Altered regional homogeneity in patients with late monocular blindness: a resting-state functional MRI study

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Many previous studies have demonstrated that the blindness patients have has functional and anatomical abnormalities in the visual and other vision-related cortex. However, changes in the brain function in late monocular blindness (MB) at rest are largely unknown. In this study, we investigated the underlying regional homogeneity (ReHo) of brain-activity abnormalities in patients with late MB and their relationship with clinical features. A total of 32 patients with MB (25 male and seven female) and 32 healthy controls (HCs) (25 male and seven female) closely matched in age, sex, and education underwent resting-state functional MRI scans. The ReHo method was used to assess local features of spontaneous brain activities. Patients with MB were distinguishable from HCs using the receiver operating characteristic curve. The relationship between the mean ReHo in brain regions and the behavioral performance was calculated using correlation analysis. Compared with HCs, patients with MB showed significantly decreased ReHo values in the right rectal gyrus, right cuneus, right anterior cingulate, and right lateral occipital cortex and increased ReHo values in the right inferior temporal gyrus, right frontal middle orbital, left posterior

Introduction

Blindness, known as the loss of response to external light stimulus, is one of the most serious eye conditions. A previous study demonstrated that there were 32.4 million people suffering from blindness in 2010 globally [1]. The prevalence of blindness was 0.33% in urban Southern China [2]. Blindness can be divided into early blindness and late blindness roughly. It can be caused by a variety of factors such as ocular trauma [3], cataract [4], and glaucoma [5]. At present, drugs and surgery are effective for reversible blindness caused by cataract [6] and optic neuritis [7]. However, there is no effective treatment for irreversible blindness. Blindness greatly affects the daily life in the patients [8]. Blindness has also become a serious social problem. Around \$5.5 billion/year is spent for the medical care for blind patients in the USA [9]. cingulate/precuneus, and left middle frontal gyrus. However, there was no significant relationship between the different mean ReHo values in the brain regions and the clinical features. Late MB involves abnormalities of the visual cortex and other vision-related brain regions, which may reflect brain dysfunction in these regions. *NeuroReport* 28:1085–1091 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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Functional MRI (fMRI) has been successfully used to evaluate the changes in brain activities in blindness. In the early blindness, the superior colliculus (visual subcortical) was reorganized with the auditory system [10]. Meanwhile, the blindness showed enhanced processing of auditory motion [11]. In addition, it has been shown that the occipital cortex is thicker in early blindness patients [12], whereas the interactions between the visual and other sensory cortices are weaker [13]. Late blindness also leads to the altered cerebral function. Gray matter volume in the visual areas is markedly decreased in late blindness [14]. Moreover, compared with late blindness, early blindness has increased functional connectivity in the ventral visual stream [15]. Bola et al. [16] demonstrated that the blindness showed the impairment of synchronization in brain networks and more specifically in temporal patterns [17]. In our previous study, we demonstrated that the late monocular blindness (MB) showed the lower brain amplitude of low-frequency fluctuation in the left cerebellum anterior lobe, right parahippocampal gyrus, right cuneus, and left precentral gyrus [18]. Meanwhile, another research reported that the macaque monkeys with MB showed decreased fractional anisotropy and increased mean diffusivity in the disease side optic tracts compared with the normal optic tracts

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[19]. However, synchronous neural activities in MB are less studied.

The regional homogeneity (ReHo) method, a resting-state fMRI measurement method, is thought to be a reliable and sensitive measurement, which can be used to evaluate the coherence of the blood oxygen level-dependent signal among neighboring voxels of the whole brain at rest. Kendall's coefficient of concordance is used to calculate the similarity of the time series of the voxel with those of its nearest neighbors. The major advantage of ReHo is the ability to detect spontaneous hemodynamic responses of resting-state fMRI [20,21]. In our previous studies, the ReHo method has been successfully used to assess the neurological conditions in certain eye diseases such as optic neuritis [22] and comitant strabismus [23].

Here, we hypothesized that the ReHo values of restingstate brain activity would be different between the MB and the healthy control (HC) groups, which might underlie the mechanism related to the dysfunction of the visual cortex. The aim of our study was to investigate brain synchronous neural activity changes in patients with late MB and investigate its relationship with the behavioral performances.

Patients and methods Patients

A total of 32 patients with MB (25 male and seven female, all with right eye blindness) were recruited from the Ophthalmology Department of the First Affiliated Hospital of Nanchang University Hospital. The diagnostic criteria of MB were as follows: (a) late stage of MB (in 18 patients it was caused by ocular trauma and in 14 patients it was due to keratitis); (b) normal contralateral eye without any ocular diseases (cataracts, glaucoma, optic neuritis, and retinal degeneration). The exclusion criteria were as follows: (i) congenital blindness; (ii) impaired contralateral eye vision; (iii) blindness caused by eye diseases (cataracts, glaucoma, optic neuritis, macular degeneration, and ocular ischemic diseases); (iv) a history of surgery in both eyes; (v) long-term medical treatment of blindness; (vi) psychiatric disorders (depression, bipolar disorder, and sleep disorder), and

Table 1 Demographics and clinical measurements

	MB	HC	Cohen's d	Gates' δ	
Male/female	25/7	25/7	NA	NA	
Age (years)	45.63 ± 13.01	45.28 ± 12.50	0.027	0.026	
Weight (kg)	58.56 ± 7.23	57.81 ± 6.70	0.108	0.104	
Handedness	32R	32R	NA	NA	
Duration of MB (years)	22.66 ± 7.68	NA	NA	NA	
Best-corrected VA-right	0.46 ± 0.55	$1.17 \!\pm\! 0.26$	1.650	1.290	
Best-corrected VA-left	1.11 ± 0.50	1.14 ± 0.26	0.075	0.06	

Effect size measures comparing two groups.

HC, healthy control; MB, monocular blindness; NA, not applicable; VA, visual acuity.

cerebral infarction diseases (cerebral hemorrhage, cerebral infarction, and cerebral vascular malformations).

Thirty-two (25 male and seven female) HCs with age, sex, and education status matched to participants in the MB group were also recruited for this study. All HCs met the following criteria: (i) no abnormalities in the brain parenchyma on cranial MRI; (ii) no ocular disease with uncorrected or corrected visual acuity (VA) more than 0.8; (iii) no psychiatric disorders; and (iv) be able to be scanned with MRI (e.g. no cardiac pacemaker or implanted metal devices). All research methods followed the Declaration of Helsinki and were approved by the principles of medical ethics. All volunteers participated voluntarily and were informed of the purposes, methods, and potential risks before signing an informed consent form.

MRI parameters

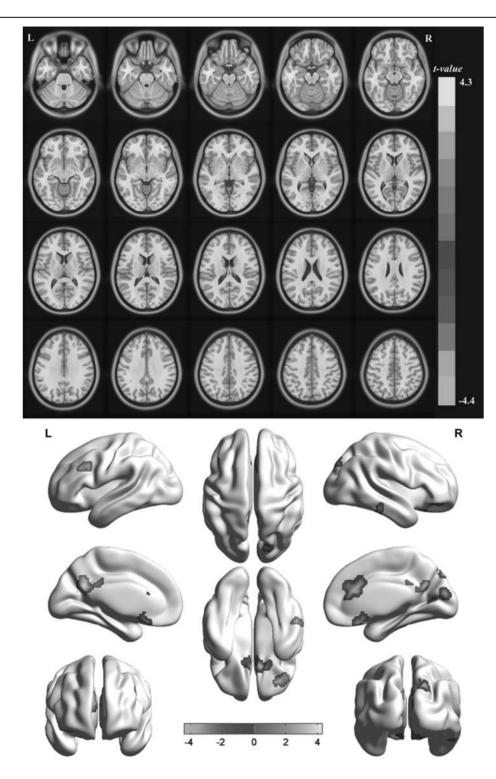
MRI scanning was performed on a 3 T MR scanner (Trio; Siemens, Munich, Germany). The functional data were obtained with spoiled gradient-recalled echo sequence with the following parameters: repetition time = 1900 ms, echo time = 2.26 ms, thickness = 1.0 mm, gap = 0.5 mm, acquisition matrix = 256×256 , field of view = 250×250 mm, and flip angle = 9°; 176 structural images were obtained. Finally, 240 functional images (repetition time = 2000 ms, echo time = 30 ms, thickness = 4.0 mm, gap = 1.2 mm, acquisition matrix = 64×64 , flip angle = 90° , field of view = 220×220 mm, and 30 axial slices with gradient-recalled echo-planar imaging pulse sequence) covering the whole brain were obtained.

Functional MRI data analysis

The 240 functional images were analyzed as described previously [22]. Briefly, the data were filtered using MRIcro (Nottingham University, Nottingham, UK) and preprocessed using SPM8 (The MathWorks Inc., Natick, Massachusetts, USA) and DPARSFA (Institute of Psychology, CAS, Beijing, People's Republic of China) software. On the basis of Kendall's coefficient of concordance, ReHo computation was performed with the REST software (State Key Laboratory of Cognitive Neuroscience and Learning, Beijing, China), as previously described [22].

Statistical analysis

For fMRI data, two-sample *t*-test was performed to examine the voxel-wise difference between the MB and HC groups using the REST toolbox; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China (The statistical threshold was set at the voxel level with P < 0.05for multiple comparisons using Gaussian random field theory voxels with P < 0.01 and cluster size > 40 voxels, AlphaSim corrected.). These voxels were regarded as the regions of interest showing significant difference between the two groups.



Spontaneous brain activity in the monocular blindness and healthy control groups. Significant activity differences were observed in the right rectal gyrus, right cuneus, right anterior cingulate, right lateral occipital cortex, right inferior temporal gyrus, right frontal middle orbital, left posterior cingulate/precuneus, and left middle frontal gyrus. Black denotes higher regional homogeneity values. [P<0.01 for multiple comparisons using Gaussian random field theory (z>2.3, P<0.01, cluster>40 voxels, AlphaSim corrected)].

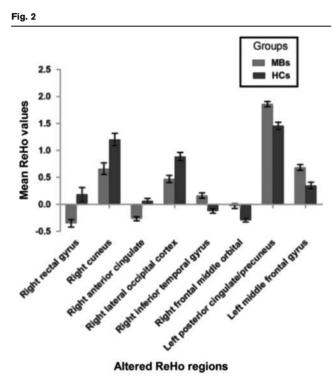
Table 2 Brai	າ areas with	significantly	different	regional	homogeneity	values	between gro	oups
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Condition	Left/right	Brain regions	BA	М	VI coordinat	tes	Cluster size	t-value	d.f.	<i>P</i> -value*
				X	Ŷ	Z				
MBs < HCs										
1	Right	Rectal gyrus	11	9	24	-21	78	-3.555	48.542	0.001
2	Right	Cuneus	18	3	-84	18	65	-3.289	61.752	0.001
3	Right	Anterior cingulate	24/32	6	30	21	115	-4.395	58.900	< 0.001
4	Right	Lateral occipital cortex	19	12	-84	45	61	-4.082	60.830	< 0.001
MBs > HCs	Ū									
1	Right	Inferior temporal gyrus	20	63	-33	-21	41	3.505	60.165	< 0.001
2	Right	Frontal middle orbital	11/47	39	39	-15	55	3.422	58.404	< 0.001
3	Left	Posterior cingulate, precuneus	23	0	-42	30	135	4.288	57.574	< 0.001
4	Left	Middle frontal gyrus	44	-48	27	36	52	3.493	61.064	< 0.001

The statistical threshold was set at the voxel level with P < 0.05 for multiple comparisons using Gaussian random field theory (z > 2.3, P < 0.01, cluster > 40 voxels, AlphaSim corrected).

*P < 0.05, significant.

BA, Brodmann area; HC, healthy control; MB, monocular blindness; MNI, Montreal Neurological Institute.



The mean values of altered ReHo values between the MB and HC groups. HC, healthy control; MB, monocular blindness; ReHo, regional homogeneity.

For behavioral performances, effect size measures were used for continuous data. Cohen's d and Gates' δ were calculated corrected for multiple comparisons.

SPSS, version 20.0 (IBM Corporation, Armonk, New York, USA) statistical software was used for all statistical analyses.

Brain-behavior correlation analysis

The relationship between the mean ReHo value and their clinical features was calculated using the correlation analysis (P < 0.05 was considered statistically significant).

Clinical data analysis

The cumulative clinical measurements, including the duration of the onset of MB and best-corrected VA were recorded and analyzed in the study with independent sample *t*-test (P < 0.05 as significantly different).

Results

Demographics and visual measurements

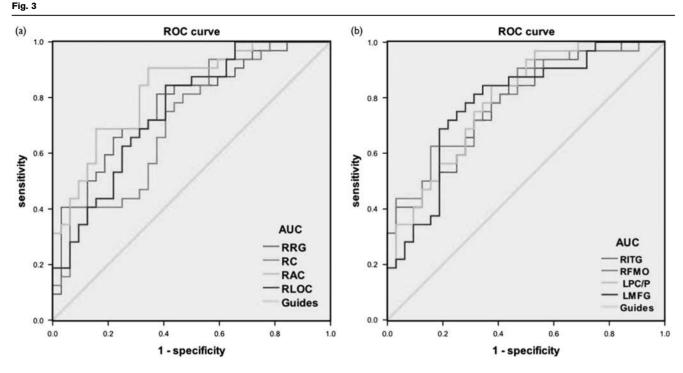
There were low Cohen's d in weight (0.108), age (0.108), and best-corrected VA-left (P=0.719) between the two groups. There was high Cohen's d in best-corrected VA-right (0.075) between the two groups (Table 1).

Regional homogeneity differences

Compared with HCs, MB patients showed lower ReHo values in the right rectal gyrus, right cuneus, right anterior cingulate, and right lateral occipital cortex [Fig. 1 (dark grey) and Table 2]. In contrast, higher ReHo values in the MB group were observed in the right inferior temporal gyrus (ITG), right frontal middle orbital, left posterior cingulate/precuneus, and left middle frontal gyrus [Fig. 1 (light grey) and Table 2]. The mean values of altered ReHo between the MB and HC groups are shown in Fig. 2. In the MB group, there was no significant correlation between the mean ReHo values of the different brain areas and the clinical manifestations (P > 0.05).

Receiver operating characteristic curve

We hypothesized that the ReHo differences between the MB and HC groups might be useful diagnostic markers. The mean ReHo values of the different brain regions were analyzed using the receiver operating characteristic (ROC) curves. The areas under the ROC curve were as follows: right rectal gyrus, 0.771; right cuneus, 0.715; right anterior cingulate, 0.828; and right lateral occipital cortex (0.756) (MBs < HCs) (Fig. 3a); the areas under the ROC curve for ReHo values were as follows: right ITG, 0.778; right frontal middle orbita, 0.795; left posterior cingulate/



ROC curve analysis of the mean regional homogeneity values for altered brain regions. The AUCs were 0.771 (P < 0.001; 95% CI: 0.657–0.886) for the RRG, 0.715 (P=0.003; 95% CI: 0.589–0.840) for the RC, 0.828 (P < 0.001; 95% CI: 0.729–0.927) for the RAC, and 0.756 (P < 0.001; 95% CI: 0.639–0.873) for the RLOC (MBs < HCs). (a) The AUCs were 0.778 (P < 0.001; 95% CI: 0.667-0.889) for the RITG, 0.795 (P < 0.001; 95% CI: 0.687–0.903) for the RFMO, 0.793 (P < 0.001; 95% CI: 0.685–0.901) for the LPC/P, and 0.782 (P < 0.001; 95% CI: 0.688–0.897) for the LMFG (MBs > HCs) (b). AUC, area under the curve; CI, confidence interval; HC, healthy control; LMFG, left middle frontal gyrus; LPC/P, left posterior cingulate/precuneus; MB, monocular blindness; RAC, right anterior cingulate; RC, right cuneus; RFMO, right frontal middle orbital; RITG, right inferior temporal gyrus; RLOC, right lateral occipital cortex; ROC, receiver operating characteristic; RRG, right rectal gyrus.

precuneus, 0.793; and left middle frontal gyrus, 0.782 (MBs > HCs) (Fig. 3b).

Discussion

In our study, compared with HCs, patients with MB showed significantly decreased ReHo values in the right rectal gyrus, right cuneus, right anterior cingulated, and right lateral occipital cortex, and increased ReHo values in the right ITG, right frontal middle orbital, left posterior cingulate/precuneus, and left middle frontal gyrus.

Analysis of the decreased regional homogeneity values in monocular blindness

The cuneus is located in the occipital lobe, playing an important role in visual processing [24]. In addition, the cuneus has been shown to be involved in the visual imagery tasks [25]. The dysfunction of the cuneus has been suggested in many diseases such as trigeminal neuralgia [26] and panic disorder [27]. A previous study demonstrated that the blindness showed decreased regional gray matter in the cuneus [28]. Consistent with that, in our study, we also found significantly decreased ReHo values in the right cuneus of the MB group. We speculated that the MB might be related to disrupted synchronous neural activity in the right cuneus.

The anterior cingulated cortex (ACC) located in the medial surface of the frontal lobes is a part of the limbic system. The ACC is involved in cognition [29] and emotion [30]. Moreover, the ACC is responsible for error detection and behavior monitoring [31]. Attention-deficit/hyperactivity disorder patients exhibit ACC functional deficits [32]. Meanwhile, a previous study suggests that the right dorsal ACC plays an important role in the visual function [33]. Abnormality of the ACC has been associated with many diseases such as depression [34], schizophrenia [35], and autism [36]. In our study, we demonstrated that the MB group showed significantly decreased ReHo values in the right ACC, indicating that the synchronous neural activity was also disrupted in the right ACC in MB patients.

The occipital lobe is the anatomical region of the visual cortex, which is critical for visual processing. The occipital lobe contains the primary visual cortex (V1), visual area V2, visual area V3, visual area V4, and visual area V5 [37]. The V1 receives information from its ipsilateral lateral geniculate. The primate visual system can be divided into a ventral stream and a dorsal stream. Liu *et al.* [38] showed decreased functional connectivity within the occipital lobe. Another research reported that early blindness patients had significantly decreased gray

matter volume in the early visual cortex [39]. Meanwhile, blindness also correlates with reduced fractional anisotropy in the primary visual cortex using the diffusion tensor imaging method [40]. In support of these findings, we also found that the MB group showed significantly decreased ReHo values in the right lateral occipital cortex. We speculated that MBs might lead to the dysfunction of the synchronous neural activity in the right lateral occipital cortex.

Analysis of the increased regional homogeneity values in monocular blindness

The ITG is located in contact with the inferior occipital gyrus below the middle temporal gyrus. The ITG is involved in the visual memory [41]. In addition, the ITG plays an important role in the classification of visual shape [42]. Abnormalities of the ITG are related to many diseases such as schizophrenia [43] and Alzheimer's disease [44]. In our study, we found that MB showed significantly increased ReHo values in the right ITG, which indicates the excessive activation of the right ITG in MB. Meanwhile, the area under the ROC curve of the RITG was 0.778. We speculated that high activities of the right ITG might reflect the compensation of the monocular vision loss in MB patients.

The frontal orbital is a part of the frontal cortex, which is below the brain areas BA 47. The BA 47 is involved in language and grammatical processing [45,46]. Moreover, the BA 47 is also suggested to control the perception of musical structure [47]. In our study, we found that MB showed significantly increased ReHo values in the right frontal middle orbital, which may reflect the enhancement of language understanding in MBs. The middle frontal gyrus is one-third of the frontal lobe, and is involved in attention [48,49] and inhibitory errors [50]. The impairment of the middle frontal gyrus is related to many diseases such as attention-deficit hyperactivity disorder [51] and schizophrenia [52]. In our study, we found that MB showed significantly increased ReHo values in the left middle frontal gyrus. We surmised that MB might lead to the dysfunction of the middle frontal gyrus.

Conclusion

In summary, our results showed abnormal spontaneous activities in many brain regions, which might reflect the altered synchronous neural activity in the visual cortex and other vision-related brain regions in MB. There are some limitations to our study. First, the noise during the MRI scanning might have some influence on the brain activity in all participants. Second, we did not differentiate different clinical outcomes of the MBs, such as right eye blindness and left eye blindness. Third, MBs can be caused by a variety of factors, such as ocular trauma and keratitis, which might affect the accuracy of the results. Future study should distinguish different types of MBs to more accurately assess brain activities and functional changes.

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Conflicts of interest

There are no conflicts of interest.

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