Orientation of the preferred retinal locus (PRL) is maintained following changes in simulated scotoma size

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Although macular lesions often enlarge, we know little about what happens when the preferred retinal locus (PRL) is enveloped by the lesion. We present a prospective study of subjects with normal vision who were trained to develop a PRL using simulated scotomas with a gaze-contingent visual display. We hypothesized that, when subjects had developed a robust PRL and the scotoma size was increased, the PRL would move to remain outside the scotoma and in a direction that maintained the orientation (theta) of the PRL relative to the fovea.

Nine subjects with normal vision were trained to develop a PRL and were then exposed to scotoma sizes that ranged from 4° to 24° in diameter. Subjects tracked a stimulus using saccades or smooth pursuits. Fixation stability was measured by calculating the bivariate contour ellipse area (BCEA). To measure the reassignment of the oculomotor reference (OMR) to the PRL, we analyzed the spread (BCEA) of saccade first landing points.

All subjects developed a robust PRL that did not vary more than 0.8° on average between blocks of trials of a scotoma size, and they maintained the orientation of the PRL as the simulated scotoma size varied (±9° median standard deviation in theta, defined as orientation angle). Fixation stability and OMR to the PRL worsened (larger BCEA) with increasing scotoma size. This, and related studies, could guide development of a PRL training method to help people with central vision loss.

Introduction

Age-related macular degeneration (AMD), which results in central vision loss (CVL), is the leading cause of vision loss in the United States, affecting at least 4 million people (Congdon et al., 2004; Klein & Klein, 2013). These numbers are expected to rise in the coming years (U.S. Census Bureau, 2017); thus, there is a dire need to better understand CVL and how people cope with its effects. CVL affects many aspects of daily living, including reading (Bullimore & Bailey, 1995), recognizing faces (Bernard & Chung, 2016), driving (Bowers, Peli, Elgin, McGwin, & Owsley, 2005), and watching television and movies (Woods & Satgunam, 2011; Costela, Saunders, Rose, Kajtezovic, Reeves, & Woods, 2019). When CVL involves the loss of the fovea, an eccentric retinal location is usually adopted, termed a pseudo-fovea or preferred retinal locus (PRL) (Cummings, Whittaker, Watson, & Budd, 1985; Timberlake, Mainster, Peli, Augliere, Essock, & Arend, 1986; Schuchard & Raasch, 1992). Typically, a PRL develops within 1 month for patients with juvenile macular degeneration and within 6 months for patients with AMD (Crossland, Culham, Kabanarou, & Rubin, 2005).

In addition to crowding and loss of resolution, major problems in using a PRL include the ability to make appropriate eye movements and control the positioning of the PRL on objects of interest. Fixation with a PRL is much more unstable than with the fovea

(Culham, Fitzke, Timberlake, & Marshall, 1993; Crossland, Culham, & Rubin, 2004), and unstable fixation further impairs target detection and identification (Falkenberg, Rubin, & Bex, 2007). The control of eye movements is difficult when using eccentric vision (Peli, 1986; Whittaker, Cummings, & Swieson, 1991), making transitions between fixations (i.e., saccades) less efficient. The fovea is the natural reference point for eye movements, the oculomotor reference (OMR) (White & Bedell, 1990; Whittaker et al., 1991). In long-standing bilateral foveal loss, there is a shift in the OMR (re-referencing) for some patients such that saccades place the object of interest close to the PRL, instead of the fovea, when attention shifts to a new object of interest (White & Bedell, 1990; Whittaker et al., 1991). Although fixation stability with the PRL has received considerable attention, little research has been conducted on the re-referencing process in patients with retinal lesions that involve the fovea.

Fixational PRLs tend to be below, left, or right in visual space (superior, left, and right on the retina, respectively), and much less commonly above in visual space (Guez, Le Gargasson, Rigaudiere, & O'Regan, 1993; Sunness, Applegate, Haselwood, & Rubin, 1996; Fletcher & Schuchard, 1997; Crossland, Culham, Kabanarou, et al., 2005; Cacho, Dickinson, Reeves, & Harper, 2007; Rubin & Feely, 2009), thus keeping their lower visual field clear. The reason for this unequal distribution is not known, nor is it understood why an individual's choice of PRL location is idiosyncratic (Costela, Kajtezovic, & Woods, 2017). It has been shown that PRL locations can be trained among neophytes with scotoma simulation (Liu & Kwon, 2016; Barraza-Bernal, Rifai, & Wahl, 2018) and among people with an established PRL (Nilsson, Frennesson, & Nilsson, 1998; Tarita-Nistor, Gonzalez, Markowitz, & Steinbach, 2009), although the value of such training for daily living activities has not been clearly demonstrated.

Most retinal lesions that cause macular degeneration change over time, with the lesion increasing in size. Those changes can cause the PRL location to be engulfed by the lesion. It is not well known what happens to the PRL when the location is no longer viable, as the only natural history study that has addressed this issue only monitored PRL location for 12 months and found no change in PRL location of people with Stargardt disease (Schonbach et al., 2018). Much longer duration studies are required, particularly in people with AMD, which is the most common cause of CVL. A recent study that used a gaze-contingent system showed that the PRL will move to a nearby location (Barraza-Bernal et al., 2018). As most macular degeneration cases are progressive, there is undoubtedly a need to better understand how patients may or may not adapt their PRL to changing retinal lesion sizes. Identifying the factors

underlying the formation of a PRL and re-referencing of the OMR in patients with CVL is a critical step toward the development of more effective rehabilitative regimens.

Unfortunately, there are limitations in studying patients with CVL, including the difficulty of long experimental sessions for elderly patients, confounding effects of comorbid disorders, individual differences related to pathology, retinal changes with disease progression, and, most importantly for a study that tracks change, the slow rate of change in macular lesions in most patients (thus, the study could take decades). An alternative method is to use a simulation as a model system. Model systems are an effective tool to study a complex system, as they enable examination of the relationships among key variables while controlling for extraneous variables, allowing easily testable hypotheses that can be applied later on patient populations. Commonly used simulations include optical defocus (refractive blur), diffusive filters, and image blur (through image processing). None of these induces a PRL, as they merely suppress image resolution at the fovea. Central scotomas have been simulated with contact lenses (Almutleb, Bradley, Jedlicka, & Hassan, 2018). This approach requires a small pupil size and is thus useful for daytime outdoor studies, but it would not work with the luminances from electronic displays that are currently available at a reasonable price. When stimuli are presented on an electronic display, the best approach to simulate CVL with a central scotoma is a gaze-contingent display. These have been used to study the impacts of central scotomas on various visual tasks (e.g., Bertera, 1988; Fine & Rubin, 1999; Varsori, Perez-Fornos, Safran, & Whatham, 2004; Kwon, Nandy, & Tjan, 2013; Walsh & Liu, 2014; Janssen & Verghese, 2015). To conduct such gaze-contingent studies, it is crucial to train the subjects, as performance changes over time (Kwon et al., 2013; Liu & Kwon, 2016; Barraza-Bernal et al., 2018), so results obtained without sufficient training may not be representative of the experience or performance of people with an established PRL. Our study used a gaze-contingent display and included an extended training period for all subjects.

A major difference between gaze-contingent simulated scotomas and a retinal lesion is that the simulated-scotoma viewer sees the blocking stimulus ("scotoma"), whereas most people with a retinal lesion are unaware of their vision loss or simply notice an area that disappears (Fletcher, Schuchard, & Renninger, 2012); sometimes, the visual system may fill in the region of disappearance (Zur & Ullman, 2003). With a simulated scotoma there is a loss of useful vision in a region imposed on an otherwise healthy visual system. In the period soon after loss of the fovea, the experience may be similar, in that the visual system is otherwise intact (PRLs usually develop within 1

to 6 months) (Crossland, Culham, & Rubin, 2005). However, function in the visual cortex eventually changes through cortical reorganization (Dilks, Baker, Peli, & Kanwisher, 2009; Liu et al., 2010; Chen, Shin, Millin, Song, Kwon, & Tjan, 2019), and there is loss of cortical structure (Hernowo et al., 2014; Yoshimine et al., 2018). Changes in function have been shown at the trained PRL (i.e., with a simulated scotoma) (Chen et al., 2019), specifically the reduction in crowding consistent with a similar finding in patients (Chung, 2013). These demonstrations of changes in visual performance imply cortical reorganization but are not direct measurements like functional magnetic resonance imaging. We are not aware of any evidence to date of degeneration of the oculomotor system in response to CVL. That is not to say that oculomotor control is not worse without clear vision, but rather it is a consequence of poor input information. Development of a PRL is likely a combination of the visual (e.g., attention) and oculomotor (e.g., eye control) systems. Development of an OMR to the PRL is likely primarily a function of the oculomotor system (it requires a remapping) with some visual input (e.g., coordinates of the object of interest). Thus, the adaptations with a simulated scotoma may be somewhat comparable to that of a person with a retinal lesion that has recently enveloped the fovea, despite the fact that a person with a retinal lesion is not necessarily aware of the location of the scotoma. Like most model systems, a gaze-contingent simulation system does not exactly replicate the real experience.

Most gaze-contingent systems may not update a fovea-blocking scotoma on the display quickly enough when a saccade is made, so that occasional brief foveal views occur (previews). This problem is independent of display update rate (Saunders & Woods, 2014), deriving from the inherent system latency (time between event and display update). Most systems have more system latency than the operators calculate or estimate (e.g., McConkie, 1997). Direct measurement of system latency is not difficult or expensive (Saunders & Woods, 2014). As eye movements are asynchronous with frame updates, there is always a range of latencies, and that range may be greater than one frame (e.g., >8 ms with a 120-Hz refresh rate), as most digital displays process the input before it is displayed, and that processing period can be variable. When the system latency is known, it is possible to update the display to the expected gaze location at the time of display update, rather than the last gaze location available (e.g., 20 ms previously). We applied this approach by using real-time saccade prediction (Han, Saunders, Woods, & Luo, 2013).

In lieu of a natural history study, we used a gaze-contingent model system to examine how the PRL relocates following a change in the size of the (simulated) scotoma and changes in the OMR. This extends the study of Barraza-Bernal et al. (2018) that

showed that the PRL can relocate following changes in scotoma size, and that it relocates to a nearby region. In our study, we (1) provided an extended training period with the smallest scotoma size, (2) included scotoma sizes from 4 to 24° in diameter, (3) followed the largest scotoma size with the smallest size on which the subject had trained, and (4) analyzed the OMR for all subjects. We hypothesized that when a subject had developed a robust PRL (as described previously in Kwon et al., 2013), that subject would maintain the orientation of the PRL (θ in polar coordinates) in response to increasing scotoma sizes. This simulates the natural history of retinal lesion expansion, except that our changes in scotoma size were abrupt (although that can occur in neovascular AMD). Also, we hypothesized that if the scotoma size was reduced, the PRL would revert to the location previously used for that scotoma size. This response to reduction in scotoma size is relevant for future gaze-contingent studies in which a random order of scotoma sizes would be employed to avoid confounding scotoma size with order effects. In our study, unlike the study of Barraza-Bernal et al. (2018), subjects had extensive training in PRL use before data with changing scotoma sizes were obtained.

Methods

Subjects

Nine subjects (mean age 25 years old; range, 22–29 years) with normal sight were recruited from the community in and around Boston, Massachusetts. Seven of the nine subjects were female, and all subjects had at least a bachelor's degree. They had no known vision problems (per self-report questionnaires); had normal central visual fields (Humphrey Field Analyzer 30-2 test); had no central retinal abnormalities, based on evaluations using the Nidek MP-1 (Nidek Co., Ltd., Aichi, Japan) or OptosOCT SLO (Optos, Dunfermline, UK); and had normal binocular vision (Randot stereoacuity ≤ 100 seconds of arc and normal Worth four-dot test). The average visual acuity for all subjects was –0.08 logMAR (20/17; range, –0.06 to –0.11 logMAR).

Setup and materials

We used an Eyelink 1000 infrared video gaze tracking system (SR Research, Ottawa, ON, Canada) with a tower mount configuration and a sample frequency of 1000 Hz. Subjects were seated at a table 1 meter from an AeroView 70 rear-projection screen (Stewart Filmscreen, Torrance, CA). Head movements were restricted by a chin and brow rest. Stimuli

were presented using a Barco F50 projector (Gamle Fredrikstad, Norway), which produced a 120-Hz display with an area that was 130 cm wide and 100 cm tall (4:3 aspect ratio; 66° by 53°). A display area of this size allowed optimal presentation of large scotomas (up to 24° diameter) without requiring that the subject look, with the fovea, beyond the edge of the display (and hence outside the gaze-calibrated region). All subjects viewed the display with both eyes. This is more natural than monocular testing and more relevant to functional tasks of interest to us. Even though we tracked only one eye, as the two eyes are yoked binocular vision was normal. Because binocular fusion is mainly driven by peripheral vision (Burian, 1939; Kertesz & Hampton, 1981; Cooper, Feldman, & Eichler, 1992), the location of the simulated scotoma would have been the same in each eye with binocular viewing.

We made direct measurements of system latency (Saunders & Woods, 2014) and found the average system latency to be 18 ms (range, 14–22 ms). Based on that known latency, we updated the display to the expected location of gaze at the time of display update, based on real-time saccade prediction (Han et al., 2013). We calculated that the median residual error with an 18-ms updating delay of the saccade prediction (Han et al., 2013) was 3.5°, compared to 6.3° with the current-location method (Aguilar & Castet, 2011). With the real-time saccade prediction, we measured a reduction in update locations (Costela & Woods, 2018). To confirm that the system was updating sufficiently well, we plotted a small, high-contrast bipolar circle at the gaze (foveal) location. Even on large saccades, we noticed only small (<1°) errors on saccade landing; the stimulus was not noticeable during saccades (i.e., saccadic suppression). That test stimulus was only shown in system testing. That test confirmed that the scotoma simulation would block the foveal view at all times.

Experimental design

The experimental protocol consisted of three parts set in a codified sequence for all subjects. Each subject experienced three phases: (1) learning the task, without a simulated scotoma (i.e., foveal viewing), (2) training the PRL with a simulated scotoma, and (3) using the developed PRL with varying scotoma sizes. The task in each phase (comprised of multiple blocks) was similar, as described below. At the beginning of each block of the experiment, the subject performed a successful nine-point calibration and validation with the Eyelink 1000 and was asked to fixate on a cross for 6 seconds. These fixation trials were used to calculate fixation stability (see Fixation stability section). Each block of the experiment consisted of 30 trials and lasted about 25 minutes.
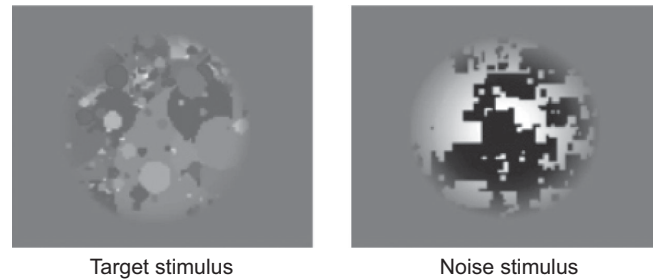

Figure 1. An example target stimulus is displayed on the left. An example noise stimulus (mask) is displayed on the right.

Both stimuli (Figure 1) were 1.5° in diameter when viewed without a simulated scotoma (foveal fixation) and were one-quarter the diameter of the simulated scotoma in simulated-scotoma trials (fixation with PRL). Thus, at the largest simulated-scotoma size of 24° diameter, the two stimuli were 6° diameter. This scaling of stimuli was intended to make the stimuli suprathreshold for all conditions. The target stimuli were different for every trial.

Each trial started with the presentation of a noise patch (Figure 1b). When the noise patch had been fixated and was not obscured by the scotoma, the subject pressed the space bar to initiate the trial. After 500 ms, a textured target stimulus then appeared (Figure 1a) and was presented for about 6 seconds. During that time, the target made sudden shifts, smooth drifts, or stayed in place, requiring the subject to make a saccade, make a smooth pursuit, or fixate on the target, respectively. Then, a noise mask (Figure 1b) was displayed for 500 ms, followed by a target stimulus that appeared for 2 seconds and again made shifts, drifts, or stayed in place. The choice of drifts or jumps before and after the noise mask was random. When the stimulus made sudden shifts to a new location (i.e., jumped), the new locations were constrained so that they were never within the current location of the simulated scotoma. Stimuli were constrained to a region that ensured that, independent of the θ of the PRL, the subject would not need to look with their fovea outside the boundary of the gaze-calibrated area (screen). After the noise mask disappeared, the subject's task was to determine if the two target stimuli (before and after the mask) were the same. After a keystroke response, a sound indicated whether the subject's response was correct. The transition between trials was a noise stimulus that was the same for all transitions (Figure 1b). The next trial was initiated via keystroke. Each subject's experience of the trials and blocks was different, as each individual chose a unique PRL location, experienced a different (randomized) sequence of trials, and performed a varying number of blocks (which related to their ability to use their PRL, as described below).

The purpose of the same/different task was simply to ensure that the subjects attended to the training (real task). Task performance was not monitored during the study. Subjects were able to perform the task at all scotoma sizes, with performance ranging from 67% to 94% with a scotoma (77% to 100% without a scotoma). The only exception was subject 5, who performed at chance for all conditions including foveal (no scotoma), and we do not know why; otherwise, she performed like the other eight subjects. Among the other eight subjects, there was no trend for reducing task performance with increasing scotoma size ($p = 0.64$; Supplementary Figure S5), indicating that the task was suprathreshold at all PRL eccentricities.

The gaze-contingent central scotoma was circular, centered on the tracked gaze location (fovea), black with feathered edges, and visible at all times (except in the second part of the training phase, as described below), which facilitated training (Kwon et al., 2013). It is not possible to simulate the real experience of a person with a retinal lesion, in which there is an absence of vision (Fletcher et al., 2012) and filling in (Zur & Ullman, 2003).

Learning the target stimulus (with foveal viewing)

The first block for each subject was conducted with no simulated scotoma, so subjects were able to use their fovea to perform the task. This allowed the subject to become familiar with the task and the target appearance. The data collected in this phase were used to measure baseline saccade accuracy (i.e., OMR) and fixational stability for each subject.

Training the PRL (with a simulated scotoma)

To train the PRL, there was first a period of free viewing (average, 6.3 blocks; range, 3–8 blocks), followed by a period of refining of the PRL location (average, 6.1 blocks; range, 2–11 blocks). During free viewing, subjects were exposed to a small (4°-diameter), black, gaze-contingent central scotoma and were able to choose and develop their PRL without time constraints (as done by Kwon et al., 2013). During the free-viewing (first) phase of PRL training with a simulated scotoma (Figure 2, Supplementary Movie 1), the change in the average location of the PRL between blocks was monitored. The free-viewing training phase ended when the change in PRL location between blocks was less than 1° on successive blocks and was seen to be tending to asymptote. The refining (second) phase of training was identical to the free-viewing phase except for two changes: (1) for each subject, we calculated the PRL from the last two blocks and displayed a 3° × 3° box that was centered on the location chosen by the subject (PRL) and visible at all times; and (2) the (4°-diameter) central scotoma was set to background luminance so that it was invisible but could still occlude the target (Figure 3, Supplementary Movie 2). The subject was instructed to keep the stimulus within the box during all trials of the refining phase. This training was very similar to the approach of Kwon et al. (2013).

For both parts of PRL training, the target was always visible (Figures 2 and 3). If the subject obscured the stimulus with the simulated scotoma, then the target would stop moving until the subject made an eye movement that made the stimulus visible again. In all, these measures encouraged subjects to develop an efficient and robust PRL. Subjects were able to develop a PRL free from time constraints. On average, subjects successfully completed PRL training in about 5 hours (range, 2.1 to 7.9 hours); the training consisted of multiple training sessions usually spread out over a period of a few weeks. Subjects performed no more than five blocks per session.

Using the PRL with varying scotoma sizes

This was both the last and main phase of the study. The size of the scotoma gradually increased across diameters of 4°, 8°, 12°, 16°, and 24° (with slight differences in sizes for subjects 2 and 4; Figure 4). Subjects completed at least two blocks (60 trials) at each scotoma size. After completing the task with the largest scotoma condition, participants completed additional blocks at the initial (4°) scotoma size. This varying-scotoma phase was completed in about 6.2 hours (average, 18.5 blocks; range, 13–37 blocks). Figure 4 illustrates the number of blocks completed by each subject and the scotoma size used during each block throughout the experiment. This procedure served as a simulation of the effect of natural changes in a retinal lesion on PRL development, although with abrupt changes in scotoma size (corresponding to retinal lesion size).

In the varying-scotoma phase, all aspects of the trial sequence remained the same as previous phases (Figure 2), except that the stimulus was visible for only 2 seconds (not 6 seconds) prior to the appearance of the mask. This was done to shorten the duration of each trial (and thus the duration of the varying-scotoma phase). The simulated scotoma was black, as in the free-viewing phase.

Saccade detection

For analyses related to fixation stability and the OMR, it was necessary to detect and remove saccades from the gaze data. We employed the same velocity criteria and additional criteria as previous studies that have examined saccades made while viewing video (Wang, Woods, Costela, & Luo, 2017; Costela & Woods, 2018). In summary, blinks were removed
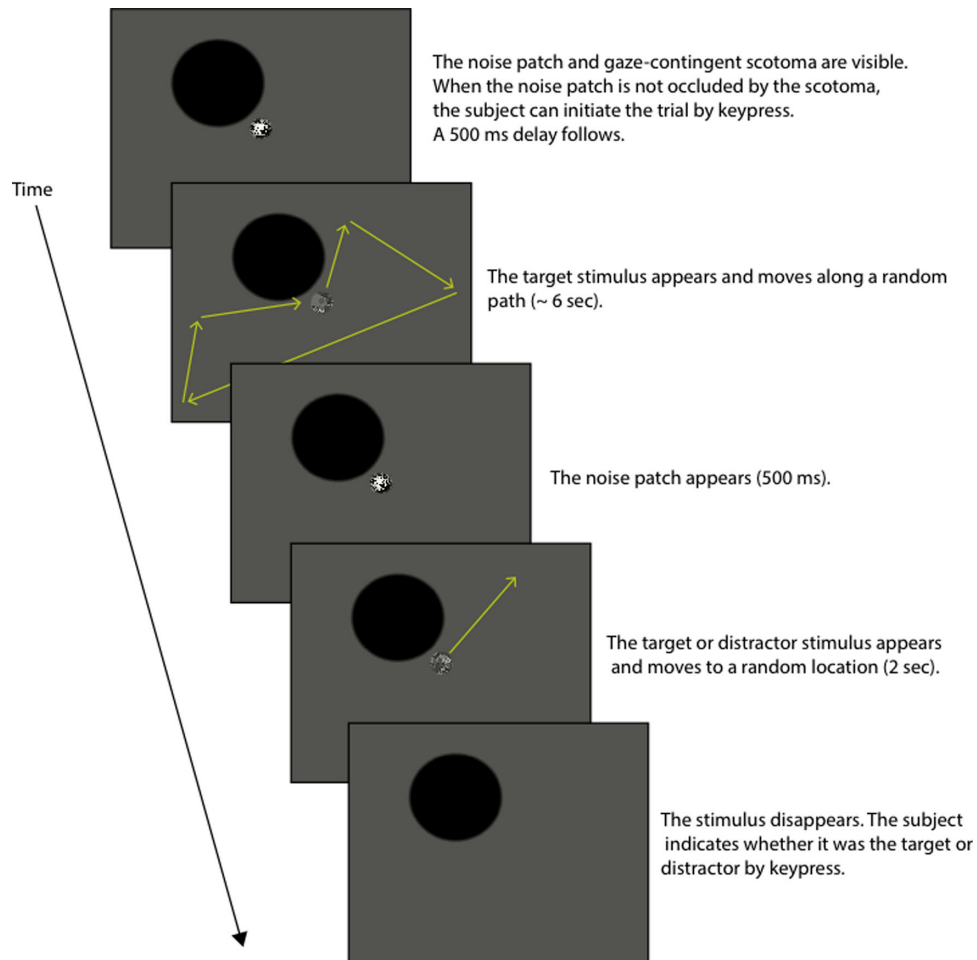
The noise patch and gaze-contingent scotoma are visible. When the noise patch is not occluded by the scotoma, the subject can initiate the trial by keypress. A 500 ms delay follows.

The target stimulus appears and moves along a random path (~ 6 sec).

The noise patch appears (500 ms).

The target or distractor stimulus appears and moves to a random location (2 sec).

The stimulus disappears. The subject indicates whether it was the target or distractor by keypress.

Time

Figure 2. Illustration of the core trial sequence.
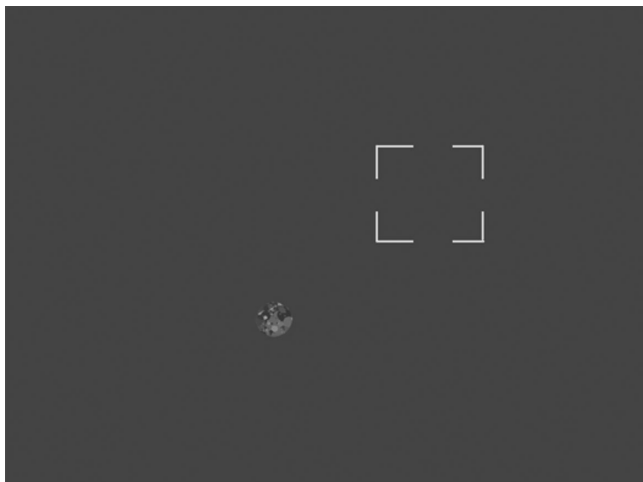
Figure 3. Illustration of the changes to the visual stimuli during the second (refining) phase of PRL training. In this example, the invisible simulated scotoma was above and to the right of the box (below, left PRL), so the subject's gaze (fovea) was near the upper right corner of this illustration.

and periods around missing data were removed if the velocity exceeded 30°/second. Data were interpolated over the removed blink data, and then the raw data were smoothed. Saccade start was signaled when speed exceeded 30°/second for at least 10 ms. Saccade end was signaled when speed dropped below 30°/second. Additional criteria removed eye-position overshoots and saccades that did not initiate or end with a fixation (including glissades).

Fixation stability

Fixation stability was measured at the beginning of each block (as described in the Experimental design section) as the bivariate contour ellipse area (BCEA) (Steinman, 1965) that included 1 standard deviation (68%) of the fixation points after removing saccades and data more than 3.3 standard deviations (0.1%) from the mean of the raw data after removing points that were more than 10° farther from fixation than the scotoma border (presumably a data collection error). Although not ideal (Castet & Crossland, 2012), the
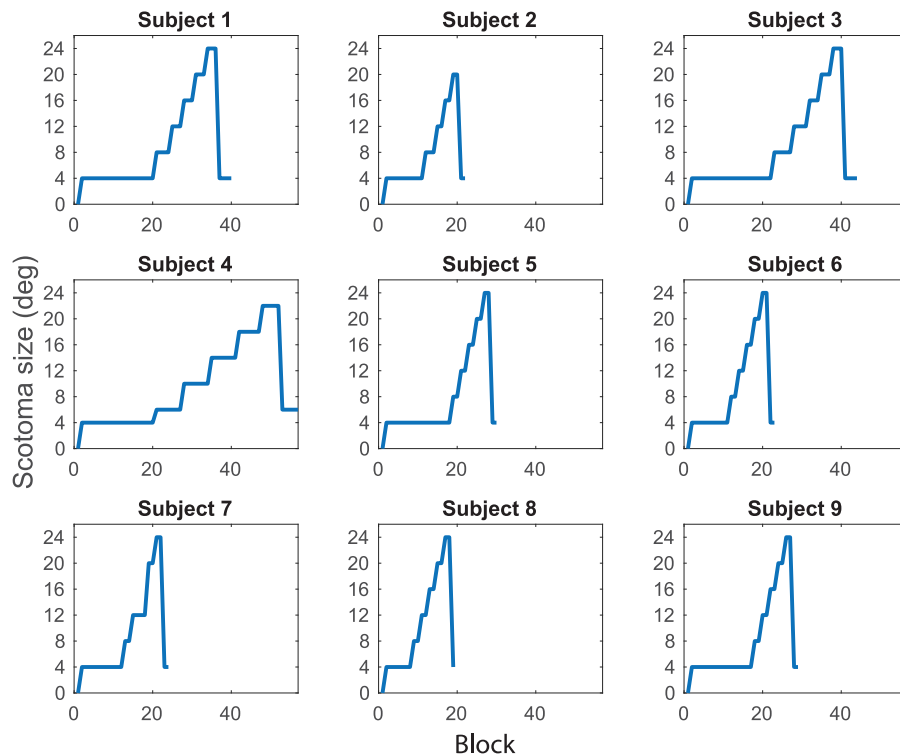
Figure 4. Scotoma size at each block for each subject.

BCEA has been previously used to measure the spread of fixation data. To examine the effect of training on fixation stability (BCEA), we used a linear mixed model of the logarithm of BCEA with phase as a fixed effect and subject as a random effect. Post-estimation Wald tests were used for simple linear paired comparisons (i.e., for comparisons not inherent in the linear mixed model). To examine the effect of scotoma size on fixation stability, we used a linear mixed model of the logarithm of BCEA with scotoma size as a fixed effect and block number as a random effect within subject (i.e., allowed each subject to have a different learning–effect slope).

Oculomotor reference

We defined the OMR as the first saccade landing point in response to an instantaneous shift to a new fixation target. More exactly, OMR was measured for each participant by examining the difference in position between the target position and the fixation points following the landing of the first saccade in those trials where participants were instructed to look at a target that disappeared and appeared elsewhere. First, landing density maps were derived from these retinal positions (example shown in Figure 6) and measured using the BCEA (Steinman, 1965). BCEA values were calculated for each trial and aggregated for each block and phase for each subject. To examine the effect of training on

OMR (BCEA), we applied a linear mixed model of the logarithm of BCEA with phase as a fixed effect and subject as a random effect. Post-estimation Wald tests were used for simple linear paired comparisons. For fixation stability and OMR metrics, we accepted $p \leq 0.05$ as significant.

Results

PRL development

All nine subjects developed a robust PRL that did not vary more than 0.8° in orientation, on average, among trial blocks of a scotoma size. The development of the PRL is illustrated in Figure 5, which shows an example of fixation stability for one subject (shown as Gaussian kernel density distributions), including (1) the learning phase (no scotoma, so foveal viewing; Figure 5a); (2) the first block of the free-viewing phase of the PRL training (Figure 5b); (3) the last block of the refining phase at the end of the PRL training phase (Figure 5c); and (4) the final block of the varying-scotoma phase, after having the experience of larger scotomas but coming back to the same size scotoma as used in the training phase (Figure 5d). As expected, subjects had poorly defined fixation abilities when first exposed to the simulated scotoma, as the PRL was only just becoming established (Figure 5b). All of the subjects
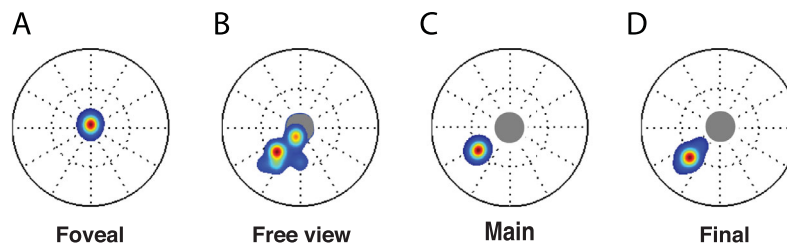
Figure 5. Fixation stability example: Gaussian kernel density polar maps for subject 5 during (A) foveal viewing in the learning phase; (B) the first block of the free-viewing phase of training with the 4° scotoma; (C) the last block with the 4° scotoma in the main phase (before increasing scotoma sizes); and (D) on return to the 4° scotoma following the use of larger scotomas in the varying-scotoma (final) phase. The radii of the two eccentricity circles correspond to 10° and 20° visual angle relative to the fovea. The simulated scotoma (shown as the 4°-diameter filled gray circle) was centered on the fovea. The successive panels show the change in fixation stability as the PRL developed, in this case at about "half past 7" ($\theta = 225$).
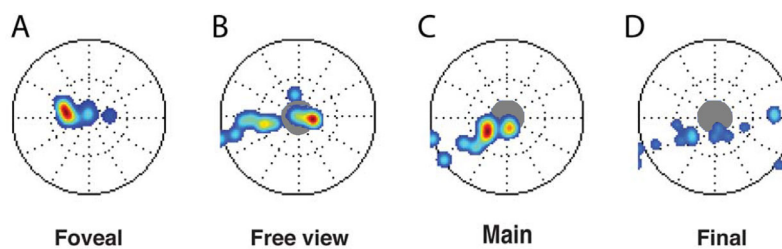

Figure 6. Oculomotor re-referencing (OMR) example showing first landing density maps for subject 5 for those blocks with simulated scotoma size of 4° diameter during the foveal, free-view training, main, and final phases, as shown in Figure 5. The filled gray circle represents the scotoma.

developed a PRL that was close to the border of the simulated scotoma (Supplementary Figure S1), as has been found previously (Kwon et al., 2013; Liu & Kwon, 2016; Barraza-Bernal et al., 2018).

The development of the OMR to the PRL (re-referencing) is illustrated for the same subject in Figure 6, which depicts saccade first-landing-point density maps at the same time points as in Figure 5. The fovea is the natural oculomotor reference. So, when first confronted with a simulated central scotoma, there is a tendency for a saccade to a new stimulus location to land the fovea at the stimulus, but the fovea is obscured by the scotoma. Our subjects fairly quickly overcame this tendency and began to land a region at the border of the scotoma on the target. OMR distributions are shown for all nine subjects in Supplementary Figure S2. The saccade first-landing locations were very similar to the fixation (PRL) locations (compare Figures 5 and 6 and Supplementary Figures S1 and S2), suggesting that the PRL became the OMR.

Fixation stability

Fixation stability was measured as the BCEA of the fixation area during the 6-second fixation trials at the beginning of each block. Figure 7a summarizes the fixation stability of the nine subjects at the same time

points as shown in Figure 5. Supplementary Figure S3 shows the fixation stability and scotoma size at each block for each subject. As expected, fixation stability with a scotoma was significantly worse than with the fovea, particularly with first exposure to the simulated scotoma (free view in Figure 7, where $z = 2.49$ and $p < 0.001$). Over the three phases with a scotoma, there seemed to be a weak trend for a gradual improvement in fixation stability, but neither the refining phase ($\chi^2 = 2.09$, $p = 0.14$) nor the final phase ($\chi^2 = 1.78$, $p = 0.18$) differed from the free-view phase. In the varying-scotoma (main) phase, fixation stability worsened (i.e., BCEA increased) with increasing scotoma size ($z = 6.47$, $p < 0.001$; Supplementary Figure S5). This effect is consistent with previous reports of worsening fixation stability with increasing PRL eccentricity in patients with CVL (Timberlake, Sharma, Grose, Gobert, Gauch, & Maino, 2005; Reinhard et al., 2007; Calabrese, Bernard, Hoffart, Faure, Barouch, Conrath, & Castet, 2011; Bedell et al., 2015; Schonbach et al., 2017) and increasing scotoma size (Calabrese et al., 2011).

Oculomotor reference control

Oculomotor reference control (OMR quality) was measured as the BCEA of the first landing points
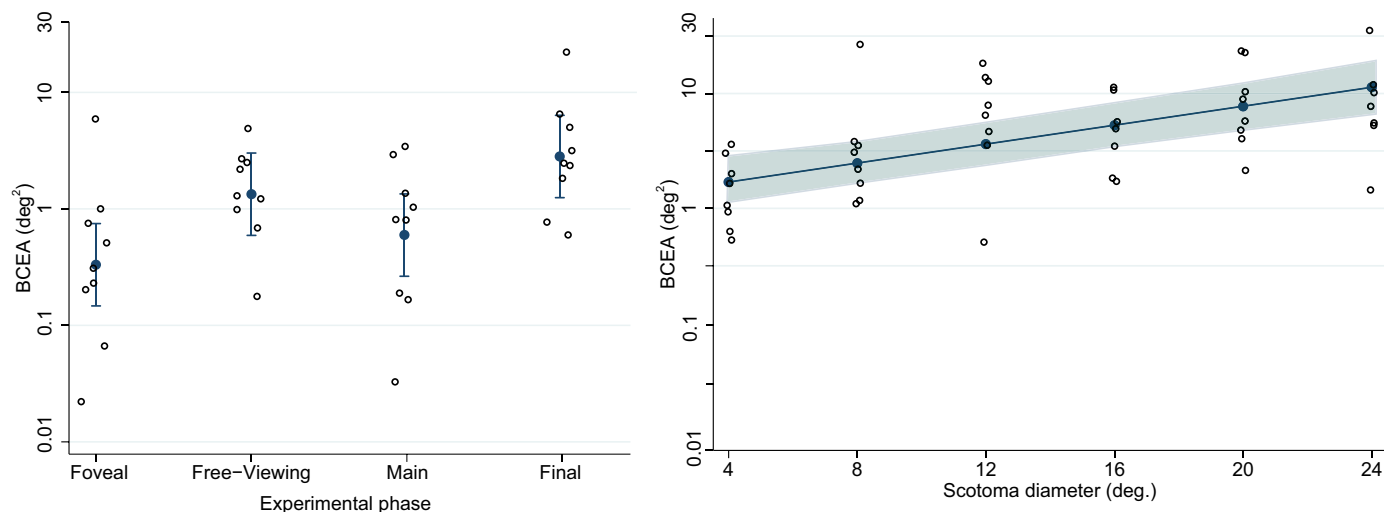
Figure 7. Fixation stability, measured as the BCEA. (A) The time points are the same as shown in Figures 5 and 6. Fitted BCEA values with 95% confidence intervals are shown by phase. The average BCEA is shown for each subject by phase (open). (B) The line represents the fit of the change in fixation stability with scotoma diameter, and the shaded region represents the 95% confidence interval of the fit. The average BCEA is shown for each subject by scotoma size (open). Some scotoma sizes were jittered for clarity.
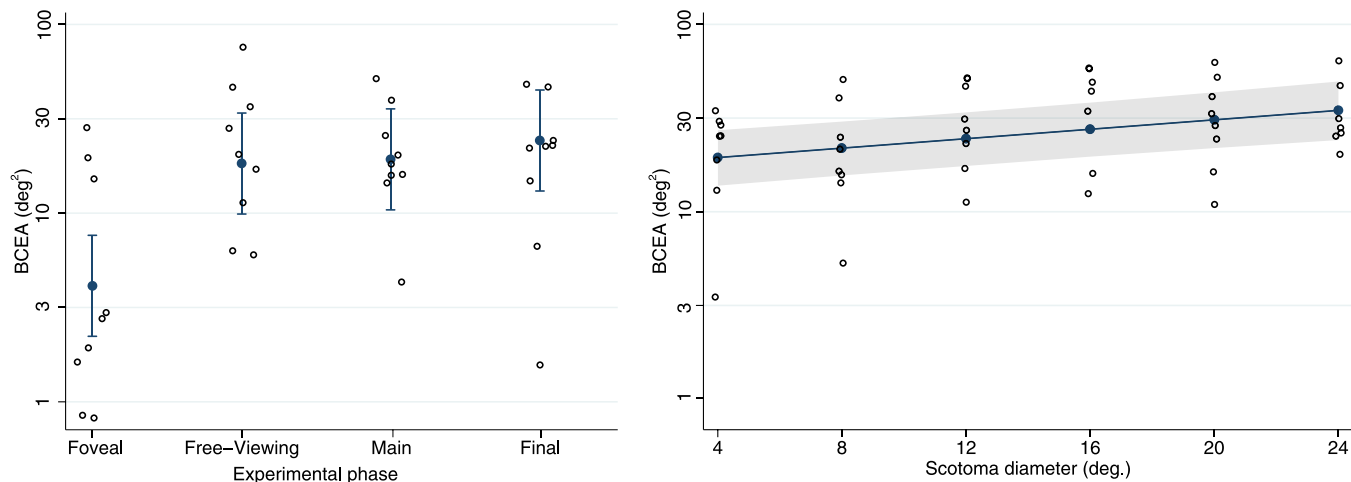

Figure 8. Oculomotor re-referencing (OMR), measured as the BCEA of saccade-first-landing locations of all saccades to new stimuli. (A) The time points are the same as Figures 5, 6, and 7a. Fitted BCEA with 95% confidence intervals are shown by phase. Average BCEA shown for each subject by phase (open). (B) The line represents the fit of the change in OMR with scotoma diameter, and the shaded region represents the 95% confidence interval of the fit. Average BCEA shown for each subject by scotoma size (open). Some scotoma sizes were jittered for clarity.

within the searching trials (when the stimulus suddenly changed location) in the learning phase (foveal viewing) and in the free-view, refining, and final phases (with a scotoma size of 4°). Figure 8a shows the OMR of the nine subjects at the same time points as shown in Figure 7. Supplementary Figure S4 shows the OMR and scotoma size at each block for each subject. As expected, the OMR with a simulated scotoma was significantly worse than with the fovea, with first exposure to the scotoma (free-view phase; $z = 3.68$, $p < 0.001$), with last exposure in the main phase ($z = 3.75$; $p < 0.001$), and at the end of the final phase ($z = 3.44$; $p = 0.001$). Across the varying-scotoma phase, OMR worsened (BCEA increased) with increasing scotoma size ($z = 4.75$, $p < 0.001$) (Figure 8b). Subjects had individual learning-effect (block number) slopes. To our knowledge, this effect has not been reported previously.
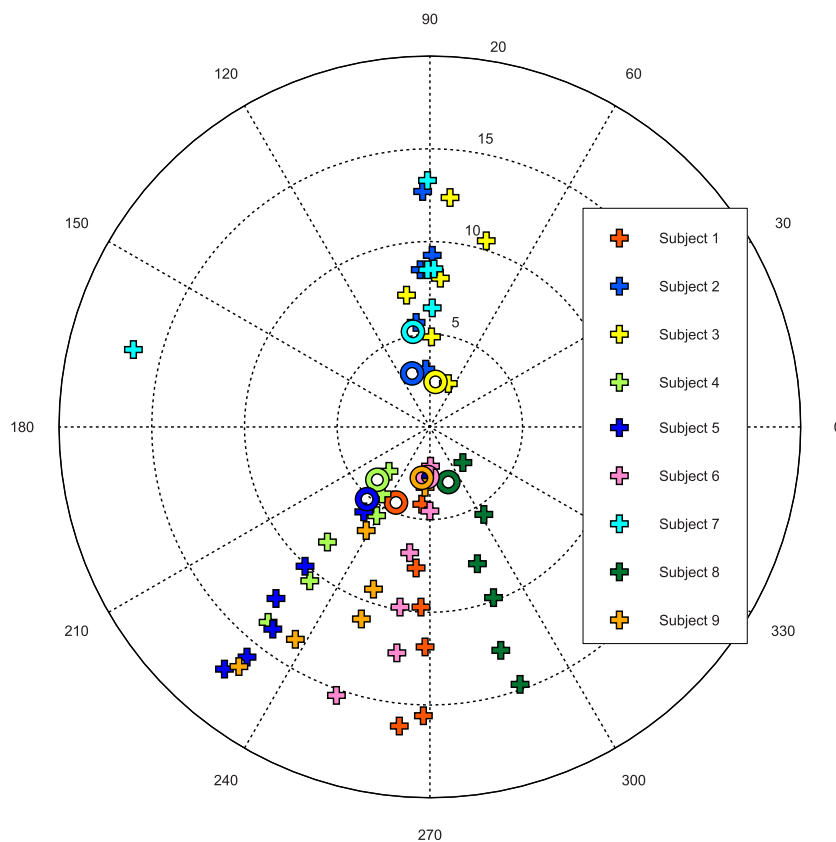
Figure 9. Changes in fixational PRL with increases in simulated-scotoma size. Each color represents a different subject. The circle is the location of the PRL when the first scotoma size was repeated following the largest. The radii of the circles in the grid are in 5° increments.

Changes in PRL location with increases in scotoma size

Three of the nine subjects used an above PRL (in visual space), six subjects used a below PRL, and no subject used a right or left PRL (Figure 9). It is striking that 33% of subjects used an above PRL, as previous studies have found that an above PRL in patients with CVL is uncommon, with 9% reported as above across six previous studies (Guez et al., 1993; Sunness et al., 1996; Fletcher & Schuchard, 1997; Crossland, Culham, Kabanarou, et al., 2005; Cacho et al., 2007; Rubin & Feely, 2009). To determine whether our prevalence of the binocular PRL locations (33% above) was unexpected, we used the chi-squared test for independent samples to compare our results to previous data from those studies of people with scotomas from retinal lesions that have reported monocular PRLs, as well as to two previous studies of gaze-contingent simulated scotomas (Kwon et al., 2013; Barraza-Bernal et al., 2018). Some previous studies of real PRLs measured only one eye (Crossland, Culham, Kabanarou, et al., 2005; Rubin & Feely, 2009), whereas others have reported the monocular PRL of each eye of most subjects (Guez et al., 1993; Sunness et al.,

1996; Fletcher & Schuchard, 1997; Cacho et al., 2007). One of the simulated-scotoma studies (Kwon et al., 2013) had binocular viewing ($n = 6$), and the other (Barraza-Bernal et al., 2018) had monocular viewing ($n = 5$). Our subjects developed a binocular PRL (as viewing was with both eyes). For the comparisons, we treated each of our subjects as one data point. The comparisons were among our sample of nine subjects, 1489 subjects with real scotomas (135 above PRL), and 11 subjects with simulated scotomas (one above PRL). When compared to the data from previous reports of patients with PRLs, our prevalence of above PRL locations was higher than expected (Fisher's exact test, $p = 0.04$) but not different from the 11 subjects reported in the two previous studies with simulated scotomas ($p = 0.34$).

As the scotoma size increased, all subjects maintained the orientation of their PRL (θ in polar coordinates), with the PRL moving farther from the fovea, consistent with the scotoma diameter (Figure 9), except for subject 7 at the largest simulated-scotoma size (as discussed below). Crosses in Figure 9 represent the average PRL locations during the fixation trials for each scotoma size to which each subject was exposed in the varying-scotoma phase. The median standard
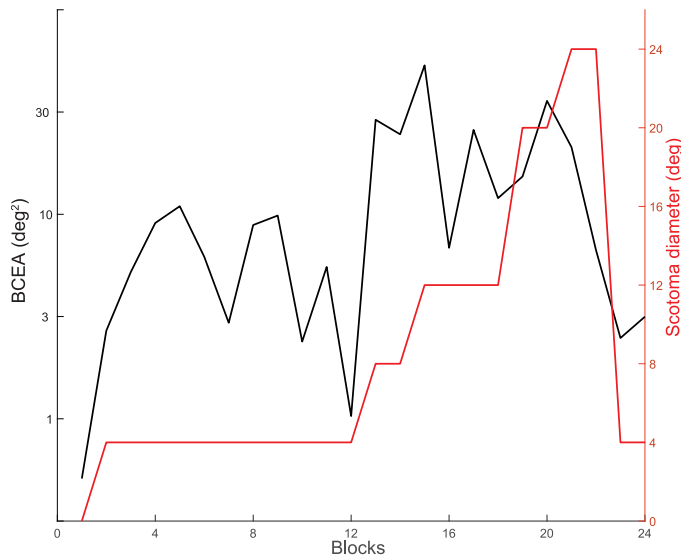
Figure 10. Scotoma diameter (red) and fixation stability (black) measured as the BCEA of subject 7. The orientation of the subject's PRL with the largest simulated scotoma was different from that with the other (smaller) scotoma sizes (see Figure 9).

deviation in θ across the scotoma sizes was $\pm 8.8°$ (range, 2° to 65°). As hypothesized, and consistent with Barraza-Bernal et al. (2018), participants adjusted their fixational PRL in response to increasing scotoma sizes, a process that emulates natural expansion of the retinal lesion.

When the scotoma size decreased back to 4° from the largest scotoma size (20° or 24°; final phase), the PRL location reverted back to the original location used during training. Circles in Figure 9 represent the final time that each subject was exposed to the 4° scotoma size. That location was very similar to the original 4° scotoma location for all subjects. Interestingly, one participant, subject 7 (light blue in Figure 9), changed his above PRL to a leftward location for the largest (24°) scotoma size before returning to the original above PRL location for the final scotoma size (4° diameter, depicted with a light blue circle). Despite the change in PRL orientation of subject 7 for the 24°-diameter scotoma, fixation stability was as good as would have been expected if the orientation had not changed (Figure 10). Thus, this subject was able to transfer his oculomotor control with apparent ease, despite the change in location (from above to left). The subject reported that interference of the upper lid with his view was the reason for the change in PRL location for the 24°-diameter scotoma.

Discussion

When the fovea is lost, most people use an eccentric retinal region to attend to objects of interest, termed the PRL (Cummings et al., 1985; Timberlake et al., 1986; Schuchard & Raasch, 1992). With eccentric fixation, oculomotor control becomes poor, and transitioning between visual targets (making saccades) becomes more difficult. As expected, we were able to train subjects with NV to develop and maintain a robust PRL, as described by Kwon et al. (2013). Our subjects were able to train the PRL in an average of 5 hours (12 blocks, in multiple training sessions spread out over multiple days). During that period, our subjects improved their fixation ability with the PRL and demonstrated re-referencing of the OMR, as shown previously (Kwon et al., 2013; Liu & Kwon, 2016), which is consistent with the improvements in visual search found by Walsh and Liu (2014).

When our subjects had established a PRL location (end of refining phase), they were able to quickly adjust to a sudden change in the size of the simulated scotoma out to a diameter of 24°. Such a large scotoma is not uncommon in subjects with real PRLs. The ability to adjust to an abrupt change in scotoma size shown here extends the work of Barraza-Bernal et al. (2018), who used scotoma diameters up to 20° and diameter increases of 1° and 2°. Our hypothesis was confirmed that subjects would maintain the orientation of the PRL (θ in polar coordinates) as the simulated scotoma size evolved through sizes that ranged from 4° to 24° in diameter (Figure 9). This demonstrates the plasticity of the developed PRL and suggests that a random order of presented scotoma sizes is possible in future studies that use gaze-contingent simulated scotomas of different sizes, as long as there has been sufficient training. A randomized scotoma size order would enhance study designs that seek to compare sizes, as randomization would avoid confounding scotoma size with order within the study. Although we have shown the plasticity of the PRL in a model system, this does not prove that this happens to patients with retinal lesions. Thus, longitudinal studies with real patients with PRLs are needed to corroborate our findings.

It is not known why the PRL develops in idiosyncratic locations for each person. Although the literature on PRL locations in patients with retinal lesions shows that the development of an above PRL (in visual space) is less common than other visual quadrants (Guez et al., 1993; Sunness et al., 1996; Fletcher & Schuchard, 1997; Crossland, Culham, Kabanarou, et al., 2005; Cacho et al., 2007; Rubin & Feely, 2009), 33% of our subjects used an above location, and that was more than expected ($p = 0.04$). It is possible that this discrepancy was age related, as our subjects were younger than the patients with retinal lesions. A more likely explanation is that in our training setting (and in the other simulated scotoma studies, from which we did not differ), there was no advantage to any particular orientation, whereas when learning to use a PRL while conducting real-world activities there may

be a substantial disadvantage to an above PRL (e.g., tripping over things) that discourages its use in the real world. This suggests that future studies that train a PRL should either train specific locations (e.g., Liu Kwon, 2016; Barraza-Bernal, Rifai, & Wahl, 2017) to obtain frequencies of PRL locations that are a better match to the population of interest or use a training task that is more similar to daily living activities, which we suspect will lead to a lower frequency of choosing an above PRL. The choice of PRL location does not seem to be related to low-level visual functions (Bernard & Chung, 2018) but instead may be related to higher level functions, such as attention (Barraza-Bernal, Ivanov, Nill, Rifai, Trauzettel-Klosinski, & Wahl, 2017). We suspect that PRL location choice is a complex function of the daily activities of the individual and higher level visual abilities that are retinotopic.

A limitation of our study, and other simulated-scotoma studies (Kwon et al., 2013; Liu & Kwon, 2016; Barraza-Bernal, Rifai, & Wahl, 2017; Barraza-Bernal et al., 2018), is that our subjects were "young" (<30 years of age), whereas most people with bilateral foveal loss are substantially older, having AMD. Our sample does overlap with the ages of many people with early-onset maculopathies (e.g., Stargardt disease, Best disease, juvenile retinoschisis). Being younger, our subjects may have responded differently from older subjects. That is worthy of future study. Crossland, Culham, Kabanarou, et al. (2005) found that their subjects with early-onset maculopathy developed PRLs very quickly (within 1 month) as compared to subjects with AMD (6 months or longer). This may reflect a more agile visual system that is faster to adapt to the new visual state in younger subjects. It might also relate to differences in the topography of the scotomas. Broadly, AMD scotomas tend to be asymmetric within and between eyes, whereas lesions found in early-onset maculopathies tend to have symmetry within and between eyes.

That our subjects were able to develop a fixational PRL and showed OMR to the PRL in so few hours might seem to conflict with the clinical experience and the only report of the natural history of fixational PRL development (Crossland, Culham, Kabanarou, et al., 2005). Crossland, Culham, Kabanarou, et al. (2005) found that a fixational PRL had developed in early-onset maculopathy in about a month, whereas our changes occurred after only hours of training. The time period of our training and the development of a PRL is consistent with other studies with young subjects (Kwon et al., 2013; Liu & Kwon, 2016). We presume that the difference between the natural history (Crossland, Culham, Kabanarou, et al., 2005) and simulated scotoma training is that the training is explicit, whereas in the natural history case the PRL develops though the use of vision for daily activities. Most of those daily activities are not providing the direct and intensive

training provided with the simulated-scotoma training. This suggests that explicit training of PRL use through oculomotor training of people with real CVL may lead to faster adoption of the PRL and higher likelihood of development of OMR to the PRL. White and Bedell (1990) reported that only seven of their 21 subjects had OMR to the PRL, and all but one of those had early-onset maculopathy.

Another limitation of our study was that the subjects were able to see the scotoma in all phases apart from the refining phase (Figure 3), whereas people with retinal lesions have no visual experience within the scotoma and often are not aware of its location or extent (Fletcher et al., 2012). Instead of seeing a black region, as in our simulation, people with retinal lesions often experience filling in (Zur & Ullman, 2003). Having the scotoma visible is likely to have enhanced the development of a PRL. Kwon et al. (2013) found that fixation quality and OMR to the fovea were much worse with an invisible scotoma.

There has been very little prior work on the development of OMR re-referencing. White and Bedell (1990) found that only seven of their 21 subjects had OMR re-referencing, and all but one of those had early-onset (juvenile) maculopathy. In that sample, many of those who had not re-referenced the OMR had experienced binocular CVL for many years, and most had a fixational PRL. Based on analysis of re-fixational saccades, Whittaker et al. (1991) proposed that, even with apparent OMR re-referencing, the mechanism was suppression of the foveal OMR rather than the development of a new OMR. This study goes a small way toward addressing the limitation in the literature and suggests that gaze-contingent simulated central scotomas may be a suitable model for further investigating the OMR re-referencing phenomenon.

In most cases, the PRL location did not vary more than 0.8° on average between blocks of trials of a scotoma size. Subject 7 was of particular interest to us, as the subject experienced a drastic change in PRL orientation (12 o'clock location to a 10 o'clock location; Figure 9) at the largest scotoma size (24° diameter), revealing that there can be transfer of oculomotor skills even with a change of orientation. This has implications for asymmetric changes in scotoma size. Like others (Kwon et al., 2013; Liu & Kwon, 2016; Barraza-Bernal, Ivanov, et al., 2017; Barraza-Bernal, Rifai, & Wahl, 2017; Barraza-Bernal et al., 2018), we used radially symmetric simulated scotomas (circles), but real retinal lesions are rarely symmetric, and we increased the scotoma sizes by simply increasing the diameter of the scotoma, whereas real lesions extend asymmetrically. Many people have asymmetric retinal lesions that lead to monocular PRLs that are not in corresponding locations in the two eyes (Labianca & Peli, 1996; Kabanarou, Crossland, Bellmann, Rees, Culham, & Rubin, 2006).

In those studies, about 30% to 40% of the subjects had monocular PRL locations that corresponded. Thus, future research should investigate asymmetric scotomas and what happens when the current PRL location is enveloped by a change in the retinal lesion that leaves other locations with a "better" retinal location available but at a different orientation.

An improved understanding of the PRL will provide insight into how the visual system adapts to restrictions, leading to new pathways relevant to vision rehabilitation. There is an urgent need for new methods related to PRL development and use to help people with CVL. Assisting people with CVL to use their PRL will improve their quality of life and may have positive effects on related problems.

Keywords: PRL, training, development, orientation, OMR, stability, fixation

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