Frequency-Dependent Changes of Spontaneous Low-Frequency Fluctuations in Patients with Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among older adults. AMD affects the patient's ability to read, write and recognize faces. Prior neuroimaging studies revealed abnormal functional connectivity within visual network and default mode network (DMN). 25 diagnosed AMD patients and 25 age, sex matched healthy controls were recruited into our study for resting-state functional magnetic resonance imaging (rs-fMRI) scans. Three different low frequency fluctuations metrics including amplitude of low-frequency fluctuation (ALFF), fractional ALFF (fALFF), and percent amplitude of fluctuation (PerAF) were introduced to detect and analyze spontaneous brain activity between AMD and HCs. For each metrics, traditional frequency band (0.01–0.08 Hz), slow-4 frequency band (0.027–0.073 Hz) and slow-5 frequency band (0.01–0.027 Hz) were examined respectively. Compared to HCs group, our result revealed that significant difference in ALFF, fALFF and PerAF showed in several brain regions including orbital frontal gyrus, fusiform gyrus, amygdala, precuneus, angular gyrus, median cingulate gyrus and rectus gyrus in AMD group at traditional frequency band. Moreover, findings of the present study demonstrated that abnormal spontaneous brain activity of fALFF in AMD is frequency-dependent, and may provide a new perspective to explain the pathological mechanism of AMD.

Introduction

Age-related macular degeneration (AMD) is a complex eye disease, characterized by progressive central vision impairment due to degenerative or neovascular changes in the macular region of the retina (Blasiak, 2020; Gehrs, Anderson, Johnson, & Hageman, 2006). Due to the lack of effective treatment for the majority of AMD patients, AMD is the leading cause of irreversible blindness among older adults, particularly aged 60 to 85 years, further results in patients' inability to read, write, recognize faces, and perform physical activities that requiring normal vision (van Leeuwen, Klaver, Vingerling, Hofman, & de Jong, 2003). In addition to being cause of visual impairment, AMD is often associated with Alzheimer's disease (AD) and depression based on previous studies (R. J. Casten, Rovner, & Tasman, 2004; Kaarniranta, Salminen, Haapasalo, Soininen, & Hiltunen, 2011; Lee et al., 2019). Therefore, exploring the underlying pathological mechanisms and finding reliable neuroimaging markers is crucial for the treatment of AMD.

Resting-State Functional Magnetic Resonance Imaging (rs-fMRI) of blood oxygenation level dependent (BOLD), as a non-invasive neuroimaging technique, has been applied for clinical research to study abnormal brain function, and has provided novel insights into the pathological mechanism of various diseases (Puig et al., 2018; Raichle & Gusnard, 2005; Sheline & Raichle, 2013; Workman et al., 2017). Previous rs-fMRI study using independent component analysis (ICA) approach showed that AMD patients exhibited reduced functional connectivity (FC) within visual networks (Zhuang et al., 2018). Another study based on regions of interest (ROIs) approach, exhibited stronger FC in phonemic fluency-related brain regions and default mode network (DMN) in AMD patients (Whitson et al., 2015). Evidences from brain network in response to decreased visual input have revealed abnormalities of FC in patients suffering

from AMD. However, they are unable to precisely provide the brain regions that produce abnormal spontaneous brain activity. Investigation of specific abnormal brain regions in patients with AMD is important for the clinical researches and applications. It has been reported that spontaneous low-frequency (0.01–0.08 Hz) fluctuations (LFFs) of BOLD signal might contain physiological information (Biswal, Yetkin, Haughton, & Hyde, 1995), and are closely linked to spontaneous neuronal activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Raichle & Gusnard, 2005).

Several rs-fMRI metrics are available for measuring the regional intensity of spontaneous LFFs. Amplitude of low-frequency fluctuation (ALFF) (Zang et al., 2007), can directly reflect the intensity of spontaneous neural activity and has been applied widely in eye diseases including glaucoma (Peng et al., 2021), strabismus (Min et al., 2018), retinal vein occlusion (Wu et al., 2019), and hypertensive retinopathy (Hu et al., 2021). ALFF has also been proven to have moderate to high test–retest reliability primarily in gray matter (Zou et al., 2008). Based on ALFF, Zuo et al. proposed fractional ALFF (fALFF) approach, which is defined as the total power within the low-frequency range (0.01–0.08 Hz) divided by the total power in the entire detectable frequency range (Zou et al., 2008). These two metrics characterize the LFFs from different aspects: ALFF reflects the intensity or strength of LFFs, while fALFF represents the relative contribution of specific LFFs to the whole detectable frequency range (Zuo et al., 2010). Another widely applied method measuring the characteristics of spontaneous brain activity is percent amplitude of fluctuation (PerAF). Unlike ALFF and fALFF, PerAF calculates the percent BOLD fluctuations relative to the average BOLD signal strength at each time point and averaging the whole time series that directly reflects the BOLD signal fluctuation in the resting state (Jia et al., 2020), and it represents the percentage of signal alteration. Previous studies have revealed that PerAF might have higher test-retest reliability than both ALFF and fALFF (Jia et al., 2020; Zhao et al., 2018). Therefore, PerAF is also a promising method for rs-fMRI signals detection. The combination of the three metrics could characterize the brain spontaneous activities of AMD patients in an all-round way.

However, most rs-fMRI studies adopting the methods above investigated LFFs amplitude at traditional frequency band (0.01–0.08 Hz) (Hu et al., 2021; Min et al., 2018; Peng et al., 2021), because this frequency band was thought to be related to neuronal fluctuations (Biswal et al., 1995; D. Zhang & Raichle, 2010). However, some studies have observed linear distribution of neuronal oscillations on the scale of natural logarithmic and the signal within independent frequency bands are produced by distinct oscillators with specific properties and physiological functions (Buzsáki & Draguhn, 2004; Penttonen & Buzsáki, 2003). According to Buzsáki and Draguhn, LFFs frequency ranges could be typically subdivided into 4 frequency bands: slow-5 frequency band (0.01–0.027 Hz), slow-4 frequency band (0.027–0.073 Hz), slow-3 frequency band (0.073–0.198 Hz) and slow-2 frequency band (0.198–0.25 Hz) (Buzsáki & Draguhn, 2004; Zuo et al., 2010). Slow-4 and slow-5 frequency bands are most closely related to gray matter signal and are useful in identifying brain functional disorders (Zuo et al., 2010). Previous Study found that ALFF in schizophrenia patients for slow-4 frequency band were higher in cingulate cortex, fusiform gyrus, basal ganglia, and midbrain, compared to ALFF in slow-5 (R. Yu et al., 2014). Another study showed that aMCI patients had greatly lower ALFF and fALFF values in the posterior cingulate cortex (PCC) and precuneus (PCu) at slow-5 frequency band than at slow-4 frequency band (Han et al.,

2011). These studies indicated frequency-dependent changes were found in specific brain regions, and thus may contribute to further exploration of the mechanism of brain function.

In our study, we compared the changes of LFFs amplitudes between AMD patients and healthy controls (HCs) using three metrics: ALFF, fALFF and PerAF. For each amplitude metrics, traditional frequency band, slow-4 frequency band and slow-5 frequency band were applied separately. Our purpose was to determine 1) whether AMD patients showed abnormalities of LFFs amplitudes in specific brain regions. 2) whether the abnormal spontaneous intrinsic neural activity was associated with specific frequency band.

Methods

Participants

Fifty participants were consecutively recruited into the study, of whom 25 diagnosed AMD patients from the Ophthalmology Department of Shanghai Tenth People's Hospital affiliated to Tongji University, and 25 HCs with matched age, gender, and education status comparing to the AMD group. Exclusion criteria: (1) patients with other eye diseases (cataract, glaucoma, optic neuritis, etc.). (2) any evidence of psychiatric disease or neurological diseases. All the HCs in this study met the subsequent criteria: (1) no ocular disease history; (2) no psychiatric disease or neurological diseases; (3) being capable of undergoing MRI examination (no cardiac pacemaker or implanted metal devices, etc.).

Best-corrected visual acuity (BCVA) in Logarithm of the Minimum Angle of Resolution (LogMAR) table, as the measurement of the best vision correction that can be achieved by glasses or contact lenses, was applied to measure visual acuity of both eyes for each participant. To evaluate cognitive ability of each participant, two routine cognitive screening scales including Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were utilized, in which MoCA is more sensitive for mild cognitive impairment than MMSE (S. Zhang et al., 2021).

Ethical approval

was given by hospital's medical ethics committee in line with the Declaration of Helsinki. All participants signed informed consents after informing of the purposes, contents, and potential risks.

MRI Acquisition

MRI data were acquired on a 3-Tesla MRI scanner (Philips Medical Systems, Best, The Netherlands) at Shanghai Tenth People's Hospital. All participants were asked to keep their eyes opened and stay awake. Brain structural MRI data was obtained using a T1-weighted 3D turbo field echo sequence for the whole brain with repetition time = 6.0 ms, echo time = 2.7 ms, field of view = 230 mm × 230 mm, voxel size = 0.9 × 0.9 × 0.9 mm, flip angle = 8°, slices = 200, slice orientation = sagittal, scan duration time = 4 min and 42 seconds. The rs-fMRI data were 240 volumes (scanning time = 8 min) of echo planar imaging (EPI)

sequence with the following parameters: repetition time = 2,000 ms, echo time = 35 ms, voxel size = $3.6 \times 3.6 \times 3.6$ mm, field of view = 250 mm $\times$ 250 mm, slices = 35, thickness / gap = 3.6 / 0 mm.

MRI data preprocessing

All functional imaging data processing were conducted by Statistical Parametric Mapping 12 (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/software/spm12>) and RESTplus (restplus_v1.25, <http://restfmri.net/forum/restplus>) toolkits implemented in MATLAB 2017b (MathWorks, Natick, MA, USA) (Jia et al., 2020). Briefly, it included following steps. The first 10 time points were removed for the reduction of the non-equilibrium effects of magnetization. The remaining 230 scans of each participant underwent slice timing correction, realignment, co-registration of the high-resolution structural images to the mean functional image. Then, the images were normalized spatially to the Montreal Neurological Institute (MNI) template in new segment and resampled to $3 \times 3 \times 3$ mm³. Any participant with head motion of >3mm or translation rotation >3° in any direction was removed. Then, we used a Gaussian kernel of 6mm full-width at half-maximum to smoothen the images. Finally, detrending was performed for the elimination of linear drift. For reduction of physiological noise, the signals of white matter (WM), cerebrospinal fluid (CSF), Friston-24 parameters model of head motion were regressed as covariates (Friston, Williams, Howard, Frackowiak, & Turner, 1996).

Calculation of rs-fMRI Metrics

In our study, ALFF, fALFF and PerAF calculation were performed using RESTplus software at three different frequency bands: traditional frequency band (0.01–0.08 Hz), slow-5 frequency band (0.01–0.027 Hz), and slow-4 frequency band (0.027–0.073 Hz), based on previous studies (Buzsáki & Draguhn, 2004).

After preprocessing, Fast Fourier Transformation (FFT) was used to convert the time series for each voxel to the frequency domain, then we obtained the power spectrum. Second, we calculated the square root of the power spectrum at each frequency. Third, the square root was averaged across a predefined frequency range at each voxel, and ALFF was obtained. The fALFF is calculated as a ratio of the ALFF within a predefined frequency range to the entire frequency band. Each voxel's ALFF/fALFF was divided by the global mean ALFF/fALFF value for standardization.

PerAF was obtained by two steps. Firstly, the percentage of BOLD signal intensity relative to the mean BOLD signal intensity for each time point was measured. Then, we calculated the average across the whole time series. The PerAF of each voxel was also divided by the global mean PerAF value to reduce the global effects of variability.

Statistical analysis

First, demographic and the clinical characteristics including age, sex, BCVA of both eyes, MoCA scores, MMSE scores, duration time and education status of AMD were imported into the SPSS 20.0 software (IBM, Armonk, NY) for comparison between AMD group and HCs.

Then, two-sample *t*-tests was performed to compare the ALFF, fALFF and PerAF maps between AMD group and HCs at three different frequency bands respectively. The multiple comparison correction was based on the Gaussian Random Field (GRF) theory with a voxel-level $P < 0.01$ and cluster-level $P < 0.05$.

Results

Demographic and Clinical Characteristics

The clinical characteristics of the AMD and HCs group including BCVA, MMSE scores, MoCA scores, education status and duration time of AMD were showed in Table 1. No significant differences in age, gender, education status and MMSE scores were observed between the AMD and HCs group. However, the AMD group exhibited relatively lower MoCA scores than HCs group ($P < 0.001$). The significant differences were obtained in BCVA-right ($P < 0.001$) and BCVA-left ($P < 0.001$) between the two groups.

Table 1
Demographic and Clinical Characteristics

Conditions	AMD	HCs	<i>T</i> -value/ χ^2	<i>P</i> -value
Age (years)	71.6 $\pm$ 1.776	68.64 $\pm$ 1.362	1.322	0.192 ^a
Sex (Male/Female)	14/11	11/14	0.837	0.406 ^b
MoCA	24.12 $\pm$ 0.570	27.16 $\pm$ 0.275	-4.807	$\times 0.001^a$
MMSE	26.48 $\pm$ 0.425	27.28 $\pm$ 0.319	-1.506	0.139 ^a
BCVA_R	0.488 $\pm$ 0.0477	0.976 $\pm$ 0.0328	-8.427	$\times 0.001^a$
BCVA_L	0.536 $\pm$ 0.0472	0.952 $\pm$ 0.0366	-6.966	$\times 0.001^a$
Duration (years)	7.2 $\pm$ 1.133	N/A	6.356	$\times 0.001^a$
Education (years)	9.92 $\pm$ 0.562	10.32 $\pm$ 0.613	-0.481	0.633 ^a
Values = mean $\pm$ standard deviation (SD); a, independent <i>t</i> -test; b, <i>Chi</i> -square test				

ALFF Analysis

As shown in Fig. 1A and Table 2, at traditional frequency band, the AMD group showed increased ALFF in right fusiform gyrus and decreased ALFF in left orbital part of inferior frontal gyrus, compared to HCs (voxel $P < 0.01$, cluster $P < 0.05$, GRF corrected).

Table 2
Brain regions with significant difference in ALFF at each frequency band between AMD group and HCs

Brain regions (AAL)	R/L	Voxels	MNI coordinates			BA	T-value
			x	y	z		
Traditional frequency band							
Fusiform	R	178	33	-72	-12	19	4.0353
Frontal_Inf_Orb	L	178	-24	30	-9	11	-4.025
Slow-4 frequency band							
Temporal_Inf	R	161	54	-57	-12	37	4.2498
Slow-5 frequency band							
Rectus	L	209	-18	15	-12	11	-4.1759

In addition, as shown in Fig. 1B, 1C and Table 2, the AMD group showed increased ALFF in right inferior temporal gyrus at slow-4 frequency band, whereas these patients showed decreased ALFF in left rectus gyrus at slow-5 frequency band, compared to HCs (voxel $P < 0.01$, cluster $P < 0.05$, GRF corrected).

fALFF Analysis

As shown in Fig. 2A and Table 3, at traditional frequency band, the AMD group showed decreased fALFF in right amygdala and increased fALFF in left PCu, left angular gyrus (AG) and left median cingulate gyrus, compared to HCs (voxel $P < 0.01$, cluster $P < 0.05$, GRF corrected).

Table 3
Brain regions with significant difference in fALFF at each frequency band between AMD group and HCs.

Brain regions (AAL)	R/L	Voxels	MNI coordinates			BA	T-value
			x	y	z		
Traditional frequency band							
Amygdala	R	55	30	0	-18	6	-4.2754
Precuneus	L	109	-3	-66	33	N/A	5.356
Angular	L	227	-42	-66	36	39	4.8804
Cingulum_Mid	L	62	-3	-36	45	N/A	5.0054
Slow-4 frequency band							
Fusiform	R	73	21	-45	-12	30	-3.7486
Supra_Marginal	L	246	-57	-45	36	40	5.0928
Cingulum_Mid	L	62	-3	-36	45	N/A	4.7206
Slow-5 frequency band							
Precuneus	L	209	-9	-57	27	23	5.0873

Additionally, as shown in Fig. 2B, 2C and Table 3, at slow-4 frequency band, the AMD group exhibited decreased fALFF in right fusiform gyrus and increased fALFF in left supramarginal gyrus and left median cingulate gyrus, whereas at slow-5 frequency band, the AMD group exhibited decreased fALFF in left PCu, compared to HCs (voxel $P < 0.01$, cluster $P < 0.05$, GRF corrected).

PerAF Analysis

As shown in Fig. 3A and Table 4, at traditional frequency band, the AMD group showed increased PerAF in right fusiform gyrus and decreased PerAF in left orbital part of middle frontal gyrus and left rectus gyrus, compared to HCs (voxel $P < 0.01$, cluster $P < 0.05$, GRF corrected).

Table 4
Brain regions with significant difference in PerAF at each frequency band between AMD patients and HCs.

Brain regions (AAL)	R/L	Voxels	MNI coordinates			BA	T-value
			x	y	z		
Traditional frequency band							
Rectus	L	350	-3	60	-21	11	-5.0733
Fusiform	R	290	36	-69	-15	19	4.0441
Frontal_Med_Orb	L	165	0	45	-12	11	-3.5634
Slow-4 frequency band							
Rectus	L	322	-6	60	-21	11	-4.8818
Temporal_Inf	R	251	54	-57	-15	37	4.085
Slow-5 frequency band							
Olfactory	L	122	-6	9	-18	25	-4.3401
Frontal Sup Orb	L	179	-21	60	-15	11	-4.1692
Fusiform	R	270	36	-69	-15	19	4.5273

Additionally, as shown in Fig. 3B, 3C and Table 4, the AMD group showed increased PerAF in right inferior temporal gyrus and decreased PerAF in left rectus gyrus at slow-4 frequency band, whereas these patients showed decreased PerAF in left olfactory cortex and left orbital part of superior frontal gyrus, and increased PerAF in right fusiform gyrus at slow-5 frequency band, compared to HCs (voxel $P < 0.01$, cluster $P < 0.05$, GRF corrected).

Discussion

In our study, three different rs-fMRI metrics were applied to detect and analyze amplitudes of LFFs in patients with AMD. Compared to HCs group, our result showed significant difference in ALFF, fALFF and PerAF respectively at traditional frequency band in AMD group. Overall, the patients with AMD showed abnormal spontaneous intrinsic brain activity in several brain regions including orbital frontal gyrus, fusiform gyrus, amygdala, PCu, AG, median cingulate gyrus and rectus gyrus. Moreover, slow-4 frequency band in fALFF exhibited a wider range of brain regions with abnormal neuronal activity than slow-5 frequency band did. Therefore, our result indicated that abnormal spontaneous brain activity of fALFF in AMD is frequency-dependent.

ALFF, ALFF and PerAF at traditional frequency band

Decreased ALFF were observed in left orbital inferior frontal gyrus in AMD patients. In addition, decreased PerAF were showed in left orbital part middle frontal gyrus and left rectus gyrus, compared to HCs. Our results are similar to a study regarding late-on depression patients which also reported decreased ALFF in left middle orbitofrontal gyrus (Yue, Jia, Hou, Zang, & Yuan, 2015). Besides, previous studies showed that rectus gyrus and orbital frontal gyrus demonstrated decreased gray matter volume in elderly depression and indicated that these region may involve in the neuropathological mechanism of depression (Ballmaier et al., 2004; S. Yu et al., 2018). Growing evidences indicated that prevalence of depression among patients with AMD was relatively higher and total depression scores were strongly associated with visual acuity severity level (Augustin et al., 2007; R. Casten & Rovner, 2008; Dawson, Mallen, Gouldstone, Yarham, & Mansell, 2014). Therefore, we speculated that the decreased brain activity in rectus gyrus and orbital frontal gyrus may represent a biomarker for depression. The most likely explanation is that deficits in physical functioning associated with impaired vision due to AMD may attribute to depression (R. J. Casten et al., 2004). In addition, it is necessary for ophthalmologists to implement the depression screening procedures for AMD patients, and refer diagnosed patients to psychiatrists for proper assessment and treatment.

Increased fALFF in left PCu was demonstrated in AMD group, compared to HCs. PCu located on the posteromedial portion of the parietal lobe has involved visuo-spatial imagery (Cavanna & Trimble, 2006). Besides, PCu also played an important role in episodic memory encoding and retrieval to spatial memory (Frings et al., 2006), and furthermore, it's an important component of DMN (Mak et al., 2017). All above studies indicated PCu play a specific role in higher-order cognitive functions. In contrast to our results, studies of cognitive impairment diseases including AD and MCI exhibited reduced regional activity of PCu in ALFF and fALFF (Han et al., 2011; Liu et al., 2014). Further, AMD patients exhibited stronger FC within the DMN, compared with HCs in a rs-fMRI study (Whitson et al., 2015). Therefore, increased regional activity in PCu possibly reflect an analogous potential compensatory changes to support cognitive performance.

Similar to previous rs-fMRI studies on patients with visual disorders including optic neuritis and corneal ulcer, our result also showed increased ALFF and PerAF in right fusiform gyrus (Huang et al., 2015; Shi et al., 2019). It has been revealed that fusiform gyrus is an important brain region involved in the visual cognitive function of facial recognition (Caspers et al., 2015). Therefore, our findings are consistent with the hypothesis that impaired vision caused by AMD affect patients' facial recognition ability. In addition to this, previous study suggested that long-term visual impairment might cause weakening intrinsic connectivity strength of visual cortex (Zhuang et al., 2018). Thus, we speculated that increased neural activity of right fusiform gyrus may indicate an compensatory mechanisms involving visual networks.

In our study, fALFF was increased in left AG at traditional frequency band. Left AG located in the posterior part of left inferior parietal lobule (IPL), make functional contribution to visual word reading and comprehension (Seghier, 2013; Sliwinska, James, & Devlin, 2015). On a neurological function level, reading requires several brain regions to work together to recognize a visual input, and correlate to its

corresponding meaning and sound. Whether distorted or blurred vision caused by AMD involves the visual word recognition processing need to be further studied.

Increased fALFF in left median cingulate gyrus was detected in our result. Study suggested midcingulate cortex (MCC) has contributions to decision making and cognitive control (Holroyd, Ribas-Fernandes, Shahnazian, Silvetti, & Verguts, 2018). During pain processing, MCC received nociceptive information from parietal areas, then guide multisensory control (such as eye or body orientation) and reflexive movements (Vogt, 2016). We speculate that loss of visual information caused by visual impairment in AMD patients affect this decision making processing. However, the mechanism of MCC function remain elusive and is worthy of further discussion.

Frequency-Dependent Effect

In current study, we investigated changes of LFFs amplitudes between AMD and HC groups at three different frequency bands (traditional frequency band, slow-4 frequency band and slow-5 frequency band), and found that the abnormalities of intrinsic brain activity detecting by fALFF in patients with AMD were associated with specific frequency band. Specifically, at slow-4 frequency band, three different brain regions with abnormal fALFF including fusiform gyrus, supramarginal gyrus and middle cingulate gyrus were observed, whereas at the slow-5 frequency band, only PCu was found. In addition, fusiform gyrus and supramarginal gyrus with abnormal fALFF at slow-4 band were not found at traditional frequency band. Thus, we conclude that abnormal spontaneous neural activity in fALFF in AMD patient might be more sensitive to the slow-4 frequency band than to slow-5 frequency band in some brain regions.

Frequency-dependent effect in specific regions was widely revealed in different diseases including attention-deficit hyperactivity disorder (ADHD) (Di Martino et al., 2008), aMCI (Han et al., 2011), schizophrenia (Hoptman et al., 2010), and depression (Zhou et al., 2020). Di Martino et al. showed fluctuations in slow-4 band provide greater diagnostic information than other bands for children with ADHD (Di Martino et al., 2008). Hoptman et al. revealed that widespread abnormal ALFF/fALFF at slow-4 frequency band was observed in schizophrenia patients (Hoptman et al., 2010). Consistent with our results, these two findings also indicate that slow-4 frequency band is more sensitive in detecting LFFs changes. Thus, the existence of sensitive frequency bands should be taken into consideration when measuring the LFFs changes of brain activity in AMD patients in further study.

Indeed, the brain regions at slow-4 frequency band and slow-5 frequency band showed a little different from which at traditional frequency band when ALFF or PerAF were calculated, but the brain regions with abnormal ALFF or PerAF measured at the slow-4 or slow-5 frequency band are either included in the traditional frequency band or adjacent to the brain regions measured at the traditional frequency band. In this case, no frequency-dependent effect was observed in ALFF or PerAF in our results. From a methodological point of view, the possible explanation is that fALFF might have higher specificity and sensitivity of detection LFFs than ALFF and PerAF (Zuo et al., 2010). However, the specific neural mechanisms of each frequency band have not been fully explained yet. Researchers suggested neuronal

oscillations are associated with the activity of chemical synaptic signaling, input selection, and neuron plasticity (Buzsáki & Draguhn, 2004). Further studies are needed to examine whether such frequency-dependent effect could be applied for disease diagnosis or monitoring AMD progression.

This study has some potential limitations. Firstly, the sample size of our study is relatively small. Studies with larger sample sizes are needed to further analyze and confirm these results. Secondly, it is a cross-sectional study in AMD patients. Patients with different stages of AMD may exhibit different patterns of brain activity alterations. The patients with AMD should be categorized into different disease stages to explore LFFs changes at different frequency bands. Thirdly, MMSE and MoCA tests of cognitive ability including tasks that relied on visual ability or involved visual cueing are unsuitable for patients with vision impairment. The validated cognitive tests would help us to detect the difference in cognitive level between AMD and HCs.

Conclusions

To our knowledge, it is the first study to report that abnormal LFFs amplitudes occur in patients with AMD. It showed significant difference in several brain region in ALFF, fALFF and PerAF, respectively at three frequency bands between AMD patients and HCs. The abnormal spontaneous neural activity in fALFF in AMD patients is possibly frequency-dependent in specific brain regions. This study expands our understanding of the potential influence of visual impairment on neural activity in specific brain regions and may provide a new perspective to explain the pathological mechanism of AMD.

Declarations

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Ethical Approval

Ethical approval was given by Shanghai Tenth People's Hospital's medical ethics committee in line with the Declaration of Helsinki.

Consent to Participate

All participants signed informed consents after informing of the purposes, contents, and potential risks.

Consent to Publish

All participants in this study consent to publish their data..

Conflict of Interest

None of the authors have a conflict of interest to declare.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available due the fact that they constitute an excerpt of research in progress but are available from the corresponding author on reasonable request.

Author Contributions

Author contributions included conception and study design (GYT and QP), data collection or acquisition (QP, FJX and PL), statistical analysis (FJX and XLS), interpretation of results (GYT, FJX, XLS and QP), drafting the manuscript work or revising it critically for important intellectual content (All authors) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

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Figures

Figure 1

ALFF differences between AMD group and HCs at traditional frequency band (A), slow-4 frequency band (B) and slow-5 frequency band (C). The red and yellow regions represent increased ALFF values in AMD group, compared to HCs. The blue regions represent decreased ALFF values in AMD group, compared to HCs.

Abbreviations: ALFF, amplitude of low-frequency fluctuation; AMD, Age-related macular degeneration; HCs, healthy controls; R, right; L, left;

Figure 2

fALFF differences between AMD group and HCs at traditional frequency band (A), slow-4 frequency band (B) and slow-5 frequency band (C). The red and yellow regions represent increased fALFF values in AMD group, compared to HCs. The blue regions represent decreased fALFF values in AMD group, compared to HCs.

Abbreviations: fALFF, fractional amplitude of low-frequency fluctuation; AMD, Age-related macular degeneration; HCs, healthy controls; R, right; L, left;

Figure 3

PerAF differences between AMD group and HCs at traditional frequency band (A), slow-4 frequency band (B) and slow-5 frequency band (C). The red and yellow regions represent increased PerAF values in AMD group, compared to HCs. The blue regions represent decreased PerAF values in AMD group, compared to HCs.

Abbreviations: PerAF, percent amplitude of fluctuation; AMD, Age-related macular degeneration; HCs, healthy controls; R, right; L, left.

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