Research Paper

Altered intrinsic brain activity in patients with diabetic retinopathy and nephropathy: a resting-state fMRI study

Yan-Mei Zeng[1,2*], Xiao-Yu Wang[1,2*], Liang-Qi He[1*], Jin-Yu Hu[2], Qian Ling[2], Jie Zou[2], Cheng Chen[1], Hong Wei[2], Xu Chen[3], Yi-Xin Wang[4], Yi Shao[5#], Yao Yu[1#]

[1]Department of Endocrine and Metabolic, The First Affiliated Hospital of Nanchang University, Jiangxi clinical research centre for endocrine and metabolic disease, Jiangxi branch of national clinical research center for metabolic disease，Nanchang, Jiangxi 330006, China;

[2]Department of Ophthalmology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China;

[3]Ophthalmology Centre of Maastricht University, Maastricht 6200MS , Limburg Provincie, Netherlands;

[4]School of optometry and vision science, Cardiff University, Cardiff, CF24 4HQ, Wales

[5]Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, National Clinical Research Center for Eye Diseases, Shanghai 200080, China;

*Equal contribution

[#]Correspondence to: Yi Shao, **email:** freebee99@163.com;

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ABSTRACT

Objective: We used percent amplitude of fluctuation (perAF) to investigate the alterations in diabetic retinopathy and nephropathy (DRN) patients.

Method: Twenty DRN patients were recruited in the DRN patient group (PG), while 20 matched healthy subjects were recruited in the healthy control group (HG). The perAF method was applied to all individuals to assess spontaneous brain activity changes. A sliding window method was utilized to explore the altered dynamics of PerAF in patients with DRN. The perAF values of the DRN patients were distinguished from those of the HCs using a receiver operating characteristic curve (ROC).

Results: In the PG, the perAF values of the medial side of the temporal lobe and the left putamen were increased

to varying degrees. The perAF values of the left medial superior frontal gyrus and the right precuneus were decreased to varying degrees. In the PG, the HADS score was significantly negatively correlated with perAF of the left medial superior frontal lobe (r = −0.9127, P < 0.0001 for anxiety and r = −0.9378, P < 0.0001 for depression). The area under the ROC curve (AUC) was 1.000 (p ＜ 0.0001; 95% CI: 1.000–1.000) for the medial side of the temporal lobe (aal) and 0.915 for left putamen (aal) (p ＜ 0.0001; 95% CI: 0.823–1.000). The area under the ROC curve was 0.993 (p ＜ 0.0001; 95% CI: 0.973–1.000) for the left medial superior frontal lobe (aal) and 0.930 for the right precuneus (aal) (p ＜ 0.0001; 95% CI: 0.849–1.000).

Conclusion: DRN is associated with abnormal variability of perAF in the specific cerebral region, possibly providing new insights into its pathophysiology and prevention and treatment of DRN patients.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease with different causes. The main characteristic is chronic hyperglycemia due to defective insulin secretion and/or utilization. Currently, the prevalence and incidence of diabetes are increasing rapidly worldwide. Diabetes comes in two primary forms. Type 1 DM is insulin-dependent, and type 2 DM (T2DM) is non-insulin-dependent,[1, 2] where 90%–95% of diabetes patients suffer from T2DM.[3, 4, 5]

The chronic complications of DM can be divided into vascular and nonvascular. The most lethal influence of diabetes is long-term microvascular complications. Due to chronically elevated blood glucose levels, blood vessels become damaged. The resulting complications can be divided into "microangiopathy" (caused by damage to small blood vessels) and "macroangiopathy" caused by damage to arteries).[1, 6] The most involved microvascular target organs in DM are the retina and kidneys.[7, 8, 9] Microvascular complications occur in many parts of the body, affecting basic functions, including diabetic retinopathy (DR), nephropathy, and neuropathy, which are discussed in this manuscript in detail.

DR is universal diabetic microangiopathy and is a major cause of vision loss and blindness in adults. It significantly affects the quality of life of many people worldwide. A total of 40% of T2DM patients will develop DR, which is the main cause of reduced vision in Western countries.[10, 11, 12] The presence of DR may indicate microcirculatory dysfunction in other organ systems.[13, 14, 15, 16] Fundus examination is the main method to diagnose DR, of which microaneurysms and small hemorrhagic plaques are always the first and more definite landmarks.[17] Figure 1(A) shows diffuse microaneurysms and hemorrhagic plate plaques in the retina on fundoscopy.

Diabetic nephropathy (DN) is now the second cause of end-stage renal disease worldwide and the major cause of end-stage renal disease in western nations.[18] Renal biopsy represents the gold standard in the diagnosis of DN. Figure 1(B) demonstrates the renal hematoxylin staining, showing severe dilation of the mesangial matrix and tuberous sclerosis of the glomerulus.

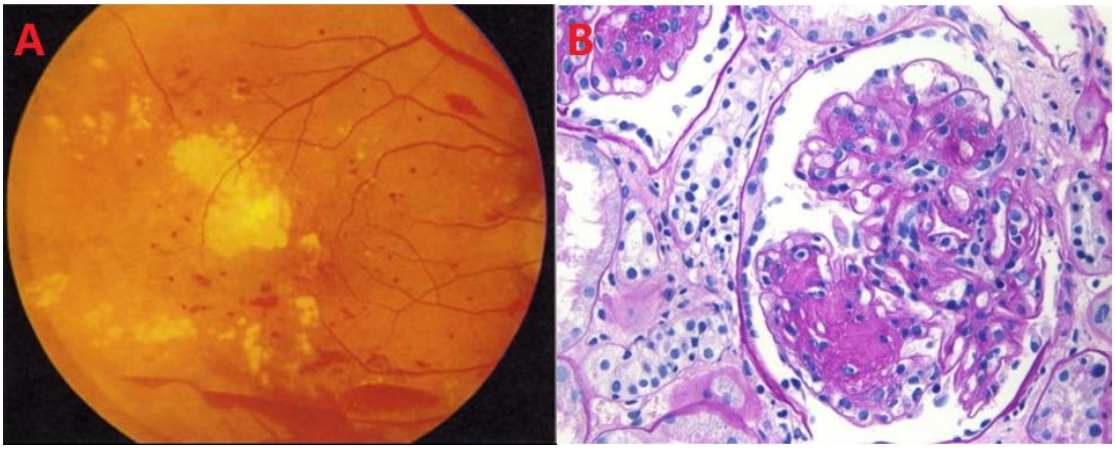

Figure 1

(A) Fundoscopy shows that the retina had diffuse microaneurysms and patches of hemorrhage. (B) Hematoxylin and eosin staining of renal tissue shows severe dilation of the mesangial matrix and tuberous sclerosis of the glomerulus.

Diabetic neuropathy is one of the most familiar chronic complications of diabetes. The etiology and clinical manifestations of diabetic neuropathy are complex, and the prognosis is poor. Depression is common in diabetes patients, especially those with microvascular complications, such as DN or DR.[19] Previous studies have indicated that the incidence of depression is measurably higher in prediabetes and undiagnosed diabetes, while it distinctly rises in diagnosed diabetes cases compared with those with healthy glucose metabolism.[20] Wang et al. have indicated that 83% of DN patients had depression.[19] On the contrary, the presence of depression may raise the risk of

T2DM (up to 60%).[21, 22, 23, 24] Therefore, early identification and diagnosis of depression can greatly improve the prognosis of patients with diabetes. Previous studies have shown a strong link between diabetes and anxiety. People with diabetes were 20 percent more likely to have anxiety than people without diabetes[25,26] It is necessary to evaluate anxiety disorders in diabetic patients.[27]

Chee et al. have found that the eye and kidney share many structural, developmental, and genetic pathways, implying that renal and ocular diseases may be connected.[28] Mirsharif Q et al. have found similar capillaries in the glomerulus, retina, and brain parenchyma.[29]

Therefore, we speculate that diabetes causes damage to brain regions as it causes DR and DN. Since research on patients with multiorgan microvascular disease of the kidney, retina, and brain has been currently scarce, we aimed to investigate altered cerebral functionality in DR and DN patients.

We referred to T2DM individuals with both DR and DN as "DRN" in this study and assumed that the presence of DRN might suggest simultaneous brain damage.

The human cerebrum is the most delicate, structurally and functionally complex system, controlling cognitive abilities, such as visual recognition, memory (long-term and short-term), action selection, and motor function, by generating an action potential. The default mode network (DMN) is a large-scale functional brain network, which are involved in emotional, memory, and cognitive function.[30,31] Given the high incidence of anxiety and depression in patients with DRNS, we predicted that there might be changes in dynamic cerebral electrical activities in patients with DRN, which might lead to neurological disease.

Functional magnetic resonance imaging (fMRI) plays a vital part in cognitive neuroscience research.[32] In cognitive neuroscience, fMRI is currently the mainstay of neuroimaging, which is an excellent tool to assess neural function.[33, 34] In fMRI, the most important technology is blood oxygen level-dependent fMRI, proposed by Ogawa.[35] As a resting-state fMRI (rs-fMRI) analysis method, the amplitude of low-frequency fluctuation (ALFF) could measure the connatural fluctuations of the blood-oxygen level-dependent (BOLD) signal. A similar metric to the percentage of signal change in rs-fMRI data can be developed by calculating the percentage of BOLD fluctuation relative to the average BOLD signal intensity per time series, known as percentage amplitude fluctuation (PerAF). [36] The PerAF could avoid the confounding mixture from voxel-specific fluctuation amplitude in fractional ALFF. PerAF reduced the influence of BOLD signal intensity, and has the best reliability relative to the regional homogeneity, ALFF, and degree centrality.[37] PerAF can also avoid from the confounding mixture from voxel-specific fluctuation amplitude in fALFF.[38] When compared to ALFF, PerAF and mPerAF can perform group-level data analysis directly. [39]Therefore, compared with other rs-fMRI methods, the PerAF method may be more sensitive to describe regional brain activity changes in patients with DRN. There has been relatively little data obtained regarding perAF so far. perAF has been used to investigate neurological conditions, such as sleep deprivation,[40] Moyamoya disease (MMD),[41] retinal detachment,[42] and acute unilateral open globe injury.[43] Thus, the perAF approach may help us improve accuracy and reduce errors when dealing with alterations in activity in brain regions linked to DRN. And exploring the dynamics perAF value can help doctors more accurately judge the progress of a patient's condition to take more precise and standardized treatment measures.

MATERIAL AND METHOD

Participants

The patient group (PG) consisted of 20 DRN patients from the Department of Ophthalmology of the First Affiliated Hospital of Nanchang University. The International Council of Ophthalmology announced the following new diagnostic criterion of retinopathy at the General Assembly in Sydney in 2002. (1) Fundoscopy reveals scattered microaneurysms and bleeding with a spot or plaque in the posterior pole of the retina after early mydriasis. White or yellow-white effusion can be seen in some patients with reduced visual acuity. (2) Angiography indicates fundus retinopathy. (3) Fundus fluorescein angiography displays a distinct increase in microangiomas. Additionally,

capillaries, especially around the retina, are markedly dilated while the permeability is increased. DN could be divided into 5 stages depending on the above mentioned standards.

Table 1. Five stages of diabetic nephropathy

	GFR （ ml/min/1.73 m2）	ACR（μg/gCr）	Clinical symptoms
Phase I	> 90		No clinical symptoms
Phase II	60-89	<30	normal urinary albumin or microalbuminuria
Phase III	30-59	30-300	early diabetic nephropathy
Phase IV	15-29	>300	diabetic nephropathy and massive proteinuria
Phase V	<15		advanced diabetic nephropathy, frank uremia

Twenty healthy controls without DM were included as a healthy control group (HG). Their age, sex, dominant hand, degree of education, and intracranial volume were similar to those in the PG group. Inclusion criteria for the HG comprised (1) absence of oculopathy; (2) no history of drug or alcohol addiction; (3) the neurological and psychiatric systems were common; (4) normal parenchyma of the cerebrum on MRI.

The study was conducted according to the Declaration of Helsinki. It was permitted by the medical ethics committee of the First Affiliated Hospital of Nanchang University. All individuals volunteered for this investigation and completed informed consent forms after learning about the study techniques, aim, and possible dangers.

MRI data acquisition

We performed MRI scanning using a 3 T MR scanner (Trio; Siemens AG, Berlin, Germany). While being awake in the scanner, all volunteers were asked to close their eyes, stay calm, and breathe evenly until the study was accomplished. The following parameters were utilized in a 3D spoiled gradient-recalled echo sequence, in which 240 images were obtained, to acquire 20 functional data: repetition time of 2,000 ms, echo time of 30 ms, thickness of 3 mm, gap of 1 mm, field of view of 240 × 240 mm flip angle of 90°, and the slice number are 29.

rs-fMRI data processing

We used Data Processing & Analysis for Brain Imaging (DPABI, http://www.rfmri.org/dpabi) to preprocess rs-fMRI data.[44] The procedure was performed as follows. (1) The first 10 time points were fitted, and slice timing was performed to rectify time disparities. (2) Realignment individual-level correction was used to rectify head movement with a Friston-24 model. (3) Possible effects of the head movement were minimized by employing average framewise displacement (FD). (4) Several covariates were regressed. (5) The data were normalized to the standard echo planar imaging (EPI) template of the Montreal Neurological Institute (MNI) at the 3 × 3 × 3 mm3 resolution. (6) The data were filtered with the temporary band filter (0.01–0.08 Hz). (7) Functional volumes were smoothed at a half-maximum Gaussian kernel with 6-mm full-width.

dynamic perAF analysis

A sliding window was used to quantitatively evaluate the perAF of every individual by the DynamicBC toolkit (v2.0, www.restfmri.net/forum/DynamicBC), which is an important parameter for assessing altered impulsive brain processes. In dynamic analysis, an appropriate window length was a vital factor. Therefore, we chose a suitable

sliding window length of 30 TR (step = 1 TR) and five TR (10 s) to compute each participant's perAF and optimize the statistical power. Then, we calculated the perAF map in each window. Standard deviation was used to measure the variance of these maps to assess the temporal variability of perAF (perAF variability). Additionally, we converted the perAF variability into z-scores.

Statistical analysis

This study used SPSS software, version 19.0 (IBM Corporation, Armonk, NY, USA), to perform a t-test on two independent samples to compare the clinical characteristics and demographics of the 2 groups. $p < 0.05$ was considered statistically significant. We performed a two-sample t-test by REST software to compare functional data. The statistical threshold of voxel level and clustering level of multiple comprehensive contrasts was set at $p <$ 0.05 by Gaussian random field theory. Meanwhile, we used receiver operating characteristic (ROC) curves, measurd by SPSS software, to compare specific cerebral subregions between the PG and HG. And we analyzed the linear correlation between HADS and the PerAF signal value in the left medial superior frontal lobe ($p<0.05$ indicates significant difference).

Correlation analysis

The Hospital Anxiety and Depression Scale (HADS) were required to accurately complete in all patients, and the differences of clinical behavior were based on scores of anxiety and depression. The GraphPad Prism 8 software (GraphPad Inc, San Diego, CA, United States) was applied to analyze Pearson's correlation, and to evaluate and plot the linear correlation between HADS scores and mean dALFF signal values in the left medial superior frontal.

RESULT

Clinical characteristics

Since the age, sex, dominant hand, degree of education, and intracranial volume of the HG were matched with the PG, the statistical significance of these indicators was not discussed here. All brain regions were modeled with automated anatomical labeling (AAL). Details are shown in Table 2.

Table2. Demographic and renal data for DRN and HGs.

condition	DRN	HGs	t value	P value
Male/female	9/11	9/11	N/A	>0.99
Age(years)	53.94±8.65	55.67±9.25	0.577	0.568
BMI	23.81±4.18	23.01±4.02	0.619	0.666
HbA1c	6.50±0.61	4.65±0.89	8.04	P<0.05
Systolic pressure	136.00±23.77	124.35±12.14	1.95	0.058
Diastolic pressure	81.45±16.04	69.70±13.93	2.48	0.018
SCr(umol/l)	270.06±125.70	63.85±6.64	7.32	P<0.05
ACR(mg/g)	2191.71±1400.62	N/A	N/A	N/A

Diabetes duration (years)	12.61±5.71	N/A	N/A	N/A
Bes-corrected VA: right eye	0.16±0.14	1.1±0.15	-19.7	P<0.05
Bes-corrected VA: left eye	0.19±0.16	1.1±0.17	-17.1	P<0.05

Abbreviations: ACR, urine albumin/creatinine ratio; BMI, body mass index; DRN, diabetic nephropathy with retinopathy; HbA1c, glycated hemoglobin; HGs, healthy controls; N/A, not applicable; SCr, Serum creatinine; VA, visual acuity.

Variance differences of perAF

We found that when compared to the HG, DRN patients had more perAF variability in the left interior temporal gyrus and left putamen. However, in the left medial superior frontal gyrus and right precuneus, DRN patients had lower perAF variability (Figure 2, Table 3). Figure 3 depicts the mean values of altered perAF. However, there was no substantial abnormality in other areas of the cerebrum.

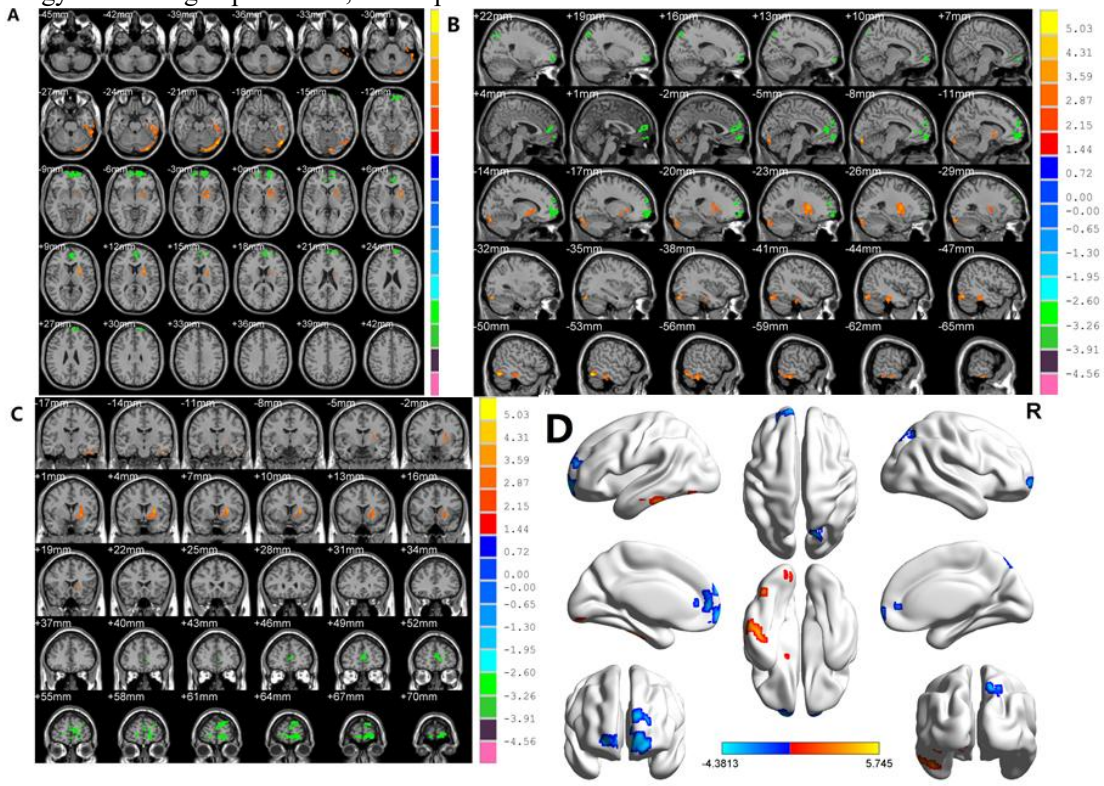

Figure 2. Marked differences inspontaneous brain activity in the DRN group compared with HCs. Notes: (ABC) The different brain regions were observed in the left interior temporal gyrus, left putamen, left medial superior frontal gyrus and right precuneus in the DRN group. The red areas denote higher perAF brain regions, and the blue areas denote lower perAF brain regions. (D) Stereoscopic form of the cerebrum.

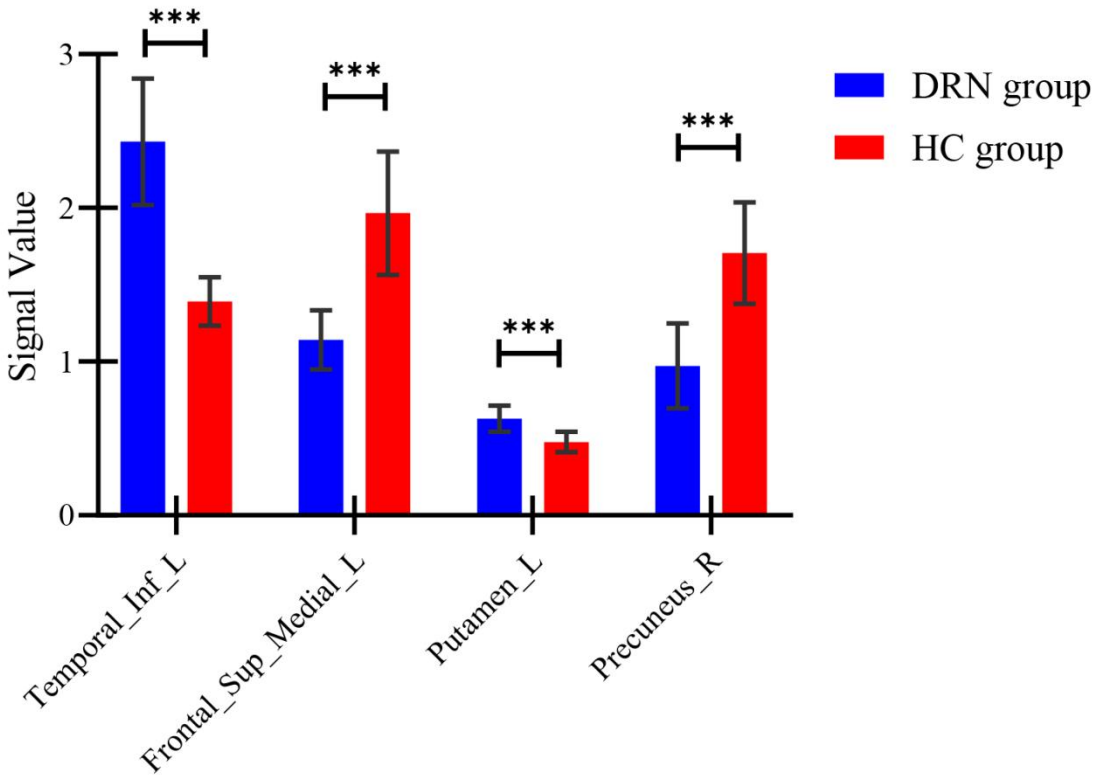

Figure 3. Means of altered spontaneous brain activity between the DRN group and HCs group (each n = 20). Notes: Compared with HCs, asterisk means the statistical significance p < 0.05. ***means p<O.OO1

Table3. perAF differences between DRN and HGs

Brain area	Voxels	MNI coordinates of peak voxel			t-value
		X	Y	Z	
DRN>HG					
Temporal_Inf_L	373	-54	-66	-21	5.745
Putamen_L	184	-24	3	9	4.3345
DRN<HG					
Frontal_Sup_Medial_L	448	-3	51	15	-4.3813
Precuneus_R	101	12	-75	57	-3.8724

Abbreviations: perAF: percent amplitude of fluctuation; PG, patients group; HGs, healthy controls group; MNI, Montreal Neurological Institute

ROC curve

An ROC curve analysis was conducted to calculate the average of changed perAF values for distinct cerebral areas, aiming to investigate if differences in perAF changes might be used to identify DRN patients from healthy controls as markers. The area under the curve (AUC) of altered perAF is shown in Figure 4.

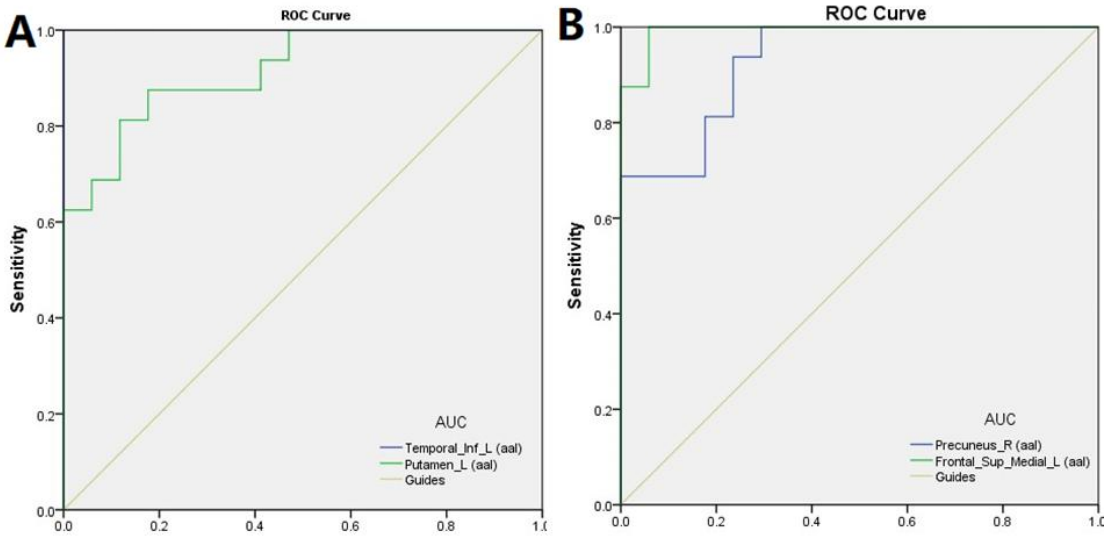

Figure 4. ROC curve analysis of the mean perAF values for altered brain regions.

Note： (A) The area under the ROC curve was 1.000 ($p < 0.0001$; 95% confidence interval [CI]: 1.000–1.000) for Temporal_Inf_L (aal) and 0.915 for Putamen_L (aal) ($p < 0.0001$; 95% CI: 0.823–1.000). (B) The area under the ROC curve was 0.993 ($p < 0.0001$; 95% CI: 0.973–1.000) for Frontal_Sup_Medial_L (aal) and 0.930 for Precuneus_R (aal) ($p < 0.0001$; 95% CI: 0.849–1.000).

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

Correlation analysis

We performed a series of correlation analyses to determine whether aberrant brain regions are associated with depression and anxiety. The participants completed the Hospital Anxiety and Depression Scale (HADS) to obtain statistical results. Then, we used GraphPad Prism 8 software to analyze the linear correlation between HADS and the PerAF signal value in the left medial superior frontal lobe ($p<0.05$ indicates significant difference). Finally, the results of the survey and the software analysis were used to obtain the linear correlation graph. In the PG, the HADS score was significantly negatively correlated with perAF of the left medial superior frontal lobe ($r = -0.9127$, $P < 0.0001$ for anxiety and $r = -0.9378$, $P < 0.0001$ for depression; Figure 5).

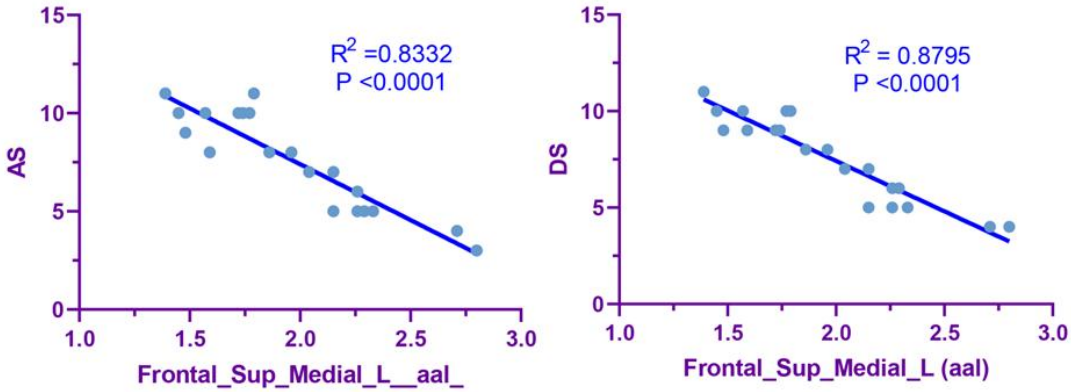

Figure 5. Correlations between perAF values of left medial superior frontal and the clinical behaviors.

Note: (A) The anxiety scores show a negative correlation with perAF values ($r = -0.9127$, $P < 0.0001$); (B) The depression scores show a negative correlation with perAF values ($r = -0.9378$, $P < 0.0001$).

Abbreviations: perAF, percent amplitude of fluctuation; AS, anxiety scores; DS, depression scores.

DISCUSSION

This study was performed to explore whether DRN caused damage to brain function. It revealed that significant changes in spontaneous neurological activity in the specific cerebral region occurred in patients with DRN compared with the HG.

perAF values in the left interior temporal gyrus and the left putamen of patients with DRN were higher than the values of patients in the HG, while the perAF values in the left medial superior frontal gyrus and the right precuneus of DRN patients were lower compared to the HG. Those specific cerebral regions were involved in altered dynamic intrinsic cerebrum activities and may be related to its pathophysiology in DRN patients (Table 4).

Table 4. Brain regions alternation and its potential impact

Brain regions	Experimental results	Brain function	Anticipated results
The medial side of the temporal lobe	DRN>HG	memory, mental, emotional and behavioral	Alzheimer's disease (AD) and schizopherenia
The left putamen	DRN>HG	activity, motivation, learning language and associative learning	Parkinson's disease, Complex Motor Stereotypies, dystonia, depression, schizophrenia, and Alzheimer's disease
The left medial superior frontal gyrus	DRN<HG	movement and cognitive control	Depression and anxiety
The right precuneus	DRN<HG	visuo-spatial imagery, attention, consciousness and autobiographical memory	schizophrenia and depression

The left medial superior frontal gyrus consists of the supplementary motor area (SMA) and pre-supplementary motor area (preSMA). It contributes to motor and cognitive control, as well as to different thinking tasks.[45] Furthermore, the patients with lesions in the medial frontal lobe have been associated with the activation of emotional and social behavior, which could be corrected with some negative emotions.[46] In the present study, there was a significant negative correlation between the HADS score of DRN patients and the perAF value of the medial superior frontal gyrus, suggesting that doctors need to consider the emotional and psychological conditions of patients in addition to their physical condition.

Precuneus, which is located ahead of the cuneus, is a major association region that may be involved in many behavioral activities,[47] including visuospatial imagery,[47] attention,[48, 49] consciousness,[50] and autobiographical memory.[51] Precuneus is a functional core of DMN[52], and it is pivotal in depression and anxiety.[53] In schizophrenia and depression, the DMN is often hyperactivated and hyperconnected.[54] Decreased perAF values indicated decreased activity in the precuneus region. Therefore, we assume that DRN caused the dysfunction of the precuneus.

As a part of the limbic system, the medial side of the temporal lobe influences memory, mental, emotional, and behavioral functions. Given the dysfunction of the inferior temporal gyrus, the loss of synapses may affect cognitive function, and further deterioration could cause Alzheimer's disease (AD)[55, 56] and schizophrenia.[57] The limbic system is a unique functional complex[58] processing sensory input from the external and internal environment.[59] The limbic system has played a pivotal part in attention, memorization, and mood.[60, 61] Additionally, the temporal lobe controls auditory functions. The potential reason for the significant enhancement of functional activity in this brain region was compensation of auditory function in visual impairment.

The left putamen is a part of the striatum, which has been implicated in sensorimotor function. Meanwhile, it also helps with signal integration and relay for a range of purposes, such as muscular activity, motivation, language learning, and associative learning.[62] The damage to putamen could induce Parkinson's disease,[63] complex motor stereotypies,[64] dystonia,[65] depression, schizophrenia, and AD.[66]

DM will not only lead to complications, such as DR and DN, but also damage to the related areas of the brain, resulting in a series of neurological lesions.[67] perAF can accurately detect the activity of the relevant brain area and then evaluate whether the function of the brain area is affected. Decreased perAF in the left medial superior frontal gyrus and precuneus indicates the decreased activity of this brain region. We can suggest that DRN damages

these brain regions. Simultaneously, the elevated perAF value of the medial temporal lobe and the left putamen may be due to the compensation in visual impairment to maintain the normal physiological function of the body and the stability of the internal network.[30]

Anxiety and cognitive impairment are both common manifestations of renal failure and diabetes, as well as indicators of depression.[68] Moreover, the association between mental illness and diabetes has been recognized for many years.[69] The comorbidity of depression and diabetes is a typical example of mental/physical comorbidity. Diabetes is a risk factor for depression, and poor blood sugar control can lead to dysfunction, higher rates of depression, and cognitive problems. The presence of diabetes increases the incidence of depression. However, there seems to be a two-way relationship between depression and diabetes. [70, 71]People with depression also have an increased risk of developing diabetes. The mechanisms involved are complex, as potential risk factors for depression in diabetics often interact with each other, such as lifestyle and obesity.

The medial frontal cortex is a portion of DMN related to different psychiatric diseases.[72, 73] DMN involves many brain regions, such as the inferior parietal cortex, frontal gyrus, and precuneus.[74] More and more evidence suggests that the DMN brain regions are involved in depression and anxiety.[53, 75] Abnormalities of the frontoparietal central executive network (CEN) and medial prefrontal-medial parietal DMN are consistent findings in depression. Transcranial magnetic stimulation (TMS) has been used to treat depression by altering the functional connectivity between CEN and DMN. [76, 77]This provides new ideas for the treatment of depression, especially in patients who have developed resistance to antidepressants.

The rs-fMRI has been used in patients with visual disorders. This technique shows considerable promise for further development (Table 5).

Table 5. rs-fMRI Method Applied in ophthalmologic and neurogenic patients in the current literatures

	Author	Year	Disease
Ophthalmologic diseases	Cai et al.[78]	2015	Primary Angle-Closure Glaucoma
	Zhu et al.[79]	2019	corneal ulcer
	Wang et al.[19]	2019	diabetic retinopathy and nephropathy
	Zhang et al.[80]	2020	high myopia
	Wu et al.[81]	2020	Adult Strabismus with Amblyopia

To sum up, patients with DRN showed signs of impairment in areas of the brain linked to emotional regulation and cognition, which increase the risk of depression and other mental illnesses.

CONCLUSION

In this study, PerAF cerebrum activity was shown to be changed in DRN patients and healthy controls (Figure 6). Abnormal variability of perAF in specific regions of the cerebrum is involved in DRN, which might contribute to better comprehension and provide fresh insights for the exploration of its etiology, as well as the prevention and treatment of DRN patients. In the DRN group, the perAF value in several areas of the cerebrum decreased significantly. There was a negative correlation between the score of anxiety and depression and the perAF value by the HADS analysis. Additionally, aberrant neural electrical activities might develop in the cerebrum region that is connected to emotions (Figure 7).

Olga et al.[82] have proposed that we should change the mode of response to diseases into predictive, preventive, and personalized medicine (PPPM) to promote the complementarity of advantages in various medical fields. There is no doubt that the application of perAF has promoted the practice of PPPM. PerAF helps doctors diagnose DRN in its early stages. For patients with diabetes, we can regularly monitor the patient's brain activity. When the corresponding changes in brain activity are observed, the first examination of retinitis and determination of urinary albumin content should be performed as soon as possible to detect the disease early. Under previous treatments, doctors would only start treating patients with symptoms, such as vision loss and proteinuria. However, by this time, the microvascular disease has often become very severe. Not only is the treatment not effective, but the patient's quality of life can be greatly affected. Therefore, doctors should not only treat the symptoms when the disease occurs but also take predictive and preventive measures before the disease occurs or at the early stage of the disease to slow down the progression and improve the prognosis. In addition to early diagnosis, perAF also aids in the observation and treatment of complications. For patients diagnosed with DRN, doctors should pay more attention to the patient's emotions and alleviate the patient's anxiety. Once a patient is found to have a tendency to depression, measures should be taken immediately to intervene. This can not only make the treatment effect better but also greatly improve the patient's quality of life. Staying in a good mood will help patients' condition recover. Additionally, the perAF value is an accurate value, which can help doctors more accurately judge the progress of a patient's condition to take more precise and standardized treatment measures.

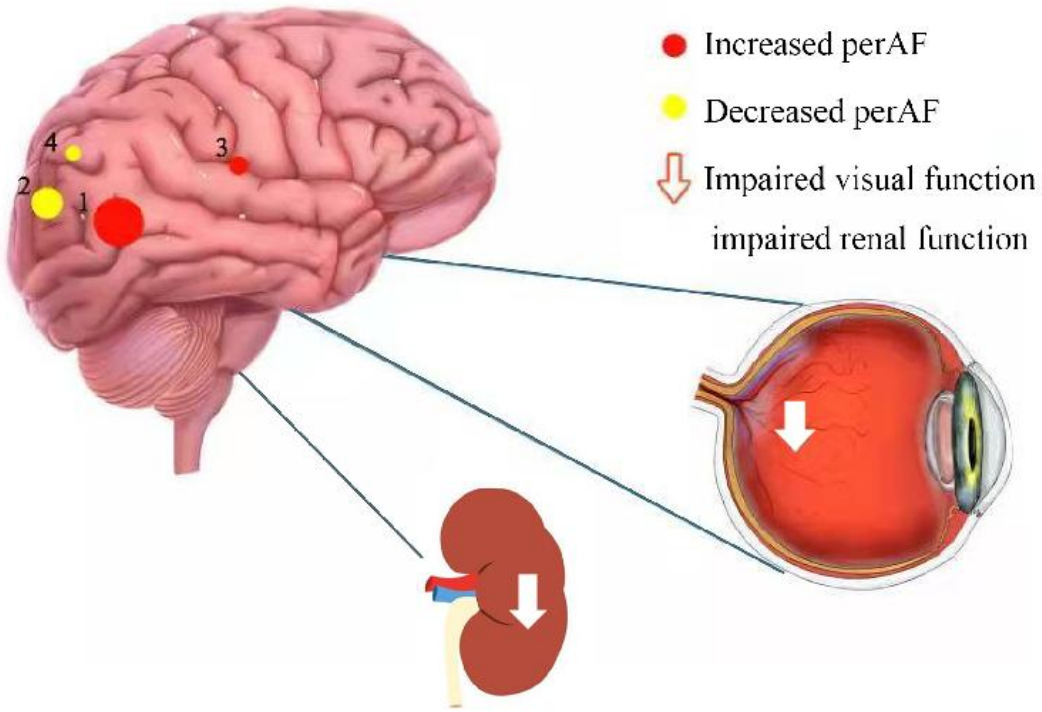

Figure 6. Altered cerebrum activity of perAF in DRN patients and healthy controls

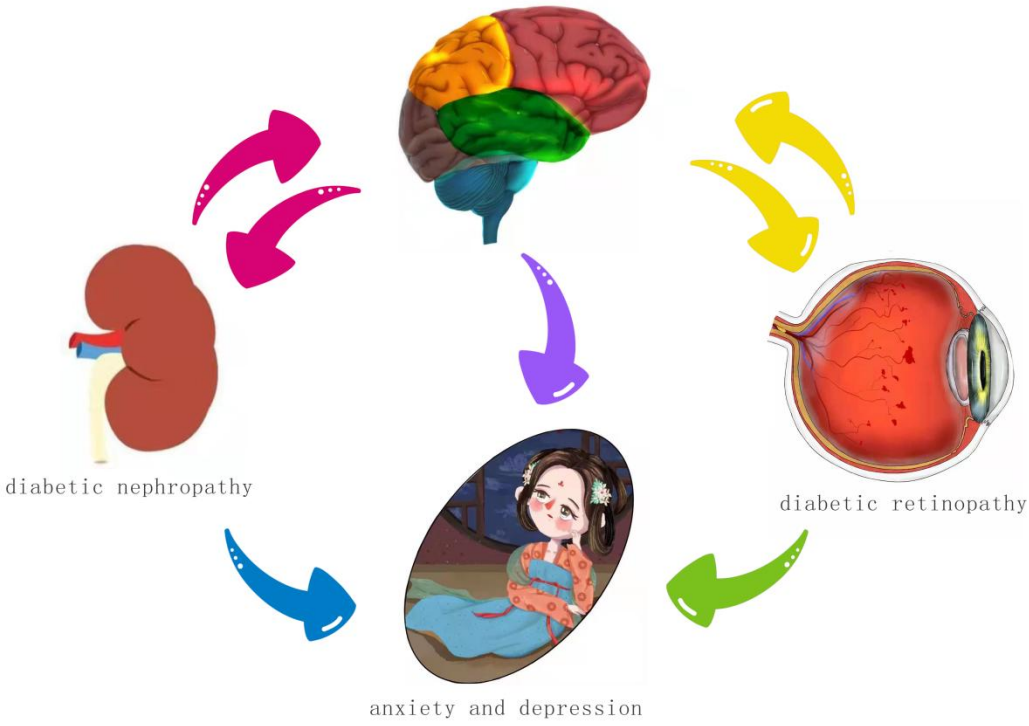

Figure 7. The relationship between DRN, brain activity, and mood changes.

Note: DRNS cause retinal and kidney lesions and abnormal neural activity in brain regions associated with emotional processing.

DECLARATIONS

Acknowledgement

Not applicable

Foundation item

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

The study methods and protocols were approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China) and followed the principles of the Declaration of Helsinki. All subjects were notified of the objectives and content of the study and latent risks, and then provided written informed consent to participate.

Patient consent for publication

Not applicable.

Competing interests

This study did not receive any industrial support. The authors have no competing interests to declare regarding this study.

Author contributions

All listed authors have contributed to the manuscript substantially and have agreed to the final submitted version.

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