

The classification performance for each structural feature is summarized in Table 2. Classification accuracy for classification between FES patients and healthy controls were 81.8% (specificity 85.0%, sensitivity 76.9%) for cortical thickness (all $p < 0.001$ for labels and data columns per class permutation tests) and 85.0% (specificity 87.0%, sensitivity 83.0%) for surface area (all $p < 0.001$ for labels and data columns per class permutation tests; Table 2).

Regions that contributed to surface area discrimination included left fusiform, left lingual, left posterior cingulate, left supramarginal, left insula, right isthmus cingulate, right lateral occipital, right lingual, and right frontal pole cortex (Table 3, see Fig. 3). The illustration of classification for surface area measures is presented in Fig. 1. ROC curve of surface area was also obtained by using the SVM classifier (Fig. 1, Area under Curve (AUC) = 0.85).

Regions that contributed to cortical thickness discrimination included left inferior parietal, left rostral anterior cingulate, left rostral middle frontal, right caudal middle frontal, right inferior parietal, right lingual, and right temporal pole cortex (Table 4, see Fig. 4). The illustration of classification for cortical thickness measures is presented in Fig. 2. ROC curve of cortical thickness was also obtained by using the SVM classifier (Fig. 2, AUC = 0.78).

4. Discussion

Using the largest sample of drug-naive FES studied to date with a single MR scanner, the current study successfully demonstrated the potential value of MRI in differentiating individual schizophrenia patients from healthy controls. Using a machine learning approach, we obtained an accuracy of 85.0% for surface area and 81.8% for cortical thickness. Thus, the findings support our hypothesis that patterns of gray matter alterations may provide a useful biomarker for identifying neuroanatomic alterations in schizophrenia at an early phase of illness prior to influences of psychiatric medications. Furthermore, the regions that

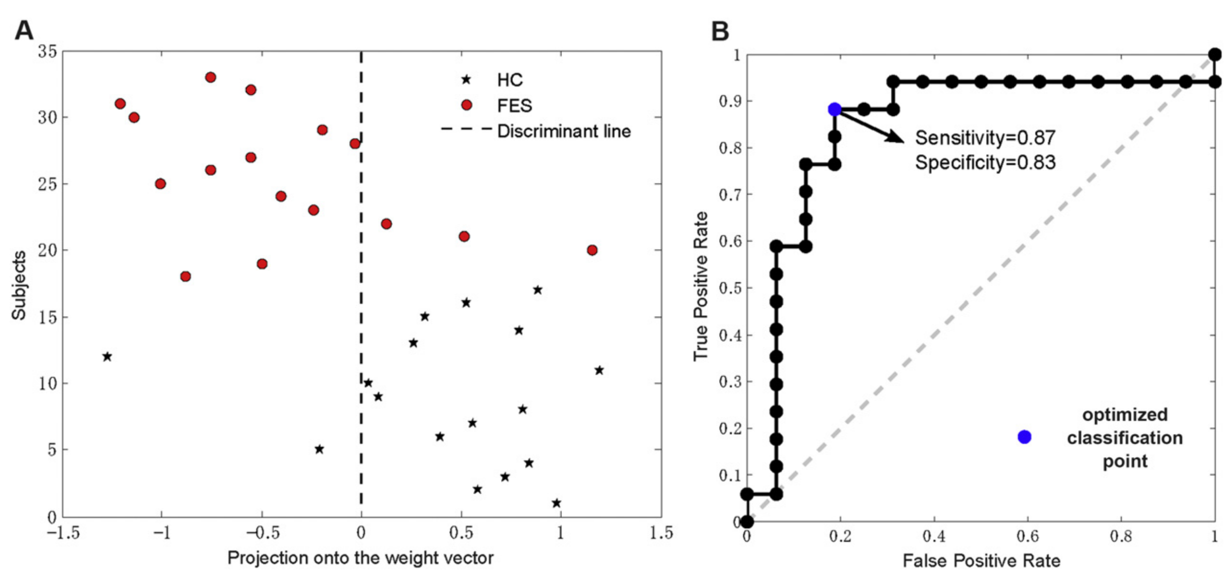

Fig. 1. Multivariate pattern classification based on surface area. (A) Classification plot for training on FES and HC data and testing on FES and HC data using surface area. (B) ROC curve. FES: first-episode schizophrenia; HC: healthy controls; ROC: receiver operating characteristic.

Table 4
Regions contributing to discrimination between first episode schizophrenia and healthy control groups based on cortical thickness.

Regions	Weight	Network
lh_inferior_parietal_thickness	0.747446630	default mode network
lh_rostral_anterior_cingulate_thickness	0.073074305	salience network
lh_rostral_middle_frontal_thickness	0.123998723	central executive network
rh_caudal_middle_frontal_thickness	0.148789386	central executive network
rh_inferior_parietal_thickness	0.457086964	default mode network
rh_lingual_thickness	0.065754951	visual network
rh_temporal_pole_thickness	0.012785662	salience network

LH = left hemisphere; RH = right hemisphere.

contributed to the differentiation between the patients and controls are belonged to the default mode network (DMN), central executive network (CEN), salience, visual and language networks, all of which have been previously implicated in the pathogenesis of schizophrenia (Allen et al., 2008; Ffytche et al., 1998; Garrity et al., 2007; Manoliu et al., 2014; Torrey, 2007; White et al., 2010). We did not confirm the predicted regional specificity of effects to temporal and frontal cortex.

While neuroimaging studies in psychiatry have been useful for research purposes, their clinical application often has been limited by group-level analyses and analysis of different regional changes in isolation. The current study provides evidence indicating that structural MRI data analyzed with analytic procedures examining discrete imaging parameters may provide important information for individual classification of patients with FES. In fact, a number of studies using traditional region of interest analysis did not find any specific cerebral region which could be used to reliably differentiate patients with schizophrenia from healthy controls (Agarwal et al., 2010; Levitt et al., 2010). Besides methodological issues associated with medication, duration of illness and sample size, the absence of reliable markers could be due to the fact that schizophrenia is a complex disorder with anatomical and functional deficits in multiple brain regions (Shenton et al., 2010). Thus it may not be possible to identify a specific biomarker using a region of interest analysis based on standard univariate statistics. In contrast, multi variate approaches such as SVM consider statistical associations among different brain regions and therefore may have greater potential for detecting alterations, which are subtle and distributed. In the current study, SVM revealed that patterns of both cortical thickness and surface area measures are sensitive in identifying antipsychotic-naive FES from controls.

The high accuracy of cortical thickness and surface area measures in differentiating individual schizophrenia patients from healthy controls has also been reported in chronically treated and FES patients, where studies have found classification accuracy ranging between 75% and 92% (Castellani et al., 2012; Fan et al., 2011; Fan et al., 2005; Peruzzo et al., 2015; Pohl and Sabuncu, 2009; Squarcina et al., 2017; Squarcina et al., 2015; Yang et al., 2010). Our study extended previous findings in three certain aspects. First, our investigation was carried out on drug-naïve patients and therefore our results were not affected by the effects of medication and duration of illness. It is well known that medication can have a significant impact on gray matter even after a very short period of treatment (Keshavan et al., 1994; Keshavan et al., 1998). Thus, the observation that classification accuracy from our FES sample was similar to that reported in chronically ill patients suggests that group separation using MRI anatomic measures may be relatively stable after illness onset. However, the similarity of feature selection for these classifications remains to be determined. Second, the number of participants in our investigation was larger than previous SVM studies of FES. Adequate sample size is of course an important consideration regarding the robustness and reliability of the model developed for the classification system (Zarogianni et al., 2013). Third, the current study, unlike some previous SVM studies (Castellani et al., 2012; Fan et al., 2011; Fan et al., 2005; Pohl and Sabuncu, 2009; Yang et al., 2010) using regions of interest analysis, we employed whole brain analysis. An advantage of using whole brain surface based analysis is that this is a totally automatic approach that develops classification algorithms empirically without bias.

It's also interesting that the distributed regions from the discrimination map for surface area include left fusiform, left lingual, left posterior cingulate, left supramarginal, left insula, right isthmus cingulate, right lateral occipital, right lingual and right frontal pole cortex, most of which belong to the DMN or salience network. For example, the left posterior cingulate and right isthmus cingulate as well as frontal pole, belong to DMN, which is an integrated system for self-related cognitive activity, including autobiographical, self-monitoring and social functions (Menon, 2011). Previous studies have reported aberrant anatomical and functional connectivity of DMN in FES and chronic patients and in high risk subjects (Camchong et al., 2011; Clark et al., 2017; Garrity et al., 2007; Hu et al., 2017). Insular cortex and dorsal anterior cingulate cortex which are parts of the salience network, were utilized for diagnostic classification for FES (Mikolas et al., 2016). The left fusiform, bilateral lingual, and right lateral occipital areas belong to the visual system. Previous studies demonstrated significant gray matter volume

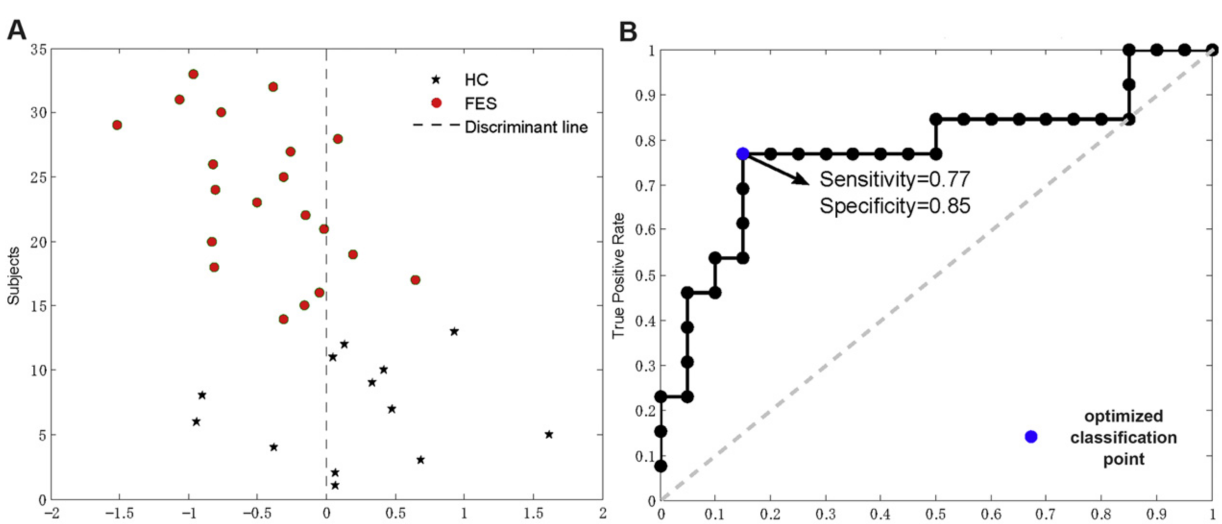

Fig. 2. Multivariate pattern classification based on cortical thickness. (A) Classification plot for training on FES and HC data and testing on FES and HC data using cortical thickness (B) ROC curve. FES: first-episode schizophrenia; HC: healthy controls; ROC: receiver operating characteristic.

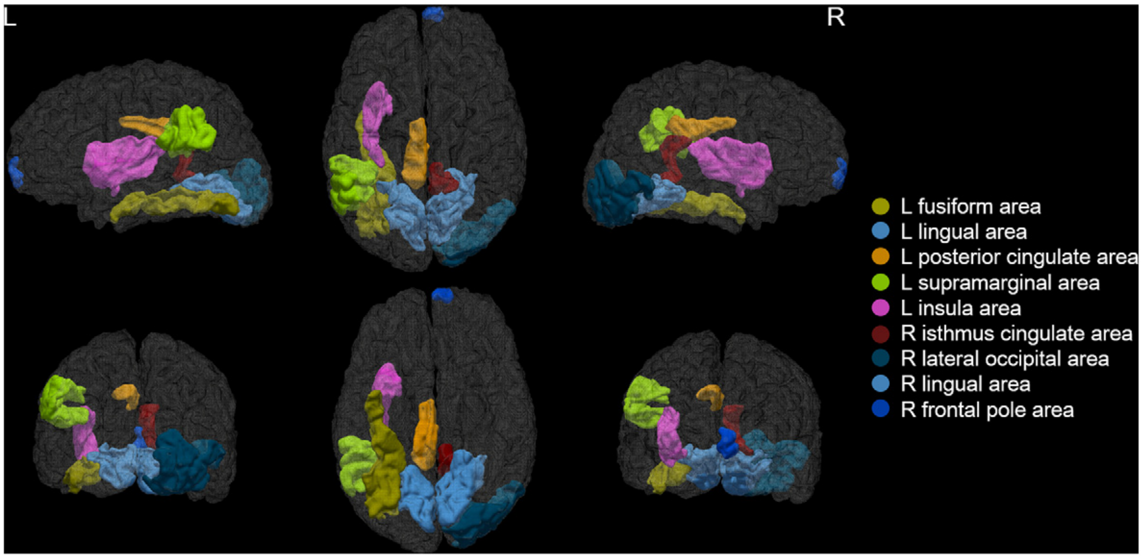

Fig. 3. Regions contributing to diagnostic classification based on surface area.

reduction in visual system and lower magnetization transfer ratio and fractional anisotropy in white matter adjacent to visual areas (Onitsuka et al., 2007; Palaniyappan et al., 2013). Alterations in the left supramarginal area and auditory cortex have been reported to be relevant for auditory verbal hallucinations in schizophrenia (Cui et al., 2017). Besides the regions mentioned above, discriminating map for cortical thickness included rostral and caudal middle frontal cortex, which are mainly involved in CEN. CEN plays an important role in working memory and attention, and impaired cognition arising from CEN deficit is recognized as a prominent feature of schizophrenia (Menon, 2011). Taken together, our findings provide evidence that the changes of the cortical patterns contributing to the difference between FES and controls involve widely distributed neural networks believed to be core targets of the pathogenesis of schizophrenia.

There are certain limitations to be considered in interpreting our results. First, all data were processed by the same protocol and the version of FreeSurfer 5.3 over the course of our 10-year recruitment to create this quite large sample of never-treated first episode patients, with results consistent across publications in this regard. Newer software might yield somewhat different findings. Second, although results from the present investigation are promising, the eventual development of a diagnostic tool to be used in everyday clinical practice will ultimately require several advances. The efficiency of a model such as ours needs to be replicated, and shown to be useful before and after treatment and across of ages and illness duration. The model will need an even greater level of accuracy than that found in the present study, perhaps by including more diverse observations from multimodal imaging. For example, diagnostic accuracy might be improved by the integration of structural and functional neuroimaging data with genetic, clinical and cognitive information. Investigators will also need to establish utility in the clinically relevant differential diagnosis contrasting psychiatric disorders rather than patient control comparisons.

5. Conclusion

In summary, the present study provides evidence that anatomical MRI shows promise in discriminating FES from healthy individuals. Using machine learning, we demonstrated that both cortical thickness and surface area data showed high accuracy in identifying FES. These findings may provide the first step towards using MRI as a tool to guide clinicians. As the field of psychiatric neuroimaging evolves, applications of MRI studies for differential diagnosis and for individualizing

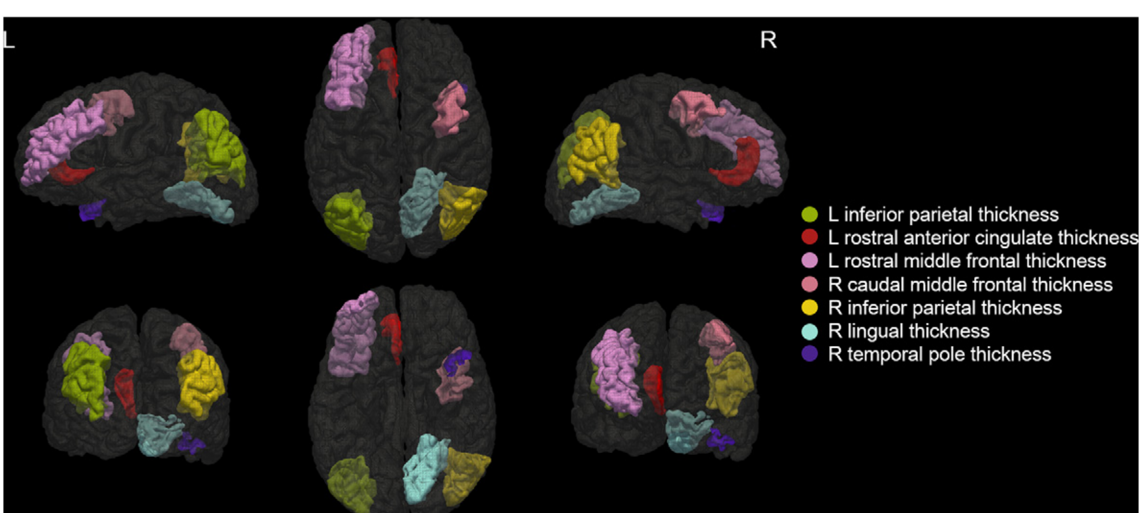

Fig. 4. Regions contributing to diagnostic classification based on cortical thickness.

and tracking treatment effects may significantly advance patient care, though much work needs to be done before translating the MRI research findings into clinical practice.

Conflict of interest

Dr. Sweeney has been a consultant to Takeda Pharmaceuticals. All other authors declare that they have no conflicts of interest.

Contributors

Su Lui conceived the study and designed the protocol. Yuan Xiao and Bo Tao did the experiments. Yuan Xiao, Zhihan Yan, and Huaiqiang Sun conducted the statistical analyses. Yuan Xiao, Youjin Zhao, Shah Chandan, Jieke Liu and Su Lui interpreted study findings and contributed to developing the manuscript. Yuan Xiao and Su Lui wrote the first draft of the manuscript that was revised and approved by all authors.

Role of the funding source

This study was supported by the National Natural Science Foundation (grant numbers 81621003, 81671664 and 81371527), National Youth Top-notch Talent Support Program of China and Chang Jiang Scholars Program (Young Scholars, Q2015154) of China. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Acknowledgement

We want to thank all participants in this study.

References

Agarwal, N., Port, J.D., Bazzocchi, M., Renshaw, P.F., 2010. Update on the use of MR for assessment and diagnosis of psychiatric diseases. Radiology 255 (1), 23–41.

Allen, P., Laroi, F., McGuire, P.K., Aleman, A., 2008. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. Neurosci. Biobehav. Rev. 32 (1), 175–191.

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., Zilles, K., 1995. The ontogeny of human gyrification. Cereb. Cortex 5 (1), 56–63.

Asmal, L., du Plessis, S., Vink, M., Chiliza, B., Kilian, S., Emsley, R., 2016. Symptom attribution and frontal cortical thickness in first-episode schizophrenia. Early Intervention in Psychiatry.

Camchong, J., MacDonald 3rd, A.W., Bell, C., Mueller, B.A., Lim, K.O., 2011. Altered functional and anatomical connectivity in schizophrenia. Schizophr. Bull. 37 (3), 640–650.

Castellani, U., Rossato, E., Murino, V., Bellani, M., Rambaldelli, G., Perlini, C., Tomelleri, L., Tansella, M., Brambilla, P., 2012. Classification of schizophrenia using feature-based morphometry. J. Neural Transm. 119 (3), 395–404 (Vienna, Austria: 1996).

Clark, S.V., Mittal, V.A., Bernard, J.A., Ahmadi, A., King, T.Z., Turner, J.A., 2018. Stronger default mode network connectivity is associated with poorer clinical insight in youth at ultra high-risk for psychotic disorders. Schizophr. Res. 193, 244–250.

Cui, L.B., Liu, L., Guo, F., Chen, Y.C., Chen, G., Xi, M., Qin, W., Sun, J.B., Li, C., Xi, Y.B., Wang, H. N., Yin, H., 2017. Disturbed brain activity in resting-state networks of patients with first-episode schizophrenia with auditory verbal hallucinations: a cross-sectional functional MR imaging study. Radiology 283 (3), 810–819.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage 9 (2), 179–194.

Dosenbach, N.U., Nardos, B., Cohen, A.L., Fair, D.A., Power, J.D., Church, J.A., Nelson, S.M., Wig, G.S., Vogel, A.C., Lessov-Schlaggar, C.N., Barnes, K.A., Dubis, J.W., Feczko, E., Coalson, R.S., Pruett Jr., J.R., Barch, D.M., Petersen, S.E., Schlaggar, B.L., 2010. Prediction of individual brain maturity using fMRI. Science (New York, N.Y.) 329 (5997), 1358–1361.

Emsley, R., Asmal, L., du Plessis, S., Chiliza, B., Phahladira, L., Kilian, S., 2017. Brain volume changes over the first year of treatment in schizophrenia: relationships to antipsychotic treatment. Psychol. Med. 47 (12), 2187–2196.

Fan, Y., Shen, D., Davatzikos, C., 2005. Classification of structural images via high-dimensional image warping, robust feature extraction, and SVM. Medical Image Computing and Computer-Assisted Intervention: MICCAI. International Conference on Medical Image Computing and Computer-Assisted Intervention. 8 (Pt 1), pp. 1–8.

Fan, Y., Liu, Y., Wu, H., Hao, Y., Liu, H., Liu, Z., Jiang, T., 2011. Discriminant analysis of functional connectivity patterns on Grassmann manifold. NeuroImage 56 (4), 2058–2067.

Ffytche, D.H., Howard, R.J., Brammer, M.J., David, A., Woodruff, P., Williams, S., 1998. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat. Neurosci. 1 (8), 738–742.

Garrity, A.G., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., Calhoun, V.D., 2007. Aberrant "default mode" functional connectivity in schizophrenia. Am. J. Psychiatry 164 (3), 450–457.

Goghari, V.M., Smith, G.N., Honer, W.G., Kopala, L.C., Thornton, A.E., Su, W., Macewan, G. W., Lang, D.J., 2013. Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naive first-episode psychosis patients. Schizophr. Res. 149 (1–3), 149–155.

Good, P.I., 2000. Permutation Tests: A Practical Guide to Resampling Methods for Testing Hypotheses. Springer-Verlag, New York.

Guo, W., Liu, F., Chen, J., Wu, R., Li, L., Zhang, Z., Chen, H., Zhao, J., 2017. Hyperactivity of the default-mode network in first-episode, drug-naive schizophrenia at rest revealed by family-based case-control and traditional case-control designs. Medicine (Baltimore) 96 (13), e6223.

Gutierrez-Galve, L., Wheeler-Kingshott, C.A., Altmann, D.R., Price, G., Chu, E.M., Leeson, V. C., Lobo, A., Barker, G.J., Barnes, T.R., Joyce, E.M., Ron, M.A., 2010. Changes in the frontotemporal cortex and cognitive correlates in first-episode psychosis. Biol. Psychiatry 68 (1), 51–60.

Hu, M.L., Zong, X.F., Zheng, J.J., Pantazatos, S.P., Miller, J.M., Li, Z.C., Liao, Y.H., He, Y., Zhou, J., Sang, D.E., Zhao, H.Z., Lv, L.X., Tang, J.S., Mann, J.J., Chen, X.G., 2016. Short-term effects of risperidone monotherapy on spontaneous brain activity in first-episode treatment-naive schizophrenia patients: a longitudinal fMRI study. Sci. Rep. 6, 34287.

Hu, M.L., Zong, X.F., Mann, J.J., Zheng, J.J., Liao, Y.H., Li, Z.C., He, Y., Chen, X.G., Tang, J.S., 2017. A review of the functional and anatomical default mode network in schizophrenia. Neurosci. Bull. 33 (1), 73–84.

Keshavan, M.S., Bagwell, W.W., Haas, G.L., Sweeney, J.A., Schooler, N.R., Pettegrew, J.W., 1994. Changes in caudate volume with neuroleptic treatment. Lancet (London, England) 344 (8934), 1434.

Keshavan, M.S., Haas, G.L., Kahn, C.E., Aguilar, E., Dick, E.L., Schooler, N.R., Sweeney, J.A., Pettegrew, J.W., 1998. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? J. Psychiatr. Res. 32 (3–4), 161–167.

Kohavi, R., 1995. A Study of Cross-Validation and Bootstrap for Accuracy Estimation and Model Selection, Proceedings of the 14th International Joint Conference on Artificial Intelligence. Volume 2. Morgan Kaufmann Publishers Inc., Montreal, Quebec, Canada, pp. 1137–1143.

Levitt, J.J., Bobrow, L., Lucia, D., Srinivasan, P., 2010. A selective review of volumetric and morphometric imaging in schizophrenia. Curr. Top. Behav. Neurosci. 4, 243–281.

Lui, S., Deng, W., Huang, X., Jiang, L., Ma, X., Chen, H., Zhang, T., Li, X., Li, D., Zou, L., Tang, H., Zhou, X.J., Mechelli, A., Collier, D.A., Sweeney, J.A., Li, T., Gong, Q., 2009. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am. J. Psychiatry 166 (2), 196–205.

Lui, S., Li, T., Deng, W., Jiang, L., Wu, Q., Tang, H., Yue, Q., Huang, X., Chan, R.C., Collier, D.A., Meda, S.A., Pearlson, G., Mechelli, A., Sweeney, J.A., Gong, Q., 2010. Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by "resting state" functional magnetic resonance imaging. Arch. Gen. Psychiatry 67 (8), 783–792.

Manoliu, A., Riedl, V., Zherdin, A., Muhlau, M., Schwerthoffer, D., Scherr, M., Peters, H., Zimmer, C., Forstl, H., Bauml, J., Wohlschlager, A.M., Sorg, C., 2014. Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. Schizophr. Bull. 40 (2), 428–437.

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15 (10), 483–506.

Mikolas, P., Melicher, T., Skoch, A., Matejka, M., Slovakova, A., Bakstein, E., Hajek, T., Spaniel, F., 2016. Connectivity of the anterior insula differentiates participants with first-episode schizophrenia spectrum disorders from controls: a machine-learning study. Psychol. Med. 46 (13), 2695–2704.

Narr, K.L., Toga, A.W., Szeszko, P., Thompson, P.M., Woods, R.P., Robinson, D., Sevy, S., Wang, Y., Schrock, K., Bilder, R.M., 2005. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol. Psychiatry 58 (1), 32–40.

Noble, W.S., 2006. What is a support vector machine? Nat. Biotechnol. 24 (12), 1565–1567.

Ojala, M., Garriga, G.C., 2010. Permutation tests for studying classifier performance. J. Mach. Learn. Res. 11, 1833–1863.

Onitsuka, T., McCarley, R.W., Kuroki, N., Dickey, C.C., Kubicki, M., Demeo, S.S., Frumin, M., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2007. Occipital lobe gray matter volume in male patients with chronic schizophrenia: a quantitative MRI study. Schizophr. Res. 92 (1–3), 197–206.

Palaniyappan, L., Mallikarjun, P., Joseph, V., White, T.P., Liddle, P.F., 2011. Folding of the prefrontal cortex in schizophrenia: regional differences in gyrification. Biol. Psychiatry 69 (10), 974–979.

Palaniyappan, L., Al-Radaideh, A., Mougin, O., Gowland, P., Liddle, P.F., 2013. Combined white matter imaging suggests myelination defects in visual processing regions in schizophrenia. Neuropsychopharmacology 38 (9), 1808–1815.

Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., Jacobson, K., Lyons, M.J., Grant, M.D., Franz, C.E., Xian, H., Tsuang, M., Fischl, B., Seidman, L., Dale, A., Kremen, W.S., 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cereb. Cortex 19 (11), 2728–2735.

Pereira, F., Mitchell, T., Botvinick, M., 2009. Machine learning classifiers and fMRI: a tutorial overview. NeuroImage 45 (1 Suppl), S199–209.

Peruzzo, D., Castellani, U., Perlini, C., Bellani, M., Marinelli, V., Rambaldelli, G., Lasalvia, A., Tosato, S., De Santi, K., Murino, V., Ruggeri, M., Brambilla, P., 2015. Classification of first-episode psychosis: a multi-modal multi-feature approach integrating structural and diffusion imaging. J. Neural Transm. 122 (6), 897–905.

Pohl, K.M., Sabuncu, M.R., 2009. A unified framework for MR based disease classification. Information Processing in Medical Imaging: Proceedings of the … Conference, pp. 300–313 (21(1011–2499 (Print)).

Rakic, P., 1988. Defects of neuronal migration and the pathogenesis of cortical malformations. Prog. Brain Res. 73, 15–37 (0079-6123 (Print)).

Reis Marques, T., Taylor, H., Chaddock, C., Dell'acqua, F., Handley, R., Reinders, A.A., Mondelli, V., Bonaccorso, S., Diforti, M., Simmons, A., David, A.S., Murray, R.M., Pariante, C.M., Kapur, S., Dazzan, P., 2014. White matter integrity as a predictor of response to treatment in first episode psychosis. Brain 137 (Pt 1), 172–182.

Ren, W., Lui, S., Deng, W., Li, F., Li, M., Huang, X., Wang, Y., Li, T., Sweeney, J.A., Gong, Q., 2013. Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. Am. J. Psychiatry 170 (11), 1308–1316.

Shenton, M.E., Whitford, T.J., Kubicki, M., 2010. Structural neuroimaging in schizophrenia: from methods to insights to treatments. Dialogues Clin. Neurosci. 12 (3), 317–332.

Squarcina, L., Perlini, C., Peruzzo, D., Castellani, U., Marinelli, V., Bellani, M., Rambaldelli, G., Lasalvia, A., Tosato, S., De Santi, K., Spagnolli, F., Cerini, R., Ruggeri, M., Brambilla, P.,

2015. The use of dynamic susceptibility contrast (DSC) MRI to automatically classify patients with first episode psychosis. Schizophr. Res. 165 (1), 38–44.

Squarcina, L., Castellani, U., Bellani, M., Perlini, C., Lasalvia, A., Dusi, N., Bonetto, C., Cristofalo, D., Tosato, S., Rambaldelli, G., Alessandrini, F., Zoccatelli, G., Pozzi-Mucelli, R., Lamonaca, D., Ceccato, E., Pileggi, F., Mazzi, F., Santonastaso, P., Ruggeri, M., Brambilla, P., 2017. Classification of first-episode psychosis in a large cohort of patients using support vector machine and multiple kernel learning techniques. NeuroImage 145 (Pt B), 238–245.

Torrey, E.F., 2007. Schizophrenia and the inferior parietal lobule. Schizophr. Res. 97 (1–3), 215–225.

White, T.P., Joseph, V., Francis, S.T., Liddle, P.F., 2010. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. Schizophr. Res. 123 (2–3), 105–115.

Xiao, Y., Lui, S., Deng, W., Yao, L., Zhang, W., Li, S., Wu, M., Xie, T., He, Y., Huang, X., Hu, J., Bi, F., Li, T., Gong, Q., 2015. Altered cortical thickness related to clinical severity but not the untreated disease duration in schizophrenia. Schizophr. Bull. 41 (1), 201–210.

Yang, H., Liu, J., Sui, J., Pearlson, G., Calhoun, V.D., 2010. A hybrid machine learning method for fusing fMRI and genetic data: combining both improves classification of schizophrenia. Front. Hum. Neurosci. 4, 192.

Yue, Y., Kong, L., Wang, J., Li, C., Tan, L., Su, H., Xu, Y., 2016. Regional abnormality of grey matter in schizophrenia: effect from the illness or treatment? PLoS One 11 (1), e0147204.

Zarogianni, E., Moorhead, T.W., Lawrie, S.M., 2013. Towards the identification of imaging biomarkers in schizophrenia, using multivariate pattern classification at a single-subject level. NeuroImage 3, 279–289.