• Review Article •

Visual function and biofeedback training of patients with central vision loss: a review

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Abstract

● Older individuals with macular diseases, such as age-related macular degeneration, experience central vision loss (CVL) due to degeneration of their photoreceptors and retinal cells. Patients with CVL may experience various vision impairments, including of visual acuity, fixation stability, contrast sensitivity, and stereoacuity. After CVL, most patients develop a preferred retinal locus outside the affected macular region, which serves as a new visual reference. In this review, we provide an overview of the visual function and impairment in individuals with CVL. In addition, the important role of biofeedback training on the visual function and activity of individuals with CVL is also reviewed. Accordingly, the location and development of the preferred retinal loci are discussed. Finally, this review discusses how to conduct biofeedback training to treat individuals with CVL.

● **KEYWORDS:** central vision loss; biofeedback training; preferred retinal locus; visual acuity; macular disease

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INTRODUCTION

Patients with macular diseases (MD), such as age-related macular degeneration (AMD) and Stargardt disease, often suffer from a loss of central vision. Central vision loss (CVL) is the main cause of visual function decline, loss of fixation stability, reduced contrast sensitivity, abnormal color vision, impaired stereovision, and limited reading and living ability[1-4]. With an aging population in China, an increasing number of older people are affected by MD[5]. MD not only irreversibly damages the fovea, which has the best visual acuity, but also affects the oculomotor nerve function, which is used by the visual system to plan and execute saccades and microsaccades[6]. As the disease progresses, the central visual acuity of patients with MD gradually decreases and forms a central scotoma, leading to a consistent decrease in fixation stability[7]. Patients present with a gradually progressive visual symptoms such as reading, face recognition, and driving difficulties. This impairs the quality of life, resulting in a significant mental and financial burden on individuals with CVL[8].

Patients with CVL spontaneously form a compensatory functional area in a relatively good position for retinal function, which is clinically called the preferred retinal locus (PRL)[9]. Using microperimetry to conduct PRL training has become the mainstay treatment for the rehabilitation of patients with low-vision MD[10]. The formation of the PRL can make full use of the residual retinal function in individuals with CVL to improve fixation stability, and improve their quality of life. Because of the complexity of the PRL formation process, the PRL location may not always correspond to the retinal location with the greatest visual acuity[11]. Retinal function seems to be underutilized, and it is difficult to wisely utilize the PRL to accomplish visual tasks[12]. A growing number of studies have suggested that PRL training is the preferred clinical option for low-vision rehabilitation. Previous studies have mostly focused on macular edema, retinal ischemia, and neovascular complications, whereas studies on visual function and visual rehabilitation processes are scarce. To address this issue, we conducted a review of the literature utilizing the PubMed database using the keywords “central vision loss”, “low vision rehabilitation”, and “preferred fixation locus”, and relevant papers were found.

This review provides a status report on contrast sensitivity, stereoscopic vision, and fixation stability in patients with CVL. Further, PRL and its important role in visual rehabilitation have been reported as well. Finally, we present an outlook on the future direction of low-vision rehabilitation.

Visual Disorders in Patients With Central Vision Loss

Patients with CVL frequently present with various visual impairments, such as reduced visual acuity, visual scotomas,

reduced contrast sensitivity, and impaired stereoacuity. Contrast sensitivity is the ability to detect sharp boundaries and slight changes in luminance in regions without distinct contours[13]. There is a reduction in contrast sensitivity in patients with MD[14]. As languages, such as Chinese, are written from left to right, their reading direction is from left to right. This leads to a continuous decline in contrast sensitivity[15]. Contrast sensitivity is tied to the ability to recognize faces and objects, and reduced contrast sensitivity is associated with a decline in the quality of life of patients[16]. MD often affects both eyes asymmetrically; however, there is a significant difference in macular function between the right and left eyes. There is a significant decline in visual acuity and contrast sensitivity when binocular vision is used in individuals with CVL, who have a significant difference in contrast sensitivity among the eyes. This phenomenon is known as the binocular inhibition[17]. In contrast, binocular summation indicates that visual acuity and contrast sensitivity improve significantly when binocular vision is used[18]. Pardhan[19] investigated the difference between binocular contrast sensitivity and the influence of this difference, and found that binocular summation appeared when the sensitivity of the two eyes was equivalent; however, binocular inhibition increased with an increase in the difference between the two eyes. Silvestri *et al*[20] observed binocular contrast sensitivity in 71 patients with CVL and found that 47% of the included patients had binocular inhibition. Because patients with CVL are more likely to use better-vision eyes to accomplish visual tasks[21], monocular PRLs are likely to occur in noncorresponding areas in these patients[22]. The non-corresponding location of the binocular PRL promotes binocular inhibition[23]. It is important to test contrast sensitivity to evaluate the quality of life and visual experience of patients with CVL.

Severe stereoptic impairment is typically observed in patients with CVL[24]. Stereopsis, or depth perception, is the visual ability that provides essential information for distance and location judgment in three dimensions. Stereopsis is thought to play an important role in depth perception[25]. Contrast sensitivity impairment has a significant impact on stereoptic impairment in individuals with CVL[26]. Some patients with CVL have partial remnant coarse stereopsis, and a previous study revealed that patients with coarse stereopsis show better hand and eye coordination than those with poor or absent stereopsis[27]. Residual coarse stereopsis is particularly important for the successful completion of various tasks in daily life, such as walking and grasping. Hence, patients with coarse stereopsis have a better quality of life[28] and motor skills[29] than those with poor or absent stereopsis. Absence of stereopsis increases the risk of falls[15]. Previous studies have shown that finding a particular location of the trained retinal locus (TRL) for PRL training can help patients with absent stereopsis regain coarse stereopsis[18].

Low reading ability is not only the most common complaint and symptom but also an important cause of decreased quality of life in patients with CVL[30]. Reading ability can be measured by the critical print size and reading speed[31]. Many patients with CVL have unequal visual status between both eyes (depending mainly on performance of the better eye). As patients are more likely to use the better-vision eye to accomplish a reading task, there was no significant difference between binocular reading acuity and better-vision eye reading acuity[30]. Kabanarou and Rubin[32] found that the reading speed of subjects with AMD was more related to the better-vision eye and that reading speed with binocular vision was not different from that with the better-vision eye. Similar to contrast sensitivity, binocular inhibition and summation can also be found in the reading acuity of patients with CVL[20]. Magnifying glasses as assistive devices are helpful for improving reading speed. However, patients with CVL still have a much lower reading speed despite the use of magnifying glasses[33]. Instead of best-corrected visual acuity (BCVA), the reading speed of patients with CVL is mainly related to fixation stability and PRL location[32]. Choosanding a particular TRL location for PRL training can enhance the reading ability of patients with CVL and improve their quality of life[34].

Use of Microperimetry in the Patient with Central Vision Loss Using microperimetry to assess macular function and monitor disease progression plays a vital role in diagnosing macular pathologies, and the results of this test have excellent inter-device repeatability and retest-reliability[35-37]. Recently, it has been used in a variety of clinical trials for PRL training and monitoring the progression of MD[38]. Microperimetry can directly show the size of the central scotoma as well as the average retinal sensitivity, which in turn helps evaluate the effects of treatments[37]. CVL often presents as a decline in fixation stability and retinal sensitivity of the macula[39]. As a tool for assessing the ability to sustain gaze at a fixed target, fixation stability is associated with the duration of the test and the visual function of the patient[37]. Fixation stability has a strong relationship with reading speed[7] and BCVA[40] in patients with CVL, but does not correlate with reading distance[41]. Fixation stability decreases with age in normal healthy people[42]. As diabetic macular edema (DME) gradually progresses, the fixation stability gradually decreases[43]. However, fixation stability is mainly affected by subfoveal hard exudatives rather than by the onset, development, and progression of diabetic macular edema[44]. Several studies have demonstrated that impaired fixation stability is prevalent in patients with AMD and Stargardt disease[40]. Tarita-Nistor *et al*[45] examined the monocular and binocular fixation stabilities of

patients with AMD. Their results showed that the fixation stability of the worse-vision eye increased by 84%–100% during binocular viewing, but no significant changes were found in the fixation stability of the better-vision eye during binocular viewing. Their results indicated that improving the fixation stability of the better-vision eye could make a critical contribution to improving binocular vision outcomes. Daily visual stimulation such as reading is helpful in enhancing visual function and improving fixation stability[46]. Decreased retinal sensitivity to microperimetry has been observed in patients with CVL. As the disease progresses, retinal sensitivity gradually decreases and the scotoma area increases[8,47]. Moreover, the retinal sensitivity of AMD is negatively correlated with retinal thickness and size of the drusen[48]. However, retinal sensitivity in DME is positively correlated with macular flow density[3]. Average retinal sensitivity and fixation stability measured using microperimetry are important indicators for detecting the progression of Stargardt disease[49].

Preferred Retinal Locus of the Patient with Central Vision Loss As a result of central field loss, people tend to rely more on peripheral vision and prefer a retinal region outside scotomas for fixation and saccades, termed PRL. PRL can be defined as follows: "One or more circumscribed regions of functioning retina, repeatedly aligned with a visual target for a specified task, that may also be used for attentional deployment and as the oculomotor reference"[50]. The PRL is often located at a position where the retina functions relatively well[51], and the microperimetry device plays an important role in detecting the exact location of the PRL. The PRL training mode of the Macular Integrity Assessment (MAIA) device can help enhance the stability of fixation when the PRL is in an appropriate position, but is not sufficiently stable[52]. If the PRL is not in the appropriate position, and the original PRL no longer supports optimal visual acuity, the MAIA device can find another retinal location (also called the TRL) with better visual capability to replace the original PRL[53]. Multiple factors may also contribute to PRL formation, and spontaneous PRL formation may take a long time[54]. In addition, two PRL locations are provided by the MAIA device[42]. The first is the preferred retinal locus initial (PRLi), which describes the centroid of fixation for the initial 10s of the test prior to perimetry testing, and the second one preferred retinal locus final (PRLf), which represents the centroid of all fixation point measurements during the examination[55]. There is a high prevalence of differential PRLi and PRLf locations in patients with unstable fixation[56]

The PRL is usually located away from the scotoma, where retinal function is relatively well preserved[57]. Most previous studies have shown that the PRL is more likely to be located in the nasal and superior quadrants of the macula[58-60]. However, other studies have reported contradictory results. Kisilevsky *et al*[61] found that the PRL of the better-vision eyes of patients with AMD or Stargardt disease tend to be located on the inferior or left side of the macula. However, no obvious rules were found for the PRL of eyes with worse vision. Silvestri *et al*[20] showed that the PRL tended to be located in the superior or inferior quadrants in the better-vision eye, and in the temporal or nasal quadrants in the worse-vision eye. Verdina *et al*[62] considered that the PRL of patients with Stargardt disease is more likely to be located in the superior quadrant. Interestingly, patients with Leber's hereditary optic neuropathy always choose an inappropriate retinal location for their PRL[63]. In summary, the conclusions of the studies were inconsistent and there were conflicting results. Therefore, further studies are warranted in this regard.

The principle and process of the spontaneous selection of the PRL location remain to be elucidated. Possible mechanisms have been proposed, including function-, performance-, and retinotopy-driven explanations[64]. In function-driven mechanisms, the location of the PRL is primarily correlated with the nature of the visual task. During visual behaviors, such as reading, people tend to pay more attention to content just below the center field of view. Therefore, the inferior visual field appeares to be more important than the superior field. This may explain why the PRL is more likely to be located in the inferior quadrant[65].

Whether the reading direction is from left to right or from right to left is an important factor affecting the location of the PRL. English native speakers prefer the left-to-right reading direction; therefore, their PRL are more often located on the right side[66]. Instead, the PRL of patients who read from right to left, such as in Hebrew, are more often located on the left side[67]. In a performance-driven mechanism, the visual system may spontaneously select a peripheral retinal location with better visual function to maximize visual performance[46]. The retinotopy-driven mechanism suggests that PRL placement is influenced by spontaneous retinotopic reorganization[68]. Moreover, multiple mechanisms determine the location of the PRL, and the location of the PRL changes as the disease progresses[69]. Tarita-Nistor *et al*[70] found that the location of the PRL in the worst-vision eye changed when changing from monocular vision to binocular vision.

Possibility and Necessity of Biofeedback Training CVL has a major impact on the quality of life and visual experience of patients[71], and the current treatment options for CVL do not completely meet patients' expectations. Patients with CVL, especially the older individuals, usually suffer from impaired abilities in daily life due to difficulties in reading newspapers or magazines, watching television, and socializing. Ultimately, the patient becomes unable to live independently and suffers

from anxiety and depressive symptoms at the same time[72]. An epidemiological survey revealed that one-third of patients with visual disorders had mild depression symptoms and one-third of them had severe depression symptoms[73]. On one hand, CVL leads to anxiety and depression; on the other hand, the anxiety and depressive symptoms will accelerate the development of CVL[74]. CVL not only leads to anxiety and depression, but also increases the risk of falls, which may lead to death[5]. White *et al*[15] presented a 12-month follow-up of patients with AMD and found that AMD-related vision loss and contrast sensitivity impairment were associated with the risk of falling. Currently, the intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) agents is the primary treatment for AMD and DME. Although the intravitreal administration of anti-VEGF agents can significantly improve the visual acuity of patients, anti-VEGF therapy requires multiple injections, and visual acuity continues to decrease despite multiple injections[75]. Sometimes, anti-VEGF injections may not fulfill the needs of patients.

Biofeedback training, also called microperimeter biofeedback fixation training, plays an important role in the visual rehabilitation of patients with CVL[10]. Clinical workers can select an appropriate location to place a new PRL (TRL) and conduct visual rehabilitation training using multiple microperimeter devices to improve fixation stability and BCVA[76]. On one hand, the spontaneous formation of the PRL is not achieved in all patients with CVL; on the other hand, the PRL may not be located in the place with the best retinal function[11]. The visual functions of the retina have not yet been fully elucidated. Therefore, an increasing number of researchers are using biofeedback training as the preferred option for low-vision rehabilitation[33]. Fully utilizing the residual function of the retina, enabling the older individuals to live an independent life, and improving their quality of life are the three important goals of low-vision rehabilitation. Improving reading ability is the key to low-vision rehabilitation[77]. When the central vision is impaired, the patient's reading ability declines significantly[78]. Studies have revealed that the BCVA reading ability and fixation stability of patients with CVL can be improved by biofeedback training[79]. The clinical benefit remained stable after the training was completed[80]. A retrospective study by Daibert-Nido *et al*[81] found that the visual acuity of patients with MD improved after biofeedback training. Another study by Qian *et al*[82] reviewed a retrospective series of 17 patients with MD using an MP-3 microperimeter device to perform biofeedback training and found that biofeedback training could improve the visual acuity, reading speed, retinal function, and fixation stability of the patient. Barboni *et al*[83] conducted a retrospective study of six patients with AMD using an MAIA microperimeter device to perform biofeedback training, and the results showed that the contrast sensitivity and BCVA of the patients improved after training 12 times. Sahli *et al*[84] conducted 10 biofeedback training sessions on patients with CVL, and the results showed that biofeedback training could improve the fixation stability and reading ability of patients with AMD, Stargardt disease, and other MD.

Training Strategies of Biofeedback Training Selecting an appropriate location for placing the PRL is essential for the efficacy of visual rehabilitation[12]. The PRL is relatively plastic; however, its location and fixation stability change with treatment or intervention[85]. Compared with the spontaneously formed PRL, selecting another retinal location with better retinal function to place the TRL may result in a better visual outcome[86]. The best personalized location of the TRL varies from person to person. While the patient has a larger scotoma, lower fixation stability, or PRL located away from the fovea, choosing a better TRL to conduct visual rehabilitation can significantly improve the visual function of patients with CVL[87]. The closer the distance between the fovea and TRL, the greater the maximum reading speed, reading acuity, and critical print size[67]. However, Altınbay and İdil[7] found that the foveal-PRL distance had no influence on fixation stability in patients with AMD.

Different TRL training frequencies and locations also influenced the effects of biofeedback training. Nevertheless, there are large differences in biofeedback training strategies between studies. Qian *et al*[82] performed a prospective cohort study that included 17 eyes of 17 patients with CVL, and biofeedback training was performed using the MP-3 device twice a week for 20wk. The results suggested that the BCVA and reading speed of the included patients significantly improved. Bozkurt Oflaz *et al*[11] used the MAIA device to perform biofeedback training eight times a week for 8wk, obtaining similar results. Melillo *et al*[88] conducted biofeedback training for patients with Stargardt's disease once a week, and their results showed that biofeedback training could improve the visual function of the patient. Barboni *et al*[83] performed biofeedback training 12 times over 3mo period and obtained a similar conclusion. However, despite differences in the frequency of biofeedback training among different studies, all studies concluded that biofeedback training can improve the visual function of patients. Therefore, further studies on training strategies are required. Additionally, studies comparing the effects of different training strategies are lacking.

SUMMARY AND FUTURE DIRECTIONS

Patients with CVL have visual symptoms characterized by decreased contrast sensitivity, absence of stereopsis, and reduced reading ability. Macular retinal function and fixation stability were measured using microperimetry. As a result of

the CVL, people often select a retinal region outside the central scotoma for fixation, known as the PRL. The spontaneously formed PRL is not always located at the location with the best residual retinal function, and residual retinal function may be underutilized. Moreover, using microperimetry, biofeedback training can improve the visual function of patients with CVL, including BCVA, reading ability, and fixation stability. Furthermore, it can relieve anxiety and depression in patients with CVL. Consequently, the quality of life and visual outcomes can be significantly improved. In conclusion, microperimetry can not only detect the location of the PRL, but also perform biofeedback training. Biofeedback training is an effective method of low-vision rehabilitation. With further research and a better understanding of PRL, biofeedback training can provide better visual rehabilitation in patients with CVL.

Nevertheless, the current review has some limitations. 1) Current studies have mainly focused on the signal disease AMD. Only a few studies have focused on other MDs such as DME and Stargardt disease. Further studies are needed to demonstrate the efficiency of biofeedback training in patients with other MDs, especially DME and Stargardt disease. 2) Randomized controlled trials were lacking. Most of the current studies were not blinded, and there were no controls. Thus, the grade of evidence in these studies is insufficient, and well-designed randomized controlled trials are urgently needed. 3) There was a wide variety of biofeedback training strategies in the current studies. It is not clear which type of training strategy is most appropriate. 4) The method for evaluating the training efficiency must be improved. Indicators such as BCVA, reading ability, and quality of life were used to evaluate training efficiency. More objective evaluation indicators would be beneficial[89].

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