Identification of texture MRI brain abnormalities on first-episode psychosis and clinical high-risk patients using explainable artificial intelligence

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Abstract

Structural MRI studies in first-episode psychosis and the clinical high-risk state have consistently shown volumetric abnormalities. Aim of the present study was to introduce radiomics texture features in identification of psychosis. Radiomics texture features describe the interrelationship between voxel intensities across multiple spatial scales capturing the hidden information of underlying disease dynamics in addition to volumetric changes. Structural MR images were acquired from 77 first-episode psychosis (FEP) patients, 58 clinical high-risk patients with no later transition to psychosis (CHR_NT), 15 clinical high-risk patients with later transition (CHR_T) and 44 healthy controls (HC). Radiomics texture features were extracted from non-segmented images, and two classification schemas were performed for the identification of FEP vs. HC and FEP vs. CHR_NT. The group of CHR_T was used as external validation in both schemas. The classification of a subject's clinical status was predicted by importing separately a) the difference of entropy feature map and b) the contrast feature map, resulting in classification accuracy above 72% in both analyses. The proposed framework enhances the classification decision for FEP, CHR_NT and HC subjects, verifies diagnosis-relevant features and may potentially contribute to identification of structural biomarkers for psychosis, beyond and above volumetric brain changes.

1. Introduction

Structural brain abnormalities have been associated with schizophrenia and volume deficits progress across the trajectory of the illness¹⁻³. These changes have been observed in early stages of psychosis as in first-episode psychosis patients (FEP)⁴⁻⁶, have a wide distribution, affecting frontal, temporal, parietal cortical regions, but also subcortical, cerebellar and callosal regions⁷⁻⁹, and have a progressive course¹⁰. Several studies have identified similar volumetric disturbances in populations at high risk for psychosis^{11,12}.

Psychosis risk definitions based on clinical criteria (clinical high risk, CHR) have low specificity for prediction of a future transition to overt psychosis, with only about a quarter of patients developing a psychotic episode 3 years after diagnosis^{13,14}. Consequently, there has been major interest in brain structural changes as biomarkers useful for predicting the future emergence of psychosis in CHR with higher accuracy than clinical criteria alone. Several studies and meta-analyses that investigated grey and white matter alterations in CHR have confirmed their potential as predictive indices, identifying a number of differences between CHR with later transition compared to those without with respect to total grey matter volume^{15,16}, specific regions such as the anterior cingulate^{17,18}, frontal cortex^{19,20}, temporal cortex²¹, parietal cortex²², cerebellum²³, and insular cortex²⁴, but also white matter volume and structure²⁵⁻²⁷.

The majority of the above studies have focused on regional volume or intensity measures and have not fully exploited the rich information contained in brain MRI, e.g. subtle differences between brain tissues or

in the microstructure of the biological tissue²⁸, complex interrelations between different regions or grey, white matter and CSF²⁹. Radiomics texture features are able to quantify the hidden patterns between voxel intensities and the spatial distribution of these patterns across brain regions. Radiomics texture features with their potential as image-based biomarkers have been widely used across several studies, like for cancer identification³⁰, Alzheimer's³¹ and Parkinson's disease³² as neurodegenerative diseases, major depression³³ and schizophrenia^{34,35}. In the field of schizophrenia research, texture features such as homogeneity and entropy have been shown to differentiate patients from healthy controls (HC)³⁶. The main advantage of applying radiomics texture features is their potential to capture microscopic alterations in tissue characteristics of the brain³⁷, even though authors have stressed the significance of repeatability and reproducibility in applying texture radiomics features^{38,39}.

In the current study, we applied radiomics texture features on FEP and CHR brain images for the first time. We examined potential differences between FEP, CHR with later transition to psychosis (CHR_T), CHR with no transition to psychosis (CHR_NT), and HC, by employing six texture feature maps extracted from non-segmented MR images and feeding into a deep neural network binary classification schema. For classification, we employed an innovative approach that addresses a frequent concern about artificial intelligence methods, i.e. the explainability of results. Our proposed algorithm integrates the complexity of the deep neural networks with the explainability of these networks as introduced by Bach et al.⁴⁰. The algorithm, which is applied on non-segmented brain MRI for the investigation of the inter-relation between white matter (WM), GM and cerebrospinal fluid (CSF) has been previously reported for the identification of schizophrenia and major depression in Korda et al.⁴¹. Based on previous findings^{42,43}, we hypothesize that radiomics texture feature models (a) discriminate FEP patients from healthy controls and CHR patients without a later transition to psychosis, and (b) predict later transition in CHR patients based on the FEP pattern.

2. Methods

2.1. Study participants

The current analyses are based on data from the early detection of psychosis project (FePsy) at the Department of Psychiatry, University of Basel, Switzerland⁴⁴. FEP, CHR patients with (CHR-T) and without later transition to psychosis (CHR-NT) and healthy controls (HC) were recruited from November 2008 to April 2014. The Basel Screening Instrument for Psychosis (BSIP) was used for assessment of CHR and FEP status. The BSIP is a 46-item instrument based on variables that have been shown to be risk factors for early symptoms of psychosis such as DSM-III-R – “prodromal symptoms,” social decline, drug abuse, previous psychiatric disorders, or genetic liability for psychosis⁴⁵. CHR status was defined based on the presence of either attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or having a first- or second-degree relative with a psychotic disorder plus at least 2 additional risk factors for psychosis. FEP status was defined according to criteria for transition to psychosis by Yung et al.⁴⁶.

Structural MRI scans of 194 subjects were used for analysis: 77 FEP, 58 CHR_NT, 15 CHR_T and 44 HC. Subjects were scanned using a SIEMENS (Erlangen, Germany) MAGNETOM VISION 1.5T scanner at the University Hospital, Basel. A three-dimensional volumetric spoiled gradient recalled echo sequence generated 176 contiguous, 1-mm-thick sagittal slices. Imaging parameters were time-to-echo, 4ms; time-to-repetition, 9.7ms; flip angle, 12°; matrix size, 200 × 256; field of view, 25.6 × 25.6cm matrix; voxel dimensions, 1.28 × 1 × 1mm. Inclusion and exclusion criteria are described in detail in ⁴.

2.2. MRI data acquisition and data preprocessing

After inspection for artifacts and gross abnormalities, MRI scans were segmented into GM, WM, and CSF tissue maps in native space by means of the Cat12toolbox (<http://dbm.neuro.uni-jena.de>), an extension of the SPM12 software package (Wellcome Department of Cognitive Neurology, London, England). All scans were reviewed by a neuroradiologist to rule out clinically significant abnormalities. The process was automated and has been described in Koutsouleris et al. ⁴⁷ and Koutsouleris et al. ⁴⁸. Computation time of the preprocess was less than 30 minutes per subject.

It is critical to keep potential variances in image pose variance entering texture feature maps calculations to a minimum as these have been noted to affect texture estimates. In detail, the CAT12 toolbox extends the unified segmentation model consisting of MRI field intensity inhomogeneity correction, spatial normalization and tissue segmentation in several preprocessing steps to further improve the quality of data preprocessing. Initially, the Optimized Blockwise Nonlocal-Means filter proposed by Coupe et al. ⁴⁹ was applied to the MRI scans using the Rician noise adaption introduced in Wiest-Daesslé et al. ⁵⁰ to increase the signal-to-noise ratio in the data. Subsequently, an adaptive maximum a posteriori segmentation approach ⁵¹ extended by partial volume estimation ⁵² was employed to separate the MRI scans into GM, WM, CSF tissue. The segmentation step was finished by applying a spatial constraint to the segmented tissue probability maps based on a hidden Markov Random Field model ⁵³ that removed isolated voxels which were unlikely to be a member of a certain tissue class and closed gaps in clusters of connected voxels of a certain class, resulting in a higher signal-to-noise ratio of the final tissue probability maps. The original voxels are projected into their new location in the warped images preserving the volume of a particular tissue within a voxel (i.e., produced by affine transformation (global scaling) and non-linear warping (local volume change), but this has the effect of introducing aliasing artifacts ⁵⁴. This latter effect was eliminated by applying discretization of the intensities in the mwp0* images, which is similar to applying a smoothing filter on the data distribution ⁵⁵.

We use histogram equalization to adjust the contrast of a grayscale image. The original image has low contrast, with most pixel values in the middle of the intensity range. The *histeq* function in Matlab produces an output image with pixel values evenly distributed throughout the range (Fig. 1 in Supplement). In Fig. 1, the difference in the intensity between the initial and the transformed image is presented. The texture feature maps were extracted from the transformed mwp0* image (see Fig. 2 for workflow).

2.3. Texture Feature Map

2.3.1 Adjust Intensity Values Using Histogram Equalization

We extracted textural parameters from non-segmented images using grey-level co-occurrence matrix (GLCM) ($N = 1,164$ feature maps in total). We extracted the texture features Entropy, Sum of Entropy, Difference of Entropy, Energy, Contrast, Homogeneity⁵⁶. The definitions of these features were as follows: GLCM-contrast reflects local variations in the GLCM; GLCM-energy reflects uniformity of grey-level voxel pairs; GLCM-entropy reflects randomness of grey-level voxel pairs; and GLCM-homogeneity reflects homogeneity of grey-level voxel pairs^{57,58}; finally GLCM-sum of entropy and difference of entropy reflect second order statistics of differentiation of grey level distribution GLCM. We used voxel-by-voxel sliding 3D cube of $7 \times 7 \times 7$ dimension as presented in a previous paper³³. The GLCM matrix was normalized by dividing the values with the total sum of the values in the matrix. The normalization was performed for each GLCM extracted in each 3D cube independently.

All the feature maps calculated from the 2d GLCM were basically a function of the probability of each GLCM entry and the difference of the grey levels, g_1 and g_2 ⁵⁹. We calculated feature maps only for cubes including non-zero values, as presented in **Appendix A**. The registered texture feature maps on the MNI space were fed into a 10×10 nested cross-validation deep learning scheme for group classification (see Fig. 2 in Supplement).

We focus the description of results on the difference of entropy feature, which measures the randomness of intensity distribution in a second level, inherits the characteristics of entropy, and typically is less sensitive to outliers in a region²⁸. The contrast gives to elements with similar grey level values a low weight but elements with dissimilar grey levels a high weight, indicating large differences between neighboring voxels⁶⁰.

2.4. Deep learning

The deep learning technique utilized the registered radiomics texture feature maps as input. We implemented two cycles of 10-times repeated nested cross-validation with 10 folds in the inner cycle and 10 folds in the outer cycle, resulting in 10'000 models. Feature selection (two-sample t-test) in the inner cycle, was cross-validated by selecting a number of features appropriate to the dimension of the database, namely, the top 200 ranked features that best discriminated the 2 classes in each classification schema (see section 3.2)⁶¹. The classifier implemented was a neural network-based classifier implemented in MATLAB (MathWorks Inc., Natick, Massachusetts, USA). The network used the hyperbolic tangent sigmoid transfer function and was batch-trained using the Levenberg-Marquardt training algorithm⁶². L2-regularization was applied to access possible types of uncertainty. We selected parameters after experimentation; 5 hidden layers (tested 2 to 5), each hidden layer consists of 2 nodes (tested 2 to 20) and 1,000 epochs. The average accuracy, sensitivity and specificity was calculated across all hold-out datasets of the 10×10 nested cross-validation, repeated 10 times.

2.5. Visualization and evaluation of heatmaps

In order to perform localization, we calculated the relevance of the voxels in each class using the LRP algorithm for multilayer neural networks, as described in Bach et al.⁴⁰. The explanation given by LRP would be a map showing which voxels of the original texture feature map contribute to the diagnosis and to what extent.

For the specific deep learning schema with 5 hidden layers and size 2, the calculation of the LRP algorithm is presented in **Appendix B**. The output of the LRP algorithm is a heatmap for each subject representing change in brain structures for FEP, CHR_NT and CHR_T patients. The final images were smoothed with a Gaussian filter of 10mm and visualized using the MRICron toolbox (<https://people.cas.sc.edu/rorden/mricron/install.html>). Similarities of the heatmaps for subjects in the same group were identified by clustering the heatmaps. Evaluation of the clustered heatmaps gives an estimation to the importance of each brain region to the diagnostic group membership (Figs. 3–5). Visualizations of the classification results on the holdout dataset are presented in Figs. 3–5. The regions of interest were extracted using the AAL-VOIs atlas (<https://neurovault.org/images/14257/>). Additionally, we investigated cortical biomarkers for psychosis in GM, WM and CSF. We used the JHU WM tractography atlas⁶³ to identify the WM tractography identified by the LRP.

2.6. Clustering of Subjects

Our intention was display the heatmap of each correctly classified subject in the hold-out testing set produced by the LRP algorithm in a grouped fashion⁶⁴. The affinity propagation (AP) algorithm⁶⁵ was selected to cluster the subject's positive relevance, which uses the concept of message passing between the samples. The main advantage of the AP algorithm is that the number of clusters is not predefined. The input in the clustering algorithm is a matrix $M \times N$, where N is the number of subjects and M is the relevance of each voxel. The output of the AP algorithm is a scalar for every subject that expresses in which cluster the subject belongs to. The average of the heatmaps from the subjects belonging to each cluster are represented.

For each classification process, the relevancies were classified using the AP algorithm. The clusters are presented in Fig. 3–5 for each texture feature map under the two-classification schema. The red color corresponds to the most intense cluster, the second one is in blue color and the green is the third one, where it exists (see Fig. 3–5).

3. Results

3.1. Sociodemographic characteristics

There were no significant differences between FEP and HC with respect to age and alcohol consumption. For the comparison between FEP and CHR, there were no significant differences with respect to age, years

of education, smoking, alcohol consumption and gender. There were significant differences between FEP and CHR with respect to BPRS total, BPRS Negative and Positives Symptoms and SANS total (see Table 1).

Table 1

Group comparison using 1-way ANOVA for continuous and χ^2 test for categorical data.

One-Way ANOVA (Welch's)		
FEP vs HC	F	p
Age	1.63	0.204
Education (Years)	19.26	< .001
Smoking (Cigarettes per Day)	28.18	< .001
FEP vs CHR		
Age	3.118	0.056
Education (Years)	0.165	0.849
Global Assessment of Functioning (GAF)	46.875	< .001
BPRS_Positive_Symptoms	19.498	< .001
BPRS_Negative_Symptoms	22.494	< .001
BPRS_total	462.930	< .001
SANS_total	128.957	< .001
Smoking (Cigarettes per Day)	2.418	0.102
χ^2 Tests		
FEP vs HC		
Sex	13.6	< .001
Alcohol	9.60	0.008
FEP vs CHR		
Sex	0.431	0.511
Alcohol	2.80	0.246
Note: BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; SANS, Scale for the Assessment of Negative Symptoms		

3.2. Classification results and visualization

Two classifiers were developed in this study: a) FEP vs. HC and b) FEP vs. CHR_NT. The average accuracy, sensitivity and specificity in the outer cycle were calculated for 10 folds in 10 repetitions. We tested the texture feature maps one-by-one in the deep learning classifier (see Tables 2–3). The specificity for FEP compared to HC (classifier a) was above 75% across features (Tables 2 and 3). The sensitivity in the classification schema b was above 70% across features, indicating adequately correct classification of FEP against CHR_NT.

Table 2
presents the accuracy, sensitivity and specificity of the hold-out testing set in schema a.

Registered texture feature map	Accuracy (%)	Sensitivity (%)	Specificity (%)
Entropy	66.55	56.93	75.08
Sum of entropy	72.02	68.22	81.92
Difference of entropy	74.56	69.58	88.02
Contrast	75.24	76.48	83.63
Homogeneity	70.43	63.87	77.23
Energy	70.29	60.71	80.08

Table 3
presents accuracy, sensitivity and specificity the hold-out testing set in schema b.

Registered texture feature map	Accuracy (%)	Sensitivity (%)	Specificity (%)
Entropy	64.52	70.01	62.90
Sum of entropy	68.48	71.49	73.20
Difference of entropy	72.01	79.29	71.00
Contrast	73.21	78.95	71.92
Homogeneity	70.52	78.59	68.06
Energy	70.24	75.59	72.30

In external validation using CHR-T, the most discriminative features were the difference of entropy and contrast resulting in an accuracy above 72%; these features are presented in further detail for the interpretation of the results below; for completeness, analysis of the remaining texture features is presented in Supplement. Applying the classification schema a, the feature difference of entropy classified 10 out of 15 CHR_T as FEP, while with the classification schema b, the feature difference of entropy classified 11 out of 15 CHR_T as FEP patients.

3.3. Clustering of subjects

Across texture feature maps, regions with the highest contribution to the difference between FEP and HC (i.e. those with highest positive relevance PR) were in cerebellum and frontal gyrus (contrast), lenticular fasciculus (difference of entropy), see Fig. 3. In addition, regions most contributing to the difference between FEP and CHR_NT patients were in parahippocampal, amygdala, precuneus, caudate, putamen, thalamus, hippocampus, insula, cerebellum, vermis, pallidum lingual and motor area (difference of entropy and contrast), see Fig. 4. By explaining the classification decision using the LRP algorithm for the four models performed using the difference of entropy map and contrast map in classification schemas a and b, the cerebellum was observed to be the key region for psychosis. Furthermore, key regions for psychosis were observed that are in line with previous studies, e.g., amygdala, caudate, insula, and hippocampus.

Regions contributing most to the CHR_T classification as FEP using the difference of entropy texture feature map (Fig. 5) were in parahippocampal areas, amygdala, precuneus, caudate, putamen, thalamus, hippocampus, insula, cerebellum, vermis, pallidum, lingual and motor area. Furthermore, for the classification schema a, two clusters of regions could be identified using the difference of entropy map. Cluster 1 included brain regions that were not part of the cluster 2 (Table 4), indicating a distinct neurobiological profile for subjects grouped in cluster 1.

Table 4
presents the regions revealed in one cluster in
schema a grouped fashion visualization.

FEP vs HC	
Difference of entropy map	
Anterior corona radiata left	Cluster 1
Insular left	Cluster 1
Lateral fronto-orbital gyrus left	Cluster 1
Middle fronto-orbital gyrus left	Cluster 1
Gyrus rectus left	Cluster 1
Appendices	
Appendix A	

We identified no consistent correlations of the PR with the volume of the regions indicated by the LRP when analyzed in the hold-out datasets that concluded to the highest accuracy. The PR was negatively correlated with the volume of the regions indicated by the LRP for FEP subjects in classification schema a) (Fig. 6 in Supplement), such as optic tract left, corticospinal tract right, hypothalamus right (difference of entropy). Volumetric changes of regions such as calcarine left, fusiform right and cuneus left (contrast) were correlated positively with PR. In classification schema b) (Fig. 7 in Supplement), the PR for the FEP subjects was positively correlated with temporal and vermis (difference of entropy), frontal

and precentral left (contrast) and uncorrelated with insula left, parahippocampal left, caudate left, calcarine left, Heschl left, cuneus left, putamen and thalamus left, lingual right (difference of entropy), frontal, temporal and parietal cortex and supplementary motor area left (contrast). PR was uncorrelated with volumetric changes across CHR_NT that classified correctly against FEP such as thalamus, insula, putamen, hippocampus and parahippocampal, caudate and amygdala (difference of entropy). CHR patients who made a transition to psychosis and were classified as FEP with high accuracy using the difference of entropy map in classification schema b), presented uncorrelated volumetric changes with PR in many regions, i.e., thalamus, amygdala left, putamen, insula and others shown in **Fig. 8** in Supplement. These regions were the dominant regions for the prediction of psychosis based on baseline MRI.

For classification schema a) (Fig. 3) LRP revealed PR in regions such as anterior corona radiata and genu of CC (contrast), posterior limb of internal capsule right, superior corona radiata right, superior fronto occipital fasciculus (difference of entropy). Regions such as cerebral peduncle right, posterior limb of internal capsule right and external capsule right (difference of entropy), body of CC, superior corona radiata right and superior longitudinal fasciculus right (contrast) contribute more to the identification of the FEP subjects in classification schema b) (Fig. 4) and the CHR_T patients that classified as FEP subjects (Fig. 5). Across classification schemas, the WM volumetric changes did not impact the values of the PR indicating that texture features capture the dynamic inter-relation between GM, WM and CSF with predictive power for psychosis. Changes in the CSF captured by the difference of entropy for the FEP against CHR_NT (Fig. 4) and CHR_T classified as FEP (Fig. 5).

4. Discussion

In this study, we used radiomic texture feature maps and the explainable AI method suggested by Bach et al.⁴⁰ to train and explain a classifier for psychosis. The model showed high accuracy in classifying CHR patients with a later transition as FEP rather than healthy subjects, thus indicating a potential use for predictive purposes. Importantly, texture features were not correlated with volumetric changes in a consistent manner, suggesting that this measure can reveal hidden neuro-biological patterns expanding beyond volumetric changes of single regions to include the interrelations and borders between GM, WM and CSF.

Our findings are in line with a previous study applying texture analysis on MR data in patients with schizophrenia, which reported altered entropy in the hippocampus and the amygdala³⁶. The regions contributing mostly to the decision of our classifier included key regions implicated in psychotic disorders in studies that have assessed grey and white matter changes in patients.

- *Grey matter.* Brain alterations with a decrease of intracranial and total brain volume have been reported in patients with chronic schizophrenia⁶⁶, particularly affecting cortical gray matter (and here predominantly in the prefrontal cortex (PFC))⁶⁷. Some of these changes such as volume decrease in the thalamus have been also observed in FEP⁶⁸, which emphasizes the presence of

brain alterations already in early stages of the disease. These alterations might be pertinent to the transition to psychosis in CHR patients: For example, CHR-T showed more deterioration over time in frontal and temporal regions than CHR_NT in early studies ^{69,70}. In other regions such as the insular or cingulate cortex, grey matter loss in CHR-T has also been reported to exceed that of CHR_NT ⁷¹. The structural alterations reported in previous studies are in line with the identified regions in the current analysis, such as temporal regions ⁷²; frontal cortex ^{73–75}; thalamus ⁶⁸; insula ⁷⁶; hippocampus and caudate nucleus ^{77,78}; pallidum, putamen ⁷⁹; parahippocampus ^{79,80}; and lingual cortex ⁸¹.

- *White matter.* There is accumulating evidence of compromised white matter function leading to abnormalities in synchronization and connectivity in patients with schizophrenia ⁸², the most widely used measure being fractional anisotropy (FA) assessed with diffusion tensor imaging (DTI). Neural changes, especially changes in the white matter connectivity could be observed throughout the different stages and progress of psychosis ⁸³. There are consistent findings of decreased FA, particularly in the inferior-fronto-occipital fasciculus (IFOF) ^{84,85}. Other studies have reported reduced white matter volume ⁸⁶ and decreased FA in superior longitudinal fasciculus (SLF) ⁸⁷ as well as in inferior fronto-orbital fasciculus (IFOF) ^{88–90}, in CHR compared to FEP.

Multiple texture maps reveal significant contribution in diagnostic group membership for FA and IFOF, for both FEP and CHR_NT who classified as FEP. The above findings are in line with our results regarding the superior longitudinal fasciculus and inferior fronto-orbital fasciculus using contrast maps, and the thalamus, insula, hippocampus, pallidus, putamen and parahippocampus using the difference of entropy maps. To exclude the possibility that our findings simply reflect volume reductions in these regions, we investigated whether regions contributing most to the diagnostic group membership (i.e. regions with PR values) were correlated with changes in brain volume in individuals with FEP and CHR (see **Fig. 6–8** in Supplement. We found no indication of correlation of the relevance of the regions in the diagnostic group membership with volumetric changes in specific areas, i.e. amygdala, putamen, thalamus, hippocampus, insula, pallidus, rectus, parahippocampus, lingula and Heschl.

The localization of alterations appeared to differ between patients in different illness stages using the difference of entropy map: whereas most prominent alterations in FEP involved the cingulate gyrus and subcortical regions such as the nigrostriatal circuit, amygdala and hypothalamus (Fig. 3a), CHR with later transition to psychosis demonstrated alterations mainly in cortical regions, the thalamus, and cerebellum (Fig. 4a). Both grey matter and white matter loss in specific brain regions were more prominent in CHR with transition to psychosis (CHR_T) compared to CHR who did make the transition. These brain alterations considered of high clinical relevance, resulting in - for example - more severe positive and negative symptoms and worse social functioning ^{87,91}.

Regarding implementation, the variability in standardization of MRI intensities influences the extraction of the texture features. In this study, the radiomic texture feature maps were extracted from the registered masked T1-weighted image in MNI space (as opposed to the original space as in Korda et al. ⁴¹.

Parameter selections such as the radius of the cubes and the structure of the neural network should be further examined. Regarding the LRP explanations, difference of entropy was the dominant texture feature map for psychosis. However, we recommend that further studies use multiple texture features, as each one expresses a different dynamic of brain heterogeneity. In summary, different methodological options need to be further explored in order to get a better understanding of the neurobiological changes in psychosis and their course from the CHR to the FEP stage, in order to make findings relevant for targeted interventions and individual treatment options. To investigate whether different neuroimaging modalities can be combined and used for increased accurate prediction, further work is required and should be addressed in future studies.

Another unresolved question concerns the effects of antipsychotic medication³. Several studies have shown that antipsychotic medication has an impact on alterations in WM disturbances between treated patients, drug-naïve patients and healthy controls^{92,93}, while smaller brain tissue volumes and larger cerebrospinal fluid volumes can be observed in long-term treatment with antipsychotics⁹⁴. It is still unclear whether brain abnormalities are already present at early stages and probably predicting the clinical onset of schizophrenia, or if these changes occur during the course of illness or are caused by pharmacological treatment⁹⁵. It is crucial that the nature, time occurrence and further course of such brain changes as well as the impact of antipsychotic treatment is further investigated.

5. Conclusions

Conventional imaging parameters are inadequate for quantification of the spatial distribution of microscopic tissue heterogeneity. A promising alternative to improve the diagnosis of psychosis on the basis of neurobiology is the application of radiomics texture features. We investigated the relation between neurobiological markers and LRP explanations. We observed that texture feature maps can be a useful representation for characterizing dissimilarities in brain structure in a complementary manner to volumetric analysis. Further studies in large cohorts are warranted to establish the key regions and key texture features that characterize psychotic disorders, in order to improve our understanding of the neurobiological changes that occur before the onset of psychosis and promote research on prevention and treatment methods for CHR patients.

Declarations

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Conflict of interest The authors declare no conflict of interest.

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Figures

Figure 1

Representation of the brain MRI in SPM12 for the a) initial MR image and b) transformed MR image using the histogram equalization.

Figure 2

Workflow for the calculation of the texture feature maps.

Figure 3

We demonstrated the PR of the correct classified subjects of each group against the other in classification schema a), FEP vs. HC for the registered texture feature map: a) difference of entropy and b) contrast. The red (cluster 1), blue (cluster 2) and green (cluster 3) color corresponds to the sorted clusters according to the number of subjects belong to each cluster.

Figure 4

We demonstrated the PR of the correct classified subjects of each group against the other in classification schema b), FEP vs. CHR_NT for the registered texture feature map: a) difference of entropy and b) contrast. The red (cluster 1), blue (cluster 2) and green (cluster 3) color corresponds to the sorted clusters according to the number of subjects belong to each cluster.

Figure 5

Classification of CHR_T as FEP using the difference of entropy in classification schema b). The red (cluster 1) and blue (cluster 2) color corresponds to the sorted clusters according to the number of subjects.

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