# Deep learning model using retinal vascular images for classifying schizophrenia

Schizophrenia Research 241 (2022) 238–243

Contents lists available at ScienceDirect

Schizophrenia Research

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

# Deep learning model using retinal vascular images for classifying schizophrenia

Abhishek Appaji [a], Vaishak Harish [a], Vittal Korann [b], Priyanka Devi [b], Arpitha Jacob [b], Anantha Padmanabha [a], Vijay Kumar [b], Shivarama Varambally [b], Ganesan Venkatasubramanian [b], Shyam Vasudeva Rao [c], H.N. Suma [a], Caroll A.B. Webers [c], Tos T.J.M. Berendschot [c], Naren P. Rao [b,*]

[a] Department of Medical Electronics Engineering, B.M.S. College of Engineering, Bangalore, India
[b] National Institute of Mental Health and Neurosciences, Bangalore, India
[c] University Eye Clinic Maastricht, Maastricht University, Maastricht, the Netherlands

ARTICLE INFO

*Keywords:*
Psychosis
Retina
Fundus
Biomarker
Artificial intelligence

ABSTRACT

Contemporary psychiatric diagnosis still relies on the subjective symptom report of the patient during a clinical interview by a psychiatrist. Given the significant variability in personal reporting and differences in the skill set of psychiatrists, it is desirable to have objective diagnostic markers that could help clinicians differentiate patients from healthy individuals. A few recent studies have reported retinal vascular abnormalities in patients with schizophrenia (SCZ) using retinal fundus images. The goal of this study was to use a trained convolution neural network (CNN) deep learning algorithm to detect SCZ using retinal fundus images. A total of 327 subjects [139 patients with Schizophrenia (SCZ) and 188 Healthy volunteers (HV)] were recruited, and retinal images were acquired using a fundus camera. The images were preprocessed and fed to a convolution neural network for the classification. The model performance was evaluated using the area under the receiver operating characteristic curve (AUC). The CNN achieved an accuracy of 95% for classifying SCZ and HV with an AUC of 0.98. Findings from the current study suggest the potential utility of deep learning to classify patients with SCZ and assist clinicians in clinical settings. Future studies need to examine the utility of the deep learning model with retinal vascular images as biomarkers in schizophrenia with larger sample sizes.

## 1. Introduction

Contemporary psychiatric diagnosis still relies on the subjective symptom report of the patient during a clinical interview by a psychiatrist. Given the significant variability of personal reporting and differences in the skill set of psychiatrists, the inter-rater reliability of psychiatry diagnosis is poor (Ditton-Phare et al., 2017; Medina et al., 2019; Santelmann et al., 2016). Hence, it is desirable to have objective diagnostic markers that could help clinicians differentiate patients from healthy individuals. In addition, biomarkers could also aid in prognostication, selection of patients for treatment trials, and individualized treatment regimens (Kraguljac et al., 2021; Scarr et al., 2015). Similar attempts have been successful and are of considerable clinical utility in other branches of medicine (Jackson and Chester, 2015). Unfortunately, such a biomarker is still an unmet need in Psychiatry.

While neuroimaging measures have been explored as candidate biomarkers (Kraguljac et al., 2021), the cost of the procedure, the requirement of specialized equipment, and lack of portability prevent their application in community settings. Due to the shared embryological origin and similar physiological properties, the retina is considered a window to the brain and proposed as a biomarker in neuropsychiatric conditions, including schizophrenia (Hosak et al., 2018; Silverstein et al., 2020). Several studies have reported the predictive utility of retinal vascular measures in cardiovascular conditions, stroke, and neurodegenerative conditions such as dementia (Dumitrascu et al., 2018; Ge et al., 2021; Li et al., 2016). In contemporary psychiatry practice, a trained psychiatrist clinically interviews the patient and arrives at a diagnosis of schizophrenia. Diagnosing schizophrenia in community settings is difficult in the absence of a trained psychiatrist leads to delay in the initiation of treatment. As early diagnosis and

* Corresponding author at: Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India.
*E-mail address:* docnaren@gmail.com (N.P. Rao).

https://doi.org/10.1016/j.schres.2022.01.058
Received 19 August 2021; Received in revised form 25 January 2022; Accepted 29 January 2022
Available online 14 February 2022

prompt initiation of treatment is an important predictor of better prognosis (Cechnicki et al., 2014), biomarker that could aid the clinician in the diagnosis are need of the hour. Given its ease of acquisition, low cost, portability and non-invasiveness, retinal vascular imaging is ideal for application in community settings (Wilson et al., 2008).

Interestingly, a few studies have recently reported abnormalities in the retinal vasculature in schizophrenia. Using fundus camera, studies have reported that schizophrenia patients have increased retinal venular caliber, trajectory, tortuosity, and decreased fractal dimension than healthy individuals (Appaji et al., 2019c, 2019a, 2019b, 2019d; Meier et al., 2013). Recent studies have also suggested a relation between retinal vascular caliber, working memory, and brain structure (Appaji et al., 2020; Korann et al., 2021). One study further claimed that a machine learning approach may be used to distinguish schizophrenia patients from healthy individuals (Appaji et al., 2019d). Recently, a few studies have examined the retinal vasculature using Optical coherence tomography angiography (OCTA). Though differing in the directionality, these studies have reported abnormalities in retinal microvasculature density and enlarged foveal avascular zones (Bannai et al., 2021; Koman-Wierdak et al., 2021; Silverstein et al., 2021).

With advances in computational methods, deep learning analysis is being increasingly utilized for biomarker-based disease diagnosis and prediction in several psychiatric disorders including schizophrenia (Cortes-Briones et al., 2021). Convolution Neural Networks (CNN) are deep-learning models that have been implemented in recent years to improve classification accuracy and better performance than the conventional machine learning methods.

CNN is a widely used model for image classification as it offers several advantages compared to traditional machine learning. In machine learning, the features must be manually extracted and fed to the neural networks for classification. CNNs automatically extract the required features from images and classify them into different groups. CNNs are less theoretically biased than the traditional machine learning approaches as they require minimal or no feature extraction (Esteva et al., 2019). In CNN, it is taught in an end-to-end manner and learns the hierarchy of features automatically, which results in better classification. In each epoch (iteration), the CNN trains a different set of images and tests another set of images. This is advantageous because it increases the optimization of the model. One Epoch is when an entire dataset in multiple batches is passed forward and backward through the neural network (backpropagation). This helps us in the proper tuning of weights which reduces error rates and makes the model reliable. However, the CNN model requires a large number of retinal images to get higher accuracy. Data augmentation techniques are used to increase the sample size for deep learning.

Recently, a few studies have examined the utility of deep learning analysis using retinal images and reported more than 90% accuracy for diabetic retinopathy, retinopathy of prematurity, and optic neuropathy (Gulshan et al., 2016; Hood and de Moraes, 2018; Moraru et al., 2020; Voets et al., 2019). However, to the best of our knowledge, no study has examined deep learning analysis to differentiate schizophrenia patients from healthy individuals using retinal vascular images. Hence, this study aims at filling this gap and investigating the discriminant accuracy of a deep learning model to classify schizophrenia patients and healthy individuals using retinal vascular images.

## 2. Methodology

### 2.1. Subjects

A total of 327 subjects [139 patients with schizophrenia (SCZ) and 188 healthy volunteers (HV)] were recruited. The patients were recruited from the inpatient and outpatient clinical services of the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India. The institute ethics committee approved the study and informed consent was taken from all study participants. The patients with SCZ were in the age range of 18 to 50 years, satisfying the diagnostic criteria of schizophrenia according to the international classification of diseases (ICD-10) (WHO, 1992). 200 of the 327 subjects were also part of our previously published study examining retinal vascular caliber (Appaji et al., 2019b). A qualified psychiatrist interviewed the patients. Subjects with a history of hypertension, diabetes, cerebrovascular accidents, or history of eye trauma were excluded from the study. We also excluded patients with current comorbid axis-I psychiatric conditions including substance abuse or dependence. The HV were recruited using word of mouth and flyers. In addition to the exclusion criteria for SCZ, HV were also excluded if they had a lifetime history of any axis-I psychiatric disorders or a history of psychotic disorder in a first-degree relative. The equipercentile score of the Brief Psychiatric Rating Scale (BPRS) (Leucht et al., 2013; Overall and Gorham, 1962) was used for determining the severity of the positive and negative symptoms in patients with SCZ. The Olanzapine equivalent for antipsychotics was computed using a preestablished technique (Leucht et al., 2015). Clinical Global Impression (CGI) (Guy, 1976)was used to assess the functioning of SCZ.

### 2.2. Retinal image acquisition and processing

Multiple retinal fundus images were acquired for each study participant using a fundus camera (Forus Health Pvt. Ltd., India). The fundus camera is a non-mydriatic camera with a 40-degree field of view. The procedure for the image acquisition was explained to the study participants. After the explanation, they sat in a dimly lit examination room for 5 min for dark adaptation, leading to auto dilation of the pupils. A trained technician acquired an optic disc-centered color fundus image. The chin was rested on the chin rest with the forehead pressed against the machine to accommodate the visibility of the eye and retina. The fundus camera was zoomed through the infrared guide to acquire the images. Multiple images of both eyes were acquired separately by flashing a light-emitting diode to illuminate the fundus, and the image was stored in the computer for further processing (Darwish et al., 2019). The image preprocessing included downsizing (from 2048 × 1536 pixels to 224 × 224 pixels) and pixel value normalization between 0 and 1.

### 2.3. Deep learning network analysis

A deep learning convolution neural network (CNN) model learns a set of features during training and using optimization, error in a classification task is further minimized. The model used in the study (Fig. 1) consisted of seven 2D convolution layers. During each training iteration, an error value is calculated by comparing the network's prediction (predicted category) to the ground truth (real category) and the network's parameters (weights and biases) are progressively modified to reduce the magnitude of the prediction error. For deep learning analysis, the data was divided into a discovery dataset and a confirmatory dataset. A CNN optimized for image classification was trained using retinal images from discovery dataset participants. This dataset contained both left and right eye images of 284 study participants (118 SCZ and 166 HV). As images were acquired multiple times, the dataset cumulatively contained 1200 images from these subjects. The input dimension was 224 × 224.

The discovery dataset was divided into training, validation, and testing subsets. The training set is for adjusting (training) the CNN's parameters, the validation dataset is for adjusting the hyper-parameters and network design (learning rate, number of layers, etc.), and the test set if for assessing the CNN's performance. Both training and validation datasets use labeled data in which the diagnostic status of the subject (HV or SCZ) is known to the model. On the other hand, the test dataset is an independent dataset that is used to assess the performance of the model for unseen, new data. The test dataset consists of the unlabeled data that is, the diagnostic status of the subject is not known to the model. It is important to note that the three subsets are independent and

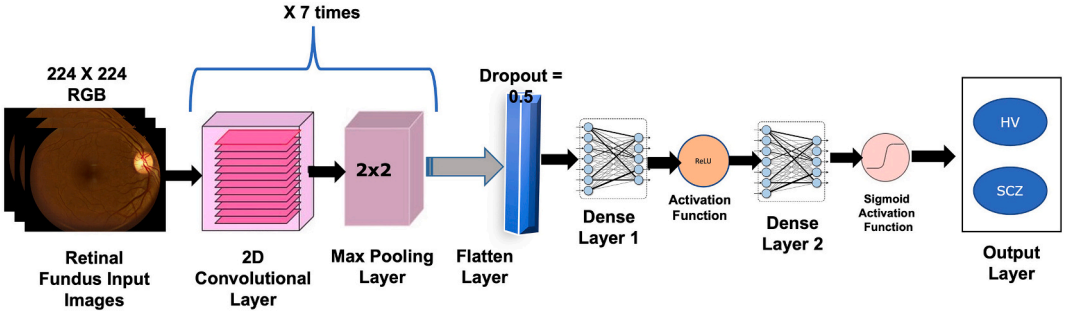


**Fig. 1.** Architecture showing an overview of proposed automated classification using Convolution Neural Network.

mutually exclusive, that is subjects do not overlap between training, validation, and testing subsets. The training subset consisted 70% of the total subjects ($n$ = 198; HV = 82 and SCZ = 116), and the validation subset consisted of 20% of the total subjects ($n$ = 56; HV = 23 and SCZ = 33). The testing subset consisted of the remaining 10% ($n$ = 30; HV = 13 and SCZ = 17). While training, the hyperparameters of the deep neural network were initiated with random images within the 70% training dataset.

The labels for the dataset were encoded using the one-hot technique (Hancock and Khoshgoftaar, 2020). As shown in Fig. 1, the deep learning architecture had 7 two-dimensional (2D) CNN layers, with max-pooling-based downsampling in each convolution layer. This was followed by a flattened layer to convert into a single dimension value with a drop out of 50%. Two dense layers were implemented; one with a rectified linear unit (ReLU) activation function and another with a sigmoid function. These are commonly used activation functions in deep learning models that return 0 if it receives any negative input but returns 1 if it receives positive input. We set the learning rate at 0.001, and the batch size at 32. RGB reordering was applied, and the final input to the proposed model was provided as a 224 × 224 × 3 image. Concerning data augmentation, for the training set, we first tailored the images according to the annotated cropping frame and then adjusted the size to 224 × 224 followed by width-shift-range = 0.1, height-shift-range = 0.1, shear-range = 0.1, zoom-range = 0.2, random horizontal flips, and normalization. For the test set, we adjusted the images that were cropped according to the annotation and then resized them to 224 × 224.

The model was trained with 20 epochs with a batch size of 32. That is, 32 images went to-and-fro through the CNN model in each epoch and the whole process was repeated 20 times. In each epoch, the training, validation, and testing datasets were randomly chosen and were completely independent without any overlap. This process ensured cross-validation of the data. Early stopping criteria were used while monitoring the validation loss to be at minimum with patience as 3 (i.e it checks whether the loss increases for 3 epochs and if it increases the training is terminated). The learning rate was set to 0.00001 and we used reduced LR on Plateau to reduce the learning rate when a metric has stopped improving. We took an average of 20 epochs. The CNN was a sequential model (building layer by layer). As shown in Fig. 1, we had seven 2D Convolution layers. 2 layers had a filter size of 32, 3 layers had a filter size of 64 and the remaining 2 layers had a filter size of 128. The filter size was chosen based on the convergence of the model. For all the layers, the strides were 2 × 2, pool size was 2 × 2, kernel size was 3 × 3, with "same" padding. That is, the layer's outputs had the same spatial dimensions as its inputs. A rectified linear unit activation function was used. We did not use a dilation factor. We used *Adam*, an optimization algorithm for training deep learning models using stochastic gradient descent (Zaheer and Shaziya, 2019). Python 3.7.10 and TensorFlow 2.0, an open-source software library for deep learning, were used to train and evaluate the proposed model. The entire process was conducted on a standard workstation (Alienware with 16GB RAM, 2.60 GHz Intel Core i7 10GEN CPU, NVidia GPU RTX 2060, 6GB VRAM).

The model performance was evaluated for continuous prediction using the area under the receiver operating characteristic curve (AUC). Areas under AUC were used to determine the binary outcomes of normal versus schizophrenia when compared with the expert diagnosis. We evaluated how the performance of the deep learning algorithm changed in distinguishing patients with SCZ and HV using AUC, i.e., the higher the AUC, the higher is the performance. If the area under the AUC and accuracy rate significantly dropped, we could infer that the retinal image information in that area mainly contributed to identifying SCZ.

To determine whether the trained deep learning algorithm could distinguish patients with SCZ from HV in a real-world setting, we used a new data set – the confirmatory dataset. This confirmatory dataset of 43 study participants (22 HV and 21 SCZ) evaluated the individual subject level accuracy of the model and the clinical utility of the deep learning model. The second dataset of these 43 subjects was independent of the first dataset of 284 participants. The confirmatory dataset would give us an idea about the transfer learning potential of the deep learning algorithm to a new dataset.

### 2.4. Statistical analysis of demographic variables

The analyses were performed using Statistical Package for Social Sciences (SPSS) version 26. The normality of the data was established using the Shapiro-Wilk test. Sex distribution across groups was examined using a chi-square test, and the age difference was analyzed using a student $t$-test. To control for the potential confounding effect of age, a subset of age-matched data was analyzed.

## 3. Results

### 3.1. Comparison of demographic variables between the groups

There was a significant difference between the groups in age (HV - 30.3 ± 7.4 years; SCZ - 32.8 ± 6.1 years; $t$ = 3.3; $p < 0.01$) and sex distribution (HV- 96M, 92F; SCZ – 91M, 48F; $\chi^2 = 6.8; p = 0.01$). SCZ patients had a mean age at onset of 24.9 ± 5.6 years with 7.9 ± 5.4 years of illness. The patients were at different stages of illness with a BPRS score of 24.4 ± 9.4. All patients were on treatment with antipsychotics, with a mean olanzapine equivalent dose of 16.2 ± 31.2 mg/day.

### 3.2. Performance of deep learning algorithm

Fig. 2 displays the performance of the deep learning CNN model graphically for various evaluation parameters. The overall accuracy of the deep learning model was found to be 95% for classifying SCZ and HV using retinal fundus images (Fig. 2A & B). The model achieved high performance in the training dataset (AUC of 0.98, Fig. 2C). The model also achieved a high precision of 95.1% (Fig. 2D). The algorithm's sensitivity at the high-sensitivity operating point was 95.9%, and the specificity at the high-specificity operating point was 90%. Below are the overall metrics of the CNN for the discovery dataset; sensitivity –

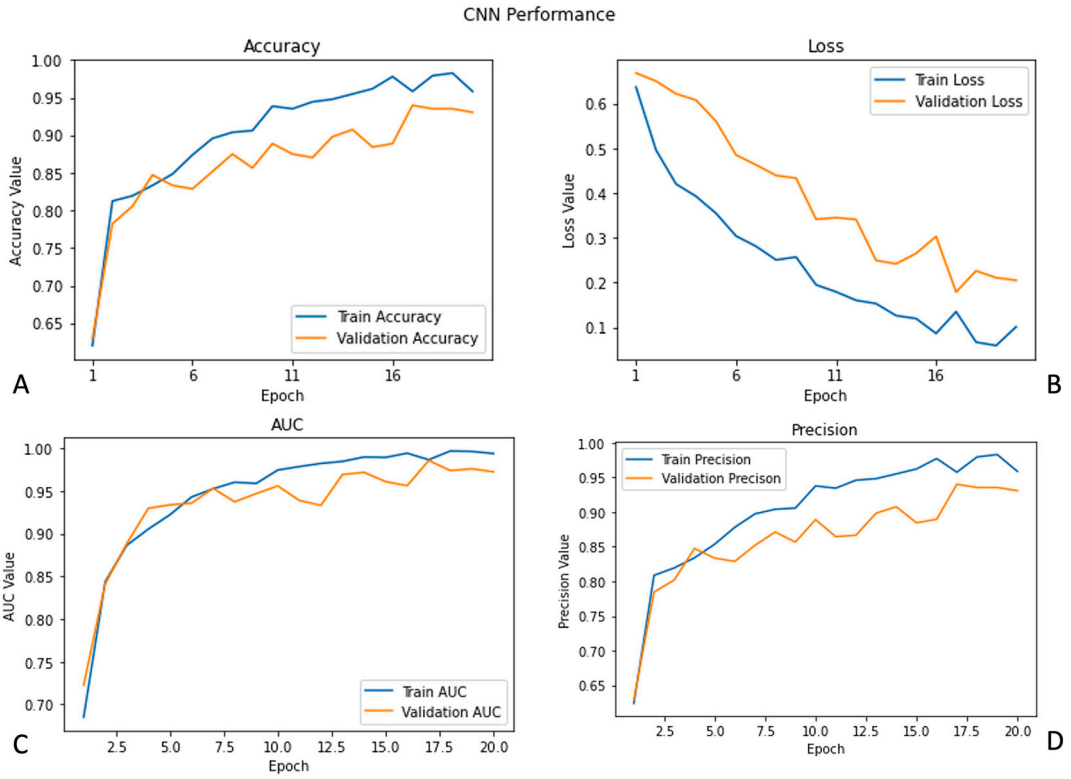


**Fig. 2.** CNN model performance in terms of (A) accuracy (B) loss (C) the area under the receiver operating characteristic curve (AUC) and (D) precision.

91.66%, specificity – 95%; positive predictive value – 94.82% and negative predictive value – 91.93%. The accuracy of the model after data augmentation remained at 93%.

### 3.3. Sub-group analysis

Since age-related differences in retinal vasculature patterns were noted in a previous study (Cífková et al., 2021), we conducted a sub-group analysis to control its potential confounding effect. In a sub-group of age-matched individuals from the discovery dataset [SCZ ($n$ = 118)-32.6 ± 6 years; HV($n$ = 153) - 31 ± 7.1 years], we analyzed the accuracy of the deep learning model. The overall accuracy rate of the model was found to be 94% for classifying SCZ and HV in this sub-group. Future studies may consider matching the groups on age. The relevant figures can be found in the supplementary material.

### 3.4. Single-subject level prediction

To examine the performance of the deep learning model at an individual subject level and to assess the potential transfer learning to a new dataset, we further evaluated the classification performance using a separate dataset. This was performed as this resembles the real-life clinical scenario wherein the clinician must diagnose individual subjects. At an individual subject level, the accuracy was found to be 76.74%; that is, out of the 43 images tested, 33 images were classified correctly. While 18 of the 22 HV were classified correctly, the accuracy was lower for SCZ - 15 out of 21 were classified correctly. The overall sensitivity of the model was 71.4%; specificity was 81.8%; positive predictive value was 78.94% and negative predictive value was 75%.

## 4. Discussion

To the best of our knowledge, this is the first study to examine the utility of a deep learning model to classify schizophrenia patients and healthy volunteers using retinal fundus images. While machine learning models depend on the input features and may require an apriori hypothesis, the deep learning model automatically extracts features. Results of the study suggest high accuracy of the model to classify patients and healthy individuals at the group level. In addition, reasonable accuracy at the individual subject level indicates the potential of this approach for clinical utility in the future.

Interestingly, the accuracy reached in the current study using the retinal vascular images is comparable to previous studies using deep learning model and structural or functional MRI data (Li et al., 2020; Oh et al., 2020, 2019; Yan et al., 2019; Zeng et al., 2018). The results are also better than our previous study examining the machine learning model using retinal vascular images (Appaji et al., 2019d). In addition, examining the model's utility at an individual subject level closely mimics a real-world setting. As a clinician must make a diagnosis at an individual subject level, we conducted this analysis in addition to the conventional group-level analysis. Traditionally, machine learning approaches employ a group-level testing to classify patients and healthy individuals; however, such an analysis is less likely to be of practical clinical utility as the clinician is interested in the accuracy at the single-subject level (Arbabshirani et al., 2017). As expected, the accuracy at the individual level was lower compared to the level of accuracy achieved when a group-level analysis was conducted using a testing dataset. While the current accuracy of 76.4% does not meet the necessary clinical precision, the reasonable accuracy seen with modest numbers is promising. It is important to note that the level of accuracy achieved at the individual subject level is comparable to the one achieved using MRI images (Lei et al., 2020a, 2020b). Moreover, the data-driven approach of deep learning model is likely to give better results with higher accuracy if the training set includes a greater number of subjects (Esteva et al., 2019). As shown earlier, combining different imaging modalities provides higher accuracy than an individual modality (Lei et al., 2020b). Future studies may consider combining different modalities, such as retinal vascular imaging and MRI, as an integrative biomarker.

The use of retinal vascular images offers several advantages for its utility when compared to other imaging modalities. It is non-invasive,

inexpensive, and less time-consuming than neuroimaging (Patton et al., 2005). Also, considering the portable nature of the equipment, it is ideal for use in community settings. As the images can be acquired with minimal training, it is suitable for application in resource-constrained settings as well. A few initiatives have also suggested the feasibility of the collection of a large number of retinal vascular images (MacGillivray et al., 2015). A previous study with a large number of images provided accuracy comparable to clinician diagnosis in diabetic retinopathy (Gulshan et al., 2016). Whether a similar accuracy can be achieved in other psychiatric disorders needs to be examined in future studies with a higher number of subjects.

Our findings need to be interpreted in the context of a few limitations. First, the study has a relatively small sample size. Considering the heterogeneity of schizophrenia, a larger sample size is desirable in future studies. Second, the groups were not matched on age and sex. While no sex difference has been reported in retinal vasculature patterns, age-related differences are noted in a previous study (Cífková et al., 2021). However, the sub-group analysis after matching for age did not reveal a significant effect as the model's accuracy was 94% in this sub-group. Future studies may consider matching the groups on age. Third, we excluded participants with diabetes mellitus, hypertension, and other potential confounding medical comorbidities to have a homogeneous population considering the proof-of-concept nature of the study. While excluding participants with these confounders increased the specificity of the findings, it might also decrease the generalizability of the findings considering the higher prevalence of metabolic disorders in schizophrenia (Mitchell et al., 2013). Fourth, we did not measure subjects' visual acuity, axial length, or intraocular pressure which could confound the findings of the study. In the future, studies need to examine the role of these potential confounding conditions. Finally, all the patients were on treatment with medications. While there was no evidence for a correlation between antipsychotic dose and retinal vascular variables in our previous studies (Appaji et al., 2019b, 2019c, 2019a), future research needs to examine drug-naïve patients to avoid the possible confounding effects of antipsychotic medications.

Our findings could have potential clinical implications. An objective marker could aid in the diagnosis and may have considerable application in clinical care as well as research. If the study findings are replicated in the future and higher accuracy is achieved at the individual subject level, retinal vascular image analysis could serve as a potential diagnostic marker for schizophrenia. The advantages of the retinal vascular images listed above also suggest its potential utility to aid primary care physicians for prompt referral for further evaluation. Future studies need to include patients from other psychiatric disorders such as bipolar disorder, to examine the specificity and discriminant validity of the retinal vascular abnormalities in schizophrenia. Also, future studies could include other imaging modalities such as OCT/OCTA/neuroimaging or genomic data along with fundus imaging. As schizophrenia is a heterogeneous disorder, a composite multimodal marker may have better accuracy in classifying when compared to a single marker. On the same lines, while the individual subject-level analysis in an independent confirmatory dataset provides important insights into the potential transfer learning of the model to new data, it is important to remember that the confirmatory dataset was acquired at the same center with the same study criteria. The real-world generalizability would have been better if the data was acquired from a different center with different subject characteristics. A multicentric study with broad study criteria including a heterogeneous patient population could overcome this limitation and may be close to the real-world scenario.

To conclude, a deep learning model using retinal vascular images classified patients with schizophrenia and healthy individuals with high accuracy. Though not achieving a similar level of accuracy, individual-level classification also showed promise and provides rationale for future research. The data-driven nature of the analysis offers potential scope for improvement with higher sample sizes. Future studies with larger sample sizes and drug-naïve patients can evaluate the utility of retinal vascular images as diagnostic biomarkers in schizophrenia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.01.058.

## Funding source

The project is partially supported by the Cognitive Science Research Initiative (CSRI) Scheme, Department of Science and Technology, Ministry of Science and Technology, India – DST/CSRI/2018/46 (PI- Dr. Suma HN). The funding agency did not have a role in the design of the study or interpretation of results.

## CRediT authorship contribution statement

NPR, AA, TB were involved in the conceptualization of the study, design of the study, interpretation of results and manuscript preparation. AJ, VK, SV, GV, SVR, CW were involved in interpretation of results and manuscript preparation. VK was involved in data collection, data analysis, interpretation of results. AA and NPR wrote the first draft of the manuscript and all authors contributed to revisions. All authors have approved the final manuscript.

## Declaration of competing interest

SVR is co-founder and Director of Forus Health Pvt. Ltd. NPR has received research grants from Forus Health Pvt. Ltd. Other authors report no conflict of interest.

*Acknowledgement*

None.

## References

Appaji, A., Nagendra, B., Chako, D.M., Padmanabha, A., Hiremath, C.V., Jacob, A., Varambally, S., Kesavan, M., Venkatasubramanian, G., Rao, S.V., Webers, C.A.B., Berendschot, T.T.J.M., Rao, N.P., 2019a. Retinal vascular fractal dimension in bipolar disorder and schizophrenia. J. Affect. Disord. 259, 98–103. https://doi.org/10.1016/j.jad.2019.08.061.

Appaji, A., Nagendra, B., Chako, D.M., Padmanabha, A., Hiremath, C.V., Jacob, A., Varambally, S., Kesavan, M., Venkatasubramanian, G., Rao, S.V., Webers, C.A.B., Berendschot, T.T.J.M., Rao, N.P., 2019b. Retinal vascular abnormalities in schizophrenia and bipolar disorder: a window to the brain. Bipolar Disord. 21, 634–641. https://doi.org/10.1111/bdi.12779.

Appaji, A., Nagendra, B., Chako, D.M., Padmanabha, A., Jacob, A., Hiremath, C.V., Varambally, S., Kesavan, M., Venkatasubramanian, G., Rao, S.V., Webers, C.A.B., Berendschot, T.T.J.M., Rao, N.P., 2019c. Retinal vascular tortuosity in schizophrenia and bipolar disorder. Schizophr. Res. 212, 26–32. https://doi.org/10.1016/j.schres.2019.08.020.

Appaji, A., Nagendra, B., Chako, D.M., Padmanabha, A., Jacob, A., Hiremath, C.V., Varambally, S., Kesavan, M., Venkatasubramanian, G., Rao, S.V., Webers, C.A.B., Berendschot, T.T.J.M., Rao, N.P., 2019d. Examination of retinal vascular trajectory in schizophrenia and bipolar disorder. Psychiatry Clin. Neurosci. 73, 738–744. https://doi.org/10.1111/pcn.12921.

Appaji, A., Nagendra, B., Chako, D.M., Padmanabha, A., Jacob, A., Hiremath, C.V., Varambally, S., Kesavan, M., Venkatasubramanian, G., Rao, S.V., Webers, C.A.B., Berendschot, T.T.J.M., Rao, N.P., 2020. Relation between retinal vascular abnormalities and working memory impairment in patients with schizophrenia and bipolar disorder. Asian J. Psychiatr. 49, 101942 https://doi.org/10.1016/j.ajp.2020.101942.

Arbabshirani, M.R., Plis, S., Sui, J., Calhoun, V.D., 2017. Single subject prediction of brain disorders in neuroimaging: promises and pitfalls. NeuroImage 145, 137–165. https://doi.org/10.1016/j.neuroimage.2016.02.079.

Bannai, D., Adhan, I., Katz, R., Kim, L.A., Keshavan, M., Miller, J.B., Lizano, P., 2021. Quantifying retinal microvascular morphology in schizophrenia using swept-source optical coherence tomography angiography. Schizophr. Bull. https://doi.org/10.1093/SCHBUL/SBAB111.

Cechnicki, A., Cichocki, Ł., Kalisz, A., Bładziński, P., Adamczyk, P., Franczyk-Glita, J., 2014. Duration of untreated psychosis (DUP) and the course of schizophrenia in a 20-year follow-up study. Psychiatry Res. 219, 420–425. https://doi.org/10.1016/J.PSYCHRES.2014.05.046.

Cífková, R., Harazny, J.M., Bruthans, J., Wohlfahrt, P., Krajčoviechová, A., Lánská, V., Gelžinský, J., Mateřánková, M., Mareš, Š., Filipovský, J., Mayer, O., Schmieder, R.E., 2021. Reference values of retinal microcirculation parameters derived from a population random sample. Microvasc. Res. 134, 104117 https://doi.org/10.1016/J.MVR.2020.104117.

Cortes-Briones, J.A., Tapia-Rivas, N.I., D'Souza, D.C., Estevez, P.A., 2021. Going deep into schizophrenia with artificial intelligence. Schizophr. Res. https://doi.org/10.1016/j.schres.2021.05.018.

Darwish, D.Y., Patel, S.N., Gao, Y., Bhat, P., Chau, F.Y., Lim, J.I., Kim, J.E., Jose, J., Jonas, K.E., Chan, R.V.P., Mehta, S.D., Lobo, A.-M., 2019. Diagnostic accuracy and reliability of retinal pathology using the forus 3nethra fundus camera compared to ultra wide-field imaging. Eye 33, 856–857. https://doi.org/10.1038/s41433-019-0339-9.

Ditton-Phare, P., Loughland, C., Duvivier, R., Kelly, B., 2017. Communication skills in the training of psychiatrists: a systematic review of current approaches. Aust. N. Z. J. Psychiatry 51, 675–692. https://doi.org/10.1177/0004867417707820.

Dumitrascu, O.M., Demaerschalk, B.M., Sanchez, C.V., Almader-Douglas, D., O'Carroll, C.B., Aguilar, M.I., Lyden, P.D., Kumar, G., 2018. Retinal microvascular abnormalities as surrogate markers of cerebrovascular ischemic disease: a meta-analysis. J. Stroke Cerebrovasc. Dis. 27, 1960–1968. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.02.041.

Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., Cui, C., Corrado, G., Thrun, S., Dean, J., 2019. A guide to deep learning in healthcare. Nat. Med. 25, 24–29. https://doi.org/10.1038/s41591-018-0316-z.

Ge, Y.-J., Xu, W., Ou, Y.-N., Qu, Y., Ma, Y.-H., Huang, Y.-Y., Shen, X.-N., Chen, S.-D., Tan, L., Zhao, Q.-H., Yu, J.-T., 2021. Retinal biomarkers in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. Ageing Res. Rev. 69, 101361 https://doi.org/10.1016/j.arr.2021.101361.

Gulshan, V., Peng, L., Coram, M., Stumpe, M.C., Wu, D., Narayanaswamy, A., Venugopalan, S., Widner, K., Madams, T., Cuadros, J., Kim, R., Raman, R., Nelson, P. C., Mega, J.L., Webster, D.R., 2016. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA 316, 2402. https://doi.org/10.1001/jama.2016.17216.

Guy, W., 1976. Clinical Global Impression Scale: ECDEU Assessment Manual for Psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Rockville.

Hancock, J.T., Khoshgoftaar, T.M., 2020. Survey on categorical data for neural networks. J. Big Data 7, 28. https://doi.org/10.1186/s40537-020-00305-w.

Hood, D.C., de Moraes, C.G., 2018. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. Ophthalmology 125, 1207–1208. https://doi.org/10.1016/j.ophtha.2018.04.020.

Hosak, L., Sery, O., Sadykov, E., Studnicka, J., 2018. Retinal abnormatilites as a diagnostic or prognostic marker of schizophrenia. Biomed. Pap. 162, 159–164. https://doi.org/10.5507/bp.2018.035.

Jackson, S.E., Chester, J.D., 2015. Personalised cancer medicine. Int. J. Cancer 137, 262–266. https://doi.org/10.1002/ijc.28940.

Koman-Wierdak, E., Róg, J., Brzozowska, A., Toro, M.D., Bonfiglio, V., Załuska-Ogryzek, K., Karakuła-Juchnowicz, H., Rejdak, R., Nowomiejska, K., 2021. Analysis of the peripapillary and macular regions using OCT angiography in patients with schizophrenia and bipolar disorder. J. Clin. Med. 10 https://doi.org/10.3390/JCM10184131.

Korann, V., Appaji, A., Jacob, A., Devi, P., Nagendra, B., Chako, D.M., Padmanabha, A., Thonse, U., Bharath, R.D., Kumar, V., Varambally, S., Venkatasubramanian, G., Rao, S.V., Webers, C.A.B., Berendschot, T.T.J.M., Rao, N.P., 2021. Association between retinal vascular caliber and brain structure in schizophrenia. Asian J. Psychiatr. 61, 102707 https://doi.org/10.1016/j.ajp.2021.102707.

Kraguljac, N.V., McDonald, W.M., Widge, A.S., Rodriguez, C.I., Tohen, M., Nemeroff, C. B., 2021. Neuroimaging biomarkers in schizophrenia. Am. J. Psychiatr. 178, 509–521. https://doi.org/10.1176/appi.ajp.2020.20030340.

Lei, D., Pinaya, W.H.L., van Amelsvoort, T., Marcelis, M., Donohoe, G., Mothersill, D.O., Corvin, A., Gill, M., Vieira, S., Huang, X., Lui, S., Scarpazza, C., Young, J., Arango, C., Bullmore, E., Qiyong, G., McGuire, P., Mechelli, A., 2020a. Detecting schizophrenia at the level of the individual: relative diagnostic value of whole-brain images, connectome-wide functional connectivity and graph-based metrics. Psychol. Med. 50, 1852–1861. https://doi.org/10.1017/s0033291719001934.

Lei, D., Pinaya, W.H.L., Young, J., Amelsvoort, T., Marcelis, M., Donohoe, G., Mothersill, D.O., Corvin, A., Vieira, S., Huang, X., Lui, S., Scarpazza, C., Arango, C., Bullmore, E., Gong, Q., McGuire, P., Mechelli, A., 2020b. Integrating machining learning and multimodal neuroimaging to detect schizophrenia at the level of the individual. Hum. Brain Mapp. 41, 1119–1135. https://doi.org/10.1002/hbm.24863.

Leucht, S., Rothe, P., Davis, J.M., Engel, R.R., 2013. Equipercentile linking of the BPRS and the PANSS. Eur. Neuropsychopharmacol. 23, 956–959. https://doi.org/10.1016/j.euroneuro.2012.11.004.

Leucht, S., Samara, M., Heres, S., Patel, M.X., Furukawa, T., Cipriani, A., Geddes, J., Davis, J.M., 2015. Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. Schizophr. Bull. 41, 1397–1402. https://doi.org/10.1093/schbul/sbv037.

Li, L., Ikram, M.K., Wong, T.Y., 2016. Retinal vascular imaging in early life: insights into processes and risk of cardiovascular disease. J. Physiol. 594, 2175–2203. https://doi.org/10.1113/jp270947.

Li, G., Han, D., Wang, C., Hu, W., Calhoun, V.D., Wang, Y.-P., 2020. Application of deep canonically correlated sparse autoencoder for the classification of schizophrenia. Comput. Methods Prog. Biomed. 183, 105073 https://doi.org/10.1016/j.cmpb.2019.105073.

MacGillivray, T.J., Cameron, J.R., Zhang, Q., El-Medany, A., Mulholland, C., Sheng, Z., Dhillon, B., Doubal, F.N., Foster, P.J., Trucco, E., Sudlow, C., Consortium, U.K.B.E, Vision, 2015. Suitability of UK biobank retinal images for automatic analysis of morphometric properties of the vasculature. PLoS ONE 10, e0127914. https://doi.org/10.1371/journal.pone.0127914.

Medina, M., Garza, D.M., Cooper, J.J., 2019. Physical examination skills among chief residents in psychiatry: practices, attitudes, and self-perceived knowledge. Acad. Psychiatry 1 (44), 68–72. https://doi.org/10.1007/S40596-019-01124-9, 2019 44.

Meier, M.H., Shalev, I., Moffitt, T.E., Kapur, S., Keefe, R.S.E., Wong, T.Y., Belsky, D.W., Harrington, H.L., Hogan, S., Houts, R., Caspi, A., Poulton, R., 2013. Microvascular abnormality in schizophrenia as shown by retinal imaging. Am. J. Psychiatr. 170, 1451–1459. https://doi.org/10.1176/appi.ajp.2013.13020234.

Mitchell, A.J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., de Hert, M., 2013. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. Schizophr. Bull. 39, 306–318. https://doi.org/10.1093/schbul/sbr148.

Moraru, A.D., Costin, D., Moraru, R.L., Branisteanu, D.C., 2020. Artificial intelligence and deep learning in ophthalmology - present and future (Review). Exp. Ther. Med. 20, 3469–3473. https://doi.org/10.3892/etm.2020.9118.

Oh, K., Kim, W., Shen, G., Piao, Y., Kang, N.-I., Oh, I.-S., Chung, Y.C., 2019. Classification of schizophrenia and normal controls using 3D convolutional neural network and outcome visualization. Schizophr. Res. 212, 186–195. https://doi.org/10.1016/j.schres.2019.07.034.

Oh, J., Oh, B.-L., Lee, K.-U., Chae, J.-H., Yun, K., 2020. Identifying schizophrenia using structural MRI with a deep learning algorithm. Front. Psych. 11, 16. https://doi.org/10.3389/fpsyt.2020.00016.

Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.

Patton, N., Aslam, T., MacGillivray, J., Pattie, A., Deary, I., Dhillon, B., 2005. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease. J. Anat. 206, 318–348.

Santelmann, H., Franklin, J., Bußhoff, J., Baethge, C., 2016. Interrater reliability of schizoaffective disorder compared with schizophrenia, bipolar disorder, and unipolar depression – a systematic review and meta-analysis. Schizophr. Res. 176, 357–363. https://doi.org/10.1016/J.SCHRES.2016.07.012.

Scarr, E., Millan, M.J., Bahn, S., Bertolino, A., Turck, C.W., Kapur, S., Möller, H.-J., Dean, B., 2015. Biomarkers for psychiatry: the journey from fantasy to fact, a report of the 2013 CINP think tank. Int. J. Neuropsychopharmacol. 18, pyv042. https://doi.org/10.1093/ijnp/pyv042.

Silverstein, S.M., Demmin, D.L., Schallek, J.B., Fradkin, S.I., 2020. Measures of retinal structure and function as biomarkers in neurology and psychiatry. Biomark. Neuropsychiatry 2, 100018. https://doi.org/10.1016/j.bionps.2020.100018.

Silverstein, S.M., Lai, A., Green, K.M., Crosta, C., Fradkin, S.I., Ramchandran, R.S., 2021. Retinal microvasculature in schizophrenia. Eye Brain 13, 205–217. https://doi.org/10.2147/EB.S317186.

Voets, M., Møllersen, K., Bongo, L.A., 2019. Reproduction study using public data of: development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. PLoS ONE 14, e0217541. https://doi.org/10.1371/journal.pone.0217541.

WHO, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization.

Wilson, R.R., Silowash, R., Anthony, L., Cecil, R.A., Eller, A., 2008. Telemedicine process used to implement an effective and functional screening program for diabetic retinopathy. J. Diabetes Sci. Technol. 2, 785–791. https://doi.org/10.1177/193229680800200506.

Yan, W., Calhoun, V., Song, M., Cui, Y., Yan, H., Liu, S., Fan, L., Zuo, N., Yang, Z., Xu, K., Yan, J., Lv, L., Chen, J., Chen, Y., Guo, H., Li, P., Lu, L., Wan, P., Wang, Huaning, Wang, Huiling, Yang, Y., Zhang, H., Zhang, D., Jiang, T., Sui, J., 2019. Discriminating schizophrenia using recurrent neural network applied on time courses of multi-site FMRI data. EBioMedicine 47, 543–552. https://doi.org/10.1016/j.ebiom.2019.08.023.

Zaheer, R., Shaziya, H., 2019. A study of the optimization algorithms in deep learning. In: 2019 Third International Conference on Inventive Systems and Control (ICISC), 00, pp. 536–539. https://doi.org/10.1109/icisc44355.2019.9036442.

Zeng, L.-L., Wang, H., Hu, P., Yang, B., Pu, W., Shen, H., Chen, X., Liu, Z., Yin, H., Tan, Q., Wang, K., Hu, D., 2018. Multi-site diagnostic classification of schizophrenia using discriminant deep learning with functional connectivity MRI. EBioMedicine 30, 74–85. https://doi.org/10.1016/j.ebiom.2018.03.017.