Abnormal cerebral blood flow in patients with Leber's hereditary optic neuropathy.

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Research Article

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Abstract

Purpose

The study aimed to unravel abnormal cerebral blood flow (CBF) in patients with Leber's hereditary optic neuropathy (LHON) using arterial spin labeling (ASL) and to investigate the associations among disrupted CBF, disease duration, and neuro-ophthalmological impairment.

Methods

ASL perfusion imaging data was collected from 20 patients with acute LHON, 29 patients with chronic LHON, and 37 healthy controls. We used a one-way analysis of covariance to test the intergroup differences in CBF. Linear and nonlinear curve fit models were applied to explore the associations among CBF, disease duration, and neuro-ophthalmological metrics.

Results

Brain regions differed in LHON patients included the left sensorimotor and bilateral visual areas ($p < 0.05$, cluster-wise family-wise error correction). Acute and chronic LHON patients demonstrated lower CBF in bilateral calcarine than the healthy controls. Chronic LHON had lower CBF in the left middle frontal gyrus and sensorimotor cortex, and temporal-partial junction than the healthy controls and acute LHON. A significant logarithmic negative correlation was shown between CBF of left middle frontal gyrus and disease duration. There showed a significant logarithmic positive correlation between retinal nerve fiber layer thickness and CBF in left middle frontal gyrus, and negative correlations between loss of variance and CBF in left middle frontal gyrus and sensorimotor cortex ($p < 0.05$, Bonferroni correction).

Conclusion

LHON patients exhibited reduced CBF in the visual pathway, sensorimotor and higher-tier cognitive areas. Disease duration and neuro-ophthalmological impairments can influence the metabolism of non-visual areas.

Introduction

LHON is a hereditary neurological disease caused by mitochondrial DNA (mtDNA) mutations characterized by painless progressive decline or loss of vision in young males (Chinnery et al., 2000; Poincenot, Pearson, & Karanjia, 2020). The main features of LHON anterior visual pathway lesions are loss of retinal ganglion cells (RGC), progressive thinning of retinal nerve fiber layer (RNFL), dilation of the radial papillary capillary (RPC) around the optic disk, and loss of optic nerve axons, and so on (Asanad et al., 2019; Balducci et al., 2016; Cui et al., 2020; Matsuzaki, Hirami, Uyama, & Kurimoto, 2018; Rizzo et al., 2012; L. Wang et al., 2017).

In addition to the progressive decline in vision, members of the LHON family may have other neurological abnormalities, including peripheral neuropathy (Finsterer & Zarrouk-Mahjoub, 2018), dystonia (Saracchi et al., 2013), hearing impairment (Rance et al., 2012), and cerebellar ataxia (Funakawa et al., 1995), etc. Besides, it suggests that LHON may damage brain tissue directly or indirectly. In recent years, some sporadic case reports have reported that LHON can cause brain gray matter (GM) and white matter abnormalities. For example, neuroimaging studies based
on magnetic resonance imaging (MRI) have reported structural and functional abnormalities along the visual pathways, such as optic radiation (Barcella et al., 2010; Manners et al., 2015; Milesi et al., 2012), optic chiasm (Barcella et al., 2010), optic nerve (Grochowski, Symms, et al., 2020; L. Wang et al., 2017), lateral geniculate nuclei (LGN) (Jonak et al., 2020; Rizzo et al., 2012; Vaphiades, 2011), medial geniculate nuclei (MGN) (Jonak et al., 2020), primary visual cortex (Barcella et al., 2010) and extrastriate cortex (d’Almeida, Mateus, Reis, Grazina, & Castelo-Branco, 2013; Jonak, 2020; Mateus, d’Almeida, Reis, Silva, & Castelo-Branco, 2016). Moreover, brain abnormalities outside the visual pathway were also reported in the LHON, including abnormal microstructural integrity of acoustic radiation and other white matter structures (Long et al., 2019; Manners et al., 2015; L. Wang et al., 2021; J. Zhang et al., 2021), disrupted functional and structural connectivities (Rocca et al., 2011; Vacchiano et al., 2019), and higher hippocampus volume (Grochowski, Jonak, Maciejewski, Stepniewski, & Rahnama-Hezavah, 2020), and so on.

Most LHON mutations are located in genes encoding mitochondrial complex I, also called nicotinamide adenine dinucleotide dehydrogenase subunit (ND1). Mutations in ND1 change the amino acids of ND1 (Yen, Wang, & Wei, 2006) and disrupt ATP function, leading to reduction in ATP production and cell respiration rate. A rapid reduction in ATP concentration was reported in all three types of LHON mutation-carrying cell cultures (ND1, ND4 and ND6) (Zanna et al., 2003). Thus, ND1 dysfunction in patients with LHON can limit ATP production, triggering brain cell metabolism changes and leading to abnormal brain activity. Thus, it is expected that LHON mutation would blunt the energy metabolism of the patients’ brain tissues and cause central never system (CNS) symptoms. Magnetic resonance spectroscopy (MRS) and arterial spin labeling (ASL) are two frequently used non-invasive MRI techniques to evaluate the brain's energy metabolism. For example, phosphorus MRS ($^{31}$P-MRS) showed defective occipital lobe energy metabolism in LHON carriers of m.11778G > A (Barbiroli et al., 1995). A proton MRS ($^{1}$H-MRS) study reported decreased absolute creatine followed by decreased absolute N-acetylaspartate concentration in the normal-appearing white matter of LHON carriers (Ostojic et al., 2009). These studies implied that LHON could cause abnormal brain metabolism, even during the pre-symptomatic period. ASL measures the rate of arterial blood transport to the capillary bed (termed cerebral blood flow (CBF)) by saturating (or labelling) the endogenous arterial blood, which is closely related to brain neural activity and metabolism (Alsop et al., 2015). Changed CBF has been detected in blind, high myopia people (De Volder et al., 1997; Ptito, Moesgaard, Gjedde, & Kupers, 2005; H. Wang et al., 2020) and neuropsychiatric diseases (Hays, Zlatar, & Wierenga, 2016; Jann et al., 2015; Xu et al., 2017). To our knowledge, there is no study reporting the brain CBF changes in LHON patients or pre-symptomatic carriers. Thus, detecting the potential CBF changes in LHON patients can help us further understand the patho-metabolic mechanism of LHON.

Based on the metabolic (Barbiroli et al., 1995; Ostojic et al., 2009), functional (Rocca et al., 2011; Vacchiano et al., 2019) and structural abnormalities (Long et al., 2019; L. Wang et al., 2021; J. Zhang et al., 2021) reported in LHON patients and carriers, we hypothesized that abnormal CBF would also be identified in both the visual and non-visual pathways; furthermore, we hypothesized that the disease process would influence the CBF changes in the LHON. To address these hypotheses, we collected ASL data from 55 LHON patients and 37 healthy controls. We first applied voxel-based data-driven statistics to explore which cerebral regions have abnormal CBF in the LHON patients. Then several curve fitting models were used to investigate the potential relationships among CBF abnormalities, disease duration, and neuro-ophthalmological metrics in these brain regions.

**Materials And Methods**

**Participants**

From May 2012 to December 2016, we recruited 55 LHON patients who were diagnosed in Henan Provincial People's Hospital. Inclusion criteria were: 1) with one of three common mtDNA point mutations (m.3460G > A, m.11778G > A,
m.14484T > C); 2) progressively non-painfully loss of vision; 3) no history of neurological, psychiatric, or substance abuse; 3) no other ophthalmic diseases; 4) no visible intracerebral and spinal cord lesions. Six LHON patients were excluded from the study, including 1 for missing neuro-ophthalmological examination, 1 for missing T1 structural MRI images, and 4 for artifacts in ASL images. Thus, the study finally enrolled 20 acute LHON (A-LHON) (disease duration < 1 year, ages ranging from 10 years to 57 years old, 18 males, 14 cases with m.11778G > A mutation, 1 case with m.3460G > A, and 5 with m.14484T > C) and 29 chronic LHON (C-LHON) (disease duration ≥ 1 year, ages ranging from 13 years to 53 years old, 20 males, 23 cases with m.11778G > A mutation, 2 cases with m.3460G > A, and 4 cases with m.14484T > C). The 49 LHON patients covered a wide range of disease duration spanning the acute and chronic phases (from 3 weeks to 422 months). All patients had no clinical manifestations and abnormal-appearing brain tissue except for vision loss. We also recruited 37 HC with comparable age and gender distribution as the LHON (ages ranging from 11 years to 44 years old, 27 males). The inclusion criteria were the same as LHON patients except for no visual impairment and mtDNA mutations.

**Neuro-ophthalmological examination**

The corrected visual acuity was evaluated by the logarithm of the minimum angle of resolution (logMAR). Octopus perimeter 101G2 program TOP Strategy (Interzeag AG, Haig-Streit Schlieren, Switzerland) was carried out to obtain the visual field and assess mean defect (MD), mean sensitivity (MS), and loss of variance (LV) (Mateus et al.). The average peripapillary RNFL thickness was measured using a high-resolution spectral-domain optical coherence tomography (Carl Zeiss Meditec, Dublin, CA, USA) with a preset diameter of 3.45 mm.

**MRI Data acquisitions**

MRI images were obtained by a 3.0T MR scanner (Discovery MR750, GE Healthcare, Waukesha, WI, USA). Resting-state CBF data were acquired by a pseudo-continuous ASL (pcASL) method with a 3D spiral fast spin-echo acquisition and background suppression. The scan parameters of resting-state ASL data were as follows: repetition time (TR) = 4632 ms; echo time (TE) = 10.5 ms; post labelling delay (PLD) = 1525 ms; flip angle (FA) = 111°; field of view (FOV) = 128mm × 128 mm; voxel size = 1.8 × 1.8 × 4 mm³; slice thickness = 4 mm; no gap; 36 slices. High-resolution three-dimensional T1-weighed images (T1WI) were also obtained using a fast-spoiled gradient echo sequence. T1WI had following parameters: TR = 8.2 ms; TE = 3.2 ms; inversion time (TI) = 450 ms; FA = 12°; FOV = 256 mm × 256 mm; voxel size = 1 × 1 × 1 mm³; slice thickness = 1 mm; no gap; 176 slices.

**CBF preprocessing**

First, the ASL differential image (perfusion-weighted images, PWI) was obtained by subtracting the label image from the control image. Second, the CBF map was calculated based on the PWI images according to the pcASL model (Wu, Lou, Wu, & Ma, 2014). Third, SPM12 (http://www.fil.ion.ucl.ac.uk/spm) was used to normalize the CBF map to the Montreal Neurological Institute(Ostojic et al.) space. Specifically, the ASL control images of each subject were coregistered to the T1WI after brain stripping; then, the T1WI of each subject was segmented and normalized into MNI space by an Exponentiated Lie algebra (DARTEL); then the derived deformation flow field was used to warp the CBF images into the MNI space. Fourth, to control for the heterogeneities in labelling efficiency among participants, the normalized CBF map was then divided by the global mean CBF value to obtain a relative CBF map (rCBF). Finally, all rCBF maps were spatially smoothed with a Gaussian kernel of 6 × 6 × 6 mm³ full-width at half maximum (FWHM).

**Statistical analysis**
All demographic and clinical statistics were performed by SPSS19.0 (https://www.ibm.com/analytics/spss-statistics-software). A Chi-square test was used to compare the sex distribution among groups. One-way analysis of variance (ANOVA) was used to compare the differences in age and neuro-ophthalmological metrics among the three groups ($P < 0.05/3$, Bonferroni correction).

Using SPM12, A voxel-based one-way ANOVA was used to compare the rCBF differences among groups with age and gender as co-variables (voxel-wise $p < 0.001$, corrected at a cluster-level threshold of $P < 0.05$ using family-wise error [FWE] method). Then the clusters with the top 100 voxels at each peak were defined as regions of interest (ROIs), and the average rCBF of each ROI for each subject was extracted using the DPABI V4.3 (http://rfmri.org/dpabi). Finally, post-hoc analysis was carried out to compare the rCBF differences in each ROI between each pair of groups after correcting for age and gender effects using SPSS19.0 ($p < 0.05/15$, Bonferroni correction).

Linear and logarithmic curve fitting were carried out to explore the association between the rCBF values of each ROI and clinical variables (including disease duration, neuro-ophthalmological metrics) after regressing out gender and age effects using SPSS 19.0 ($p < 0.05/15$, Bonferroni correction).

**Results**

**Demographic and clinical variables**

No statistical differences were found in age (One-way ANOVA, $F = 2.085, p = 0.131$) and gender (Chi-square test, $\chi^2 = 4.399, p = 0.111$) among A-LHON, C-LHON and HC. One-way ANOVA revealed that both A-LHON and C-LHON patients had higher MD ($F = 48.756, p < 1.10e^{-7}$, Bonferroni corrected) and LV ($F = 21.735, p < 0.001$, Bonferroni corrected), and lower MS ($F = 54.394, p < 1.12e^{15}$, Bonferroni corrected) than the HC. Besides, C-LHON patients had thinner RNFL than A-LHON ($F = 72.554, p =1.98e^{15}$, Bonferroni corrected) and the HC ($F = 72.554, p =3.87e^{16}$, Bonferroni corrected). There showed no statistical differences in mtDNA mutation types between the A-LHON and C-LHON ($\chi^2 = 1.121, p = 0.674$) (**Table 1**).

**CBF changes in LHON patients:**

Compared with the HC, LHON patients had significantly abnormal rCBF in the left sensorimotor cortex (SMC), left temporal-parietal junction (TPJ), left middle frontal gyrus (MFG), and bilateral posterior calcarine gyrus (Santello, Cali, & Bezzi) ($p < 0.05$, FWE corrected at cluster-level) (**Figure 1**). Post-hoc analysis demonstrated that both A-LHON and C-LHON patients demonstrated lower rCBF in bilateral CAL than the HC ($p < 2.50e^{-6}$, Bonferroni corrected); Only C-LHON had lower rCBF than the HC in left MFG, left SMC, and left TPJ ($p < 3.55e^{4}$, Bonferroni corrected). A-LHON have higher CBF than C-LHON in left MFG, left SMC, and left TPJ ($p < 1.01e^{-3}$, Bonferroni corrected) (**Figure 2**, **Supplementary Table 1**).

**Association between rCBF abruption and clinical variables:**

Among the curve-fitting model, disease duration demonstrated a significantly logarithmic negative correlation with the rCBF of the left MFG ($R^2 = 0.195, p = 7.80e^{4}$, Bonferroni corrected) (**Figure 3**, **Supplementary Table 2**). Moreover, there demonstrated a significant logarithmic positive correlation between RNFL thickness and CBF of left MFG ($R^2 = 0.190, p = 1.40e^{3}$, Bonferroni corrected) (**Figure 4a**, **Supplementary Table 3**), and logarithmic negative correlations between LV and CBF of left MFG ($R^2 = 0.199, p = 1.20e^{3}$) and SMC ($R^2 = 0.154, p = 4.40e^{3}$) (**Figure 4b-c**, **Supplementary Table 3**).
Supplementary Table 4), and a linear positive correlation between MD and CBF of left CAL ($R^2 = 0.147, p = 4.50e^{-3}$) (Figure 4d, Supplementary Table 6)

Discussion

To the best of our knowledge, this is the first study to explore CBF metabolism alteration using the ASL technique in LHON. We found that the rCBF of bilateral calcarine gyri were reduced in both A-LHON and C-LHON. In cortex outside the visual pathway (such as the sensorimotor cortex, middle frontal gyrus, and temporal parietal junction), the rCBF was reduced in only C-LHON. We identified several pairs of associations among the abnormal CBF, disease duration, and neuro-ophthalmological measures. These results may help us understand the metabolic mechanisms of LHON from the perspective of CBF perfusion.

A previous MRS study reported abnormal energy metabolism in occipital lobe of LHON(Barbiroli et al., 1995). Barcella et al. used voxel-based morphometry (VBM) analysis and found the gray matter volume of bilateral primary visual cortex are atrophied in LHON patients(Barcella et al., 2010). Kamil et al. found that the alpha band activity of neurons in the visual cortex decreased on electroencephalography (EEG)(Jonak, 2020). Reduced white matter volume(Barcella et al., 2010) and impaired white matter microscopic integrity (Manners et al., 2015; Milesi et al., 2012; Ogawa et al., 2014; Rizzo et al., 2012; L. Wang et al., 2021) of the retinofugal pathway were also frequently reported. Consistently, the present study further reported abnormal CBF metabolism in the primary visual cortex. The reduced CBF, atrophied cortex, impaired microscopic integrity, and abnormal metabolic product in the visual cortex consistently proved the involvement of visual pathway in the LHON, and the reduced CBF may reflect the neuron loss or degeneration of visual cortex. In consistence with a recent study showing no correlation between the white matter impairment and disease duration or RNFL thickness(L. Wang et al., 2021), this study also did not identify any association between the reduced CBF and RNFL thickness. Furthermore, the CBF reduction were consistently exist in both acute and chronic LHON, and it was not associated with the disease duration. Because most LHON mutations can lead to a series of mitochondrial dysfunction and energy metabolic defect(Zanna et al., 2003), the reduced CBF in both the acute and chronic LHON may indicate a direct impairment of the visual cortex, although we could not excluded the cross-neuronal degeneration mechanisms following RGC death(L. Wang et al., 2021).

Although most previous studies had reported the damage of visual pathways, such as V1(Barcella et al., 2010), extrastriate cortex(d'Almeida et al., 2013; Mateus et al., 2016), LGN(Jonak et al., 2020; Rizzo et al., 2012; Vaphiades, 2011), MGN(Jonak et al., 2020) and white matter tract(Barcella et al., 2010; Manners et al., 2015; Ogawa et al., 2014; Takemura et al., 2019); lesions outside the visual pathway in LHON have also been reported in recent years, including the basal ganglia(Cui et al., 2020; Mercuri, White, & Oliveira, 2017), vestibular nuclei(Miyaue et al., 2019), dentate gyrus(L. Wang et al., 2021), and inferior olivary nucleus(Nakaso et al., 2012), which are associated with motor control. In the present study, we also found decreased CBF in the sensorimotor cortex, posterior MFG, and temporal-parietal junction in the chronic LHON. The sensorimotor cortex plays central roles in somatosensory perception and motor control(Ebbeisen et al., 2018). The temporal-parietal junctions were also closely associated with visuospatial perspective taking(Brugger, 2002) and somatosensory processing(Blanke, Landis, Spinelli, & Seeck, 2004; Orru, Bertelloni, Cesari, Conversano, & Gemignani, 2021). The posterior MFG near the premotor area plays an essential role in executing complex motor responses(Bhoyroo et al., 2021; Kombos et al., 1999). Thus, we speculated that lower CBF in these regions might be related to non-visual sensory and motor dysfunction in the chronic stage of LHON, which could explain the abnormal audiovisual perception and motor control in LHON, such as peripheral neuropathy(Finsterer & Zarrouk-Mahjoub, 2018), dystonia(Saracchi et al., 2013), cerebellar ataxia(Funakawa et al., 1995) and hearing dysfunction(Leng et al., 2015; Rance et al., 2012). It should be noted that we only found the
chronic LHON had decreased CBF in these non-visual cortices; moreover, the CBF in the posterior MFG was logarithmically negatively correlated with the disease duration, suggesting that the reduced CBF in these areas cannot be explained by direct involvement caused by mtDNA mutation, and it is more likely a secondary chronic adaption following vision impairment.

The RNFL structure of LHON undergoes an initial thickening at the preclinical and acute stage and then progressively thinning (Asanad et al., 2019; Balducci et al., 2016; Borrelli et al., 2016; Mizoguchi et al., 2015; Y. Zhang et al., 2014). Previous studies have shown that RNFL thickness is significantly correlated with the imaging indicators of the visual pathway, such as optic tract fractional anisotropy value (L. Wang et al., 2017), LGN volume (Jonak et al., 2020), the activity of secondary visual cortex (Jonak, 2020) and morphological changes in V1 (Barcella et al., 2010). Our results provided new evidence that CBF in the posterior MFG was decreasing along with RNFL thinning, and CBF in posterior MFG and sensorimotor cortex was decreasing with visual field defects. These results suggested that the CBF reduction could progress faster with growing visual impairment. Previous studies have reported decreased functional connectivity between the primary visual cortex and sensory-motor cortex and auditory cortex in either congenital and late-onset blind people (Liu et al., 2007; Yu et al., 2008). A recent study also showed disrupted structural connectivity between the visual cortex and superior temporal gyrus in the LHON (J. Zhang et al., 2021). Thus, the decreased CBF in these sensory-motor related areas in chronic LHON may indicate a general mechanism of multimodal sensory integration deficit after visual deprivation.

**Conclusion**

This study provided evidence that LHON patients exhibited reduced CBF not only in the visual pathway but also in sensorimotor and higher-tier cognitive areas. Furthermore, the decreased metabolism of these non-visual areas can be influenced by disease duration and severity of neuro-ophthalmological impairments.

**Declarations**

**Ethical approval**

The research was approved by the Ethics Committees of Henan Provincial People's Hospital and was carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Consent to participate**

All subjects signed informed consent.

**Consent for publication**

The work described has not been published before. It is not under consideration for publication elsewhere. Its publication has been approved by all co-authors, if any. Its publication has been approved by the responsible authorities at the institution where the work is carried out.

**Authors Contributions**

Wen Qin and Chunshui Yu designed research; Yi Ji, Ling Wang and Hao Ding performed research; Yi Ji, Ling Wang, Qin Tian, Dapeng Shi and Ke Fan analyzed data; Yi Ji and Ling Wang wrote the paper. Wen Qin is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Competing Interests

All authors declare no conflict of interest.

Availability of data and materials

The individual original MRI data will not be shared with the public because the subjects’ signed permission of personal data spread had not been approved. We promised that the imaging protocols and statistical analysis results would be accessed to public once the draft has been accepted for publication. Any reader can get the shareable data by email to the corresponding author.

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Code availability

Not applicable.

Authorship

The authors of the article will take full responsibility for the data, the analyses and interpretation, and the research’s conduct. All authors and contributors have agreed to the requirement in the Authorship Agreement Form. All authors have read and approved the submission.

References

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Table 1. Demographic and clinical characteristics.
<table>
<thead>
<tr>
<th></th>
<th>A-LHON</th>
<th>C-LHON</th>
<th>HC</th>
<th>Total effects</th>
<th>A-LHON vs. HC</th>
<th>C-LHON vs. HC</th>
<th>A-LHON vs. C-LHON</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td>$F/T/c^2$</td>
<td>$p$</td>
<td>$p$</td>
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<tr>
<td>Age (years)</td>
<td>21.55</td>
<td>27.37</td>
<td>24.95</td>
<td>$F=2.085$</td>
<td>$p = 0.131$</td>
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<tr>
<td>Gender (M/F)</td>
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<td>19/11</td>
<td>27/10</td>
<td>$c^2 = 4.399$</td>
<td>$p = 0.0111$</td>
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<tr>
<td>Duration (months)</td>
<td>4.72 ± 4.01</td>
<td>126.80</td>
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<td>$T = -3.960$</td>
<td>$p = 3.158e^7$</td>
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<tr>
<td>Duration (months)</td>
<td>4.72 ± 4.01</td>
<td>126.80</td>
<td>-</td>
<td>$T = -3.960$</td>
<td>$p = 3.158e^7$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MD (dB)</td>
<td>13.35 ± 9.27</td>
<td>18.10 ± 8.00</td>
<td>1.49 ± 1.10</td>
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<td>$8.72e^{15**}$</td>
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<td>MS (dB)</td>
<td>15.83 ± 8.07</td>
<td>10.92 ± 8.15</td>
<td>27.60 ± 1.18</td>
<td>$F = 54.394$</td>
<td>$p = 4.739e^{15}$</td>
<td>$1.84e^{7**}$</td>
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<td>LV (dB$^2$)</td>
<td>24.91 ± 25.29</td>
<td>37.14 ± 25.27</td>
<td>4.05 ± 1.97</td>
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<td>RNFL thickness(μm)</td>
<td>104.53 ± 25.21</td>
<td>60.20 ± 11.08</td>
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<td>$F = 72.554$</td>
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<td>-</td>
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<td>$p = 0.674$</td>
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<td>$x^2 = 1.121$</td>
<td>$p = 0.674$</td>
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</table>

Abbreviations: A-LHON = acute LHON patients; C-LHON = chronic LHON patients; HC = healthy controls; MD = Mean defect; MS = Mean sensitivity; LV = Loss of variance; RNFL = Retinal nerve fiber layer. ** indicates significance survival under Bonferroni correction.
Figure 1
Spatial distribution maps in LHON patients compared with HC. Abbreviations: L = Left; R = Right.

Figure 2
Comparison of brain regions with differences in CBF among A-LHON, C-LHON and HC. Abbreviations: rCBF = relative Cerebral blood flow; LHON = Leber's hereditary optic neuropathy; A = Acute; C = Chronic; HC = Healthy controls; L_CAL = Left calcarine fissure and surrounding cortex; R_CAL = Right calcarine fissure and surrounding cortex; L_TPJ = Left temporal-partial junction; L_PoCG = Left postcentral gyrus.

Figure 3
Correlation between CBF in L_MFG and disease duration in LHON. Abbreviations: LHON = Leber's hereditary optic neuropathy; rCBF = relative Cerebral blood flow; L_MFG = Left middle frontal gyrus.
Figure 4

Correlation between CBF and neuro-ophthalmological metrics. Abbreviations: LHON = Leber's hereditary optic neuropathy; rCBF = relative Cerebral blood flow; RNFL = Retinal nerve fiber layer; LV = Loss of variance; L_MFG = Left middle frontal gyrus; L_PoCG = Left postcentral gyrus.

Supplementary Files

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