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Oculomotor Changes Following Learned Use of an Eccentric Retinal Locus

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Abstract

People with bilateral central vision loss sometimes develop a new point of oculomotor reference called a preferred retinal locus (PRL) that is used for fixating and planning saccadic eye movements. How individuals develop and learn to effectively use a PRL is still debated; in particular, the time course of learning to plan saccades using a PRL and learning to stabilize peripheral fixation at the desired location. Here we address knowledge limitations through research describing how eye movements change as a person learns to adopt an eccentric retinal locus. Using a gaze-contingent, eye tracking-guided paradigm to simulate central vision loss, 40 participants developed a PRL by engaging in an oculomotor and visual recognition task. After 12 training sessions, significant improvements were observed in six eye movement metrics addressing different aspects involved in learning to use a PRL: first saccade landing dispersion, saccadic re-referencing, saccadic precision, saccadic latency, percentage of useful trials, and fixation stability. Importantly, our analyses allowed separate examination of the stability of target fixation separately from the dispersion and precision of the landing location of saccades. These measures explained 50% of the across-subject variance in accuracy. Fixation stability and saccadic precision showed a strong, positive correlation. Although there was no statistically significant difference in rate of learning, individuals did tend to learn saccadic precision faster than fixation stability. Saccadic precision was also more associated with accuracy than fixation stability for the behavioral task. This suggests effective intervention strategies in low vision should address both fixation stability and saccadic precision.

Keywords

macular degeneration; eye movements; fixation stability; saccade; training; scotoma

Introduction

Macular degeneration (MD) is one of the leading causes of visual impairment worldwide (Wong et al., 2014). Progression of the disease commonly impacts the fovea, the area of highest visual acuity and the location traditionally utilized as a point of reference for directing eye movements and inspecting objects of interest. The development of scotomas,

or blind spots, in the central visual field can impact functioning of the fovea and result in permanent loss of visual acuity. Some individuals with bilateral central scotomas adopt compensatory viewing strategies that involve the use of portions of the peripheral retina. In certain cases, individuals develop a new point of oculomotor reference called a preferred retinal locus (PRL) (Fletcher & Schuchard, 1997; Sunness et al., 1996). The PRL corresponds to a relatively healthy area of the retina located eccentrically to the fovea, often near the border of the scotoma (Fletcher & Schuchard, 1997).

The mechanisms by which an individual learns to effectively control a PRL are not completely understood (Legge & Chung, 2016; Chen et al., 2019), however the oculomotor system and its relationship to typical behavior is relatively well-established. Eye movements can be classified into two main types: those that shift gaze (saccades) and those that stabilize gaze (fixations) (Leigh & Zee, 2015). Saccades are ballistic eye movements that shift the line of sight, which allows the image of an object of interest to fall within the foveae. Saccades require precise planning so that the endpoint of the movement does not place the target outside of the foveal region (Leigh & Kennard, 2004). Vision is suppressed during a saccade (Matin, 1974), leading to the need for fixations. Fixations allow for the accumulation of detailed visual information about an object of interest. They require that the foveae remain directed toward an object for the highest acuity vision to occur (Foulsham, 2015). The systems that control these movements are distributed across cortical structures, with different neural circuits responsible for different eye movements. The ability to fixate is present early in life, but continues to develop into adolescence, with improvements in both stability and duration (Luna et al., 2008). The ability to land a saccade in an optimal location for foveation is evident in infancy and improves into childhood (Luna et al., 2008).

Reduced visual acuity and impaired oculomotor control can make learning to use a PRL difficult. Abnormal fixational eye movements have been associated with increased amplitude in oculomotor drifts and microsaccades (Kumar & Chung, 2014), increased saccadic latency and landing dispersion (Whitaker et al., 1991; Van der Stigchel et al., 2013), and an increase in the number of saccades necessary to locate a target (re-fixations) (White & Bedell, 1990; McMahon et al., 1991). Research suggests that fixation stability using a PRL is highly dependent upon changes in oculomotor control that develop after central vision loss (Shima et al., 2010; Tarita-Nistor et al., 2009). Persons with MD may continue to use foveating saccades even when a PRL is present (Whitaker et al., 1991; Tarita-Nistor et al., 2009). A 2005 study of patients with recent onset macular disease observed PRL development within 6 months of onset, however, most of the patients were unaware of using the area for fixation (Crossland et al., 2005).

Low vision specialists, such as ophthalmologists, optometrists, and occupational therapists, commonly use oculomotor training to teach individuals with MD how to view eccentrically and avoid their scotomas by using a PRL or other parafoveal area with greater visual acuity (Hooper et al., 2008; Pijnacker et al., 2011). Training a retinal location other than the PRL could be more appropriately termed a trained retinal locus (TRL) (Vukicevic et al., 2012). Researchers also use this approach in laboratory settings to study compensatory strategies following simulated central vision loss using gaze-contingent displays controlled in real time by a high-resolution eye tracker (Barraza-Bernal et al., 2017; Kwon et al., 2013; Liu &

Kwon, 2016; Maniglia et al., 2020; Walsh & Liu, 2014). The ideal outcome is a shift in oculomotor reference from the fovea to the PRL so that the PRL acts as a “pseudofovea” allowing for eccentric fixation and planning of saccadic eye movements. Many of the recent intervention studies have focused on using rapid serial visual presentation (RSVP) tasks and biofeedback training with microperimetry to enhance fixation stability of the PRL (Chung, 2011; Kaltenecker et al., 2019; Vingolo et al., 2018; Morales et al., 2020).

This is an important avenue of research as decreased fixation stability is shown to be a limiting factor in peripheral visual performance (Crossland et al., 2004; Rubin & Feely, 2009; Kumar & Chung, 2014; Agaoglu & Chung, 2020). However, tasks such as reading require a rapid succession of horizontal saccades to progress across lines of text and fixations to accurately identify letters and numbers (Rayner, 1998; Chung, 2020). Static eye training alone has been shown to be less effective than gaze shift exercises in improving reading speed with a PRL (Seiple et al., 2011). This suggests that focusing on fixation stability alone, without eye movement training, might not be sufficient for promoting functional outcomes. Reading, a common goal of low vision rehabilitation, requires more than just stable fixation. Reading fluency requires the oculomotor systems for fixation stability and saccades to work together. Clinical interventions that focus exclusively on fixation stability for PRL training might fail to develop the saccadic precision skills necessary for more than just stationary reading.

Translating research into clinical interventions requires acknowledging limitations that exist in clinical settings, including restrictions on time and number of visits, the need for assistance with transportation, missed appointments, and follow-through on home assignments. Importantly, individuals with macular disease are often unaware of the location or boundaries of the scotomous region, making it difficult for them to re-reference to a new retinal location during viewing activities (Schuchard, 1993; Ramachandran & Gregory, 1991). These limitations make efficient training regimens essential. Because multiple types of eye movement control are necessary for functional outcomes, the relative rates of learning of these types of eye movements during PRL training could influence the efficiency of any given training regimen. A better understanding of the rate of learning for different aspects of eye movement control during PRL training could provide insight on the timeline of development of these skills in relation to each other. Knowing this information could support better clinician decision-making on when and where to focus interventions. In this paper, we describe how eye movements change as an individual learns to control an eccentric retinal locus.

Methods

Participants

Forty healthy participants (10 male, 30 female), mean age 24.8 years (age range 18–31 years) with normal or corrected-to-normal vision as assessed using a Snellen chart (visual acuity range as tested with both eyes 20/10–20/20) and no known ocular, cognitive or neurological impairments were recruited from the University of Alabama at Birmingham (USA) and greater Birmingham metropolitan area.

Participants received monetary compensation for their participation. Written informed consent was obtained from all participants and experimental protocols were approved in accordance with the Institutional Review Board (IRB) of the University of Alabama at Birmingham.

Stimuli and Apparatus

Stimuli were generated and controlled using MATLAB version 8.4 and Psychophysics Toolbox and EyeLink Toolbox extensions (Brainard, 1997; Pelli, 1997; Cornelissen et al., 2002). An ASUS M38 desktop computer was used to run the training program in one of two training rooms; one ran Windows 8, the other Windows 10, but otherwise all software and hardware were identical. Visual stimuli were displayed on a 32-inch liquid crystal monitor (Cambridge Research Systems Display++; refresh rate: 120 Hz; resolution: 1920×1080) located at a viewing distance of 57cm. The SR Research head and chin stabilizer was used to minimize head movements and trial-to-trial variability in estimation of gaze position. Eye movements were monitored (monocular tracking using the dominant eye) using an infrared video-based eye-tracker sampling at 500 Hz (EyeLink 1000 Plus/Desktop Mount, SR Research Ltd., Ontario, Canada.) A nine-point calibration/validation sequence was performed at the beginning of each training block. The gaze position error (i.e., difference between the target position and computed gaze position) was estimated during the nine-point validation procedure. The calibration and validation were repeated until the validation error was smaller than 1° on all or most points.

Procedure

A gaze-contingent display simulating a scotoma was used to occlude central vision during each training session. The scotoma was a gray circular patch with a radius of 6° and a luminance of 37 cd/m² set against a textured parchment background with luminance of 68 cd/m² (Figure 1). During a training session, gaze position was monitored in real-time and sent to the display computer via high-speed Ethernet link. The continuous gaze information was used to draw the artificial scotoma on the visual display monitor. To reduce the impact of a mismatch in position of the artificial scotoma and the actual gaze position, which could occur were the participant to blink or squint, the system was designed to turn the entire display screen gray as soon as it detected a blink or a decrease in pupil size to a threshold value (Aguilar & Castet, 2011). Median system latency found using a method described by Saunders and Woods (2014) was 18 ms, which is sufficient to support training task performance.

Training

The training protocol using the simulated scotoma was previously described in detail by Liu and Kwon (2016). This protocol was selected as it was demonstrated to induce a PRL in normally sighted subjects in a relatively short period of time. In addition to the simulated scotoma, the background of the screen was blurred by applying a Gaussian filter that eliminated detailed visual information but allowed for the detection of motion and color. A single clear window, circular in shape and with radius of 2.5°, was centered 8.5° to either the left or right of the center of the simulated scotoma and served as the location in which to develop a TRL. The left and right windows were selected to be used as training loci as

previous studies have shown a higher incidence of natural PRL development occurring at those locations (Sunness et al., 1996; Fletcher & Schuchard, 1997).

The training protocol included three conditions which are relevant to activities of daily living and often identified by persons with central scotoma as being difficult to perform: Face Recognition, Object Recognition, and Word Recognition (Figure 1) (Schuchard, 1995; Bullimore et al., 1991; Kleen & Levoy, 1981). The stimuli used for the discrimination tasks were also of different sizes, as it has been suggested that greater learning occurs when using multiple stimulus conditions and tasks (Maniglia & Sitz, 2018; Xie & Yu, 2020). Faces used in the task were cropped using an oval mask and set to 4.3° . The height of both objects and words was set to 1.6° with words being displayed in a lower-case Courier font. Each training session included one block of each condition. Each block consisted of 30 trials. Each trial included three phases: target following and recognition, gaze centering, and visual search. This study focuses specifically on target following and recognition, as this is the phase that requires the greatest oculomotor control and accuracy.

During the target recognition phase, participants were asked to visually direct the clear window over the current target (i.e., face, object, or word) which was obscured by the background filter. Participants were tasked with reporting as quickly and accurately as possible whether the target was a male face or female face (Face Condition), a real-world object or non-object (Object Condition), or a real- word or non-word (Word Recognition) by making a keyboard press. The target changed and moved to a new location only when either a valid keypress was detected or when the simulated scotoma did not occlude the target for at least 2.5 seconds. Each training block consisted of 180 trials, after which the participant was provided with onscreen feedback regarding (mean accuracy and task- completion time) for motivation. All participants completed the three training blocks in each session. The order of the training blocks was randomly assigned to each participant prior to the first session; however, the assigned order was maintained throughout training. Participants were assigned a clear window location (to the left or to the right of the artificial scotoma) prior to initiation that was maintained throughout training. Each training session took approximately 45 minutes to 1-hour to complete. Participants completed a total of 12 training sessions over the course of 4 to 6 weeks.

Six different oculomotor metrics were characterized to assess development of the TRL, as previously described in Maniglia et al. (2020). These metrics aim at describing different oculomotor aspects involved in the development of a TRL, specifically: *First saccade landing dispersion*, the across-trial distribution of landing locations of the first saccade made after target appearance; *Saccadic re-referencing*, the percentage of trials in which the first fixation placed the target in a visible position outside of the simulated scotoma; *Saccadic precision*, the across-trial distribution of landing locations of first fixations that placed the target outside of the scotoma (similar to *First saccade landing dispersion*, but not confined to the first ‘absolute’ saccade of the trial); *Percentage of useful trials*, the proportion of trials in which at least one saccade placed the target outside of the scotoma; *Latency of target acquisition*, the time interval between appearance of the target and the first fixation outside the scotoma; and *Fixation stability*, the dispersion of eye positions within a trial after a

first saccade, normalized for the average TRL location across trials. Figure 2 provides an illustration of each of the oculomotor metrics and a brief description.

The bivariate contour ellipse area (BCEA) was calculated for first saccade landing dispersion, saccadic precision, and fixation stability and expressed in deg^2 . In our study, the BCEA is the size of an ellipse that encompasses fixation points (Steinman, 1965) for 68% of eye positions during a trial (Crossland, 2004); a smaller BCEA indicates improvement.

Results

Oculomotor Changes

Figure 3 shows the mean change in performance for each of the six oculomotor metrics as a function of training between the first training session (Block 1) and the last training session (Block 12). A comparison of performance at the first and last training session using paired samples t-tests shows a significant improvement in performance in all of the metrics: Overall, participants showed a significant decrease in the spatial distribution of first saccades across trials (First saccade landing dispersion, $t(39) = 17.92$, $p = 9.95 \times 10^{-21}$), a significant increase in the percentage of trials in which the first absolute saccade placed the target outside of the scotoma (Saccadic re-referencing, $t(39) = 8.84$, $p = 3.68 \times 10^{-11}$), a significant decrease in the spatial distribution of first saccades that did not obscure the target (Saccadic precision, $t(39) = 14.15$, $p = 2.99 \times 10^{-17}$), a significant increase in the proportion of trials in which at least one fixation placed the target in a visible position outside the scotoma (Percentage of trials that are useful, $t(39) = 3.46$, $p < 0.01$), a significant decrease in the time interval between appearance of the target and the end point of the first useful fixation (Latency of target acquisition, $t(39) = 9.35$, $p = 8.28 \times 10^{-12}$), and a significant decrease in eye position dispersion within trials after the first saccade (Fixation stability, $t(39) = 10.63$, $p = 2.47 \times 10^{-13}$). Improvement in all six oculomotor metrics demonstrates that participants learned how to improve control after developing a TRL at their assigned clear window.

A principal components analysis (PCA) was conducted on the oculomotor metrics from the last training session to better understand how eye movement behaviors were related to each other. Figure 4 shows a plot of the first two principal components; red dots represent scores for individual participants and blue dots represent the weighting of each metric. Principal Component 1 is shown to weigh heavily on a cluster of three metrics that are highly correlated with each other: Fixation stability, Saccadic precision, and First saccade landing dispersion. The proportion of variance explained by the first two principal components was 49.74% and 27.67%, respectively.

Behavioral Changes

Table 1 shows a comparison of the mean change in accuracy between the first and last training sessions (Block 1 vs. Block 12). Accuracy is expressed as percentage of correct trials, with higher values indicating better performance. The p-value column shows the p-value of a paired samples t-test comparing Block 1 to Block 12. For the Letter Task, Object Task, and Face Task participants improved performance significantly by 19.78%

($t(39) = -12.97, p = 1.02 \times 10^{-15}$), 18.38% ($t(39) = -13.33, p = 4.22 \times 10^{-16}$), and 20.88% ($t(39) = -12.08 \times 10^{-15}$), respectively.

A correlation analysis (Figure 5) measured the strength and direction of association between the oculomotor metrics post-training and the overall mean accuracy between the three tasks. Fixation stability had a strong, positive correlation with First saccade landing dispersion ($r(38) = .87, p = 5.6 \times 10^{-13}$) and Saccadic precision ($r(38) = .63, p = 1.2 \times 10^{-5}$). As fixation stability improves, saccadic precision also tends to improve. There was a moderate, negative correlation between saccadic precision and accuracy ($r(38) = -.36, p = 0.022$). As saccadic precision improves accuracy tends to improve.

Learning Rates

An analysis of learning rates was completed to compare the proficiency of each eye metric or behavioral task with increasing levels of experience. The learning curves for metrics where improvements resulted in increases (for example, accuracy) were modeled to fit the form $y = A(1 - e^{-k(x-1)}) + B$ (Equation 1) where y is the value at session x . $A+B$ is the value y can take at its plateau, A is a measure of the amount of learning, and k corresponds to the learning rate. Metrics where improvements in performance resulted in decreases (for example, fixation stability where a lower BCEA is better) were fit to the form $y = Ae^{-k(x-1)} + B$ (Equation 2), where the variables have the same meaning, but B is the smallest value of y at its plateau.

Eye Movement Metrics Learning Rates

Figure 6 shows in orange lines the training curves for all six of the eye metrics for each participant. The blue line represents the mean value across all participants at each training session. The fastest rate of learning was seen in First saccade landing dispersion ($k=1.49$), followed by Percentage of useful trials ($k=1.33$), Saccadic precision ($k=1.14$), Saccadic re-referencing ($k=1.07$), Fixation stability ($k=0.99$), and Saccadic latency ($k=0.61$).

Accuracy Learning Rates

Figure 7 shows in orange lines the training curves for each of the three behavioral training tasks (face, object, and letter) for each participant. The blue line represents the mean value across all participants at each training session. The fastest rate of learning was seen for the Letter task ($k=1.04$), followed by Object ($k=0.48$), and Face ($k=0.45$). Table 2 shows the differences in learning rates (k) between the behavioral training tasks and each of the six eye movement metrics. Statistical significance (p -value) was calculated using paired samples t-tests.

Effect of Eye Metric and Task on Performance

Additional analyses were completed to examine how day-by-day improvements in performance related to improvements in eye metrics. Percent correct scores for each of the 12 blocks for each participant was correlated to their eye metrics for each of the 12 blocks. This gave a Pearson correlation for each participant for each task. These Pearson correlations were converted to Fisher Z-transformed correlations for further analysis. A two-way repeated measures ANOVA was performed on these scores to assess whether

different metrics had different relationships to behavior with factors of eye metric (First saccade landing dispersion, Saccadic precision, Saccadic re-referencing, Fixation stability, Saccadic latency) by task (face, object, letter). Percentage of useful trials was excluded since values were unreliable across subjects (some subjects had 100% useful trials on all blocks, making correlations meaningless). Results revealed a significant main effect of eye metric on Z-transformed correlations to performance ($F_{(4,156)}=8.96, p<0.0001$). There was also a significant main effect of task ($F_{(2,78)}=4.387, p=0.016$). There was no significant interaction of eye metric by task ($F_{(8,312)}=1.316, p=0.235$). Follow-up tests showed that Z-transformed correlations were strongest for First saccade landing dispersion (mean=1.048), Saccadic precision (mean=1.008), and Fixation stability (mean=0.978) followed by Saccadic latency (mean=0.890) and Saccadic rereferencing (mean=0.739). Targeted post-hoc t-tests did not indicate significant differences between first saccade landing dispersion, saccadic precision, or fixation stability (all $p>0.05$). Post hoc t-tests indicated that participants performed similarly when completing the Letter (mean=1.127) and Object (mean=1.060) tasks, but differently when completing the Face (mean=0.934) task as compared to Letters ($p=0.004$) or Objects ($p=0.039$).

Discussion

In this paper we examined eye movement changes and their time course in healthy participants trained to use a peripheral retinal location while performing a visual task in conditions of simulated scotoma. Participants were assigned a specific locus outside the simulated scotoma (a trained retinal locus [TRL], in analogy with the preferred retinal locus [PRL] found in patients suffering from central vision loss). In particular, we extracted six oculomotor metrics (previously described in Mangilia et al., 2020) from the eye movement data recorded during the 12 training sessions. Our results support the hypothesis that eye movement control is influenced by peripheral vision training, which is consistent with previous literature (Tartia-Nistor et al., 2009; Kwon et al., 2013; Janssen & Verghese, 2016; Maniglia et al., 2020). The majority of participants demonstrated significant improvements in Saccadic precision, meaning the ability to place the peripheral target in a consistent retinal location, and in Fixation stability, meaning the ability to maintain steady fixation once the peripheral target is acquired. We also observed statistically significant improvements in First saccade landing dispersion, Saccadic re-referencing, Saccadic latency, and Percentage of useful trials. Interestingly, Fixation stability, Saccadic precision, and First saccade landing dispersion were strongly correlated with each other and explained a great deal of across-subject performance variance post-training. These results, together with previous literature, suggests that training improved these particular eye movement metrics (Seiple et al., 2005; Mandelcorn et al., 2013; Xie et al., 2020). Although there was a strong, positive correlation between Fixation stability and Saccadic precision, the rate of learning for these two metrics was similar, with Saccadic precision being learned slightly faster than Fixation stability. This supports the idea that learning was occurring separately but simultaneously between neurological systems; those which initiate saccades (including the parietal cortex, caudal superior colliculus, and horizontal and vertical brainstem gaze centers) and those which inhibit saccades or maintain fixation (including the suppression center of the frontal eye fields, rostral superior colliculus, nucleus raphe interpositus, and the medio-posterior

cerebellum) (Takahashi et al., 2022; Stewart et al., 2020; Mirpour et al., 2018; Kraulis et al., 2017; Gancarz & Grossberg, 1999).

In addition to examining the learning rates for the eye movement metrics, we also looked at the learning rates for each of the three behavioral tasks. While not statistically different, the learning rates for the eye movement metrics were faster than those for the behavioral tasks in almost all cases. This supports the idea that learning eye movement control of the TRL is a prerequisite for learning to accurately complete a behavioral task, as suggested by previous studies associating increased TRL control with greater accuracy on behavioral tasks (Seiple et al., 2005; Tarita-Nistor et al., 2009; Rose & Bex, 2017).

While we demonstrated associations between certain eye movement metrics and task performance across subjects, we also showed these associations to be true within subjects. Day-by-day performance on a given discrimination task is best predicted by First saccade landing dispersion, followed by Saccadic precision, and then by Fixation stability. This adds additional support to the importance of addressing Saccadic precision when providing peripheral or eccentric viewing training.

In this experiment, participants with healthy vision learned to use an eccentric retinal locus over the course of 12 weeks, a timeline that can be different from the lived experience of a person with MD. Progression from the initial diagnosis of MD to advanced stages of geographic atrophy can occur over a period of many years (Klein et al., 2008), with first appearance of foveal involvement at 2.5 years on average (Linblad et al., 2009). Functional visual changes, however, can begin to occur much earlier (Sunness et al., 1997; Midena et al., 2007; Dimitrov et al., 2011). Considering that MD is often a gradual progression of vision loss, the timing of learning compensatory eye movements in patients diagnosed with MD is much slower (White & Bedell, 1990; Rohrschneider et al., 1997; Crossland et al., 2005; Tarita-Nistor et al., 2008) and adjustments continue to be needed as scotoma size increases (Whitaker et al., 1988; Renninger et al., 2008). Additionally, there exist a number of differences between training healthy participants to perform visual tasks with an artificial scotoma and visual rehabilitation in MD, such as the much clearer location, consistent size and even awareness of the scotoma and clear window in this training paradigm compared to the lived experience of many individuals with MD (Walsh & Liu, 2014).

An important question is whether laboratory-based training strategies, such as the one used in this study, are translatable to clinical settings and generalizable to activities of daily living. Outside of microperimetric biofeedback training, there is limited ability to accurately track or monitor eye movements during traditional clinical eccentric viewing training and many of the laboratory studies utilize on-screen visual aids (Maniglia et al., 2020; Astle et al., 2015). In addition, previous literature is not clear on differences in the rate of learning for specific types of eye movements using a PRL for persons diagnosed with MD, however, knowing how training in a laboratory environment influences eye movements may help advance understanding of what is possible in patients living with MD and promote future experiments with the MD population which intentionally demarcate the location of the individual's anatomical scotoma in the visual field. This type of experiment will facilitate

better understanding of the similarities or differences in the MD and healthy populations and whether these types of training paradigms have a place in the clinic.

Fixation stability has been an important outcome measure in recent years (Mandelcorn et al., 2013; Vingolo et al., 2018) as it is positively correlated with visual acuity at the PRL (Tarita-Nistor, 2009; Erbezi & Ozturk, 2018) and with reading speed (Crossland et al., 2004; Falkenberg et al., 2007; Amore et al., 2013). However, the naturally selected PRL is often not the peripheral area with highest visual acuity (Bernard & Chung, 2018), and many of these studies succeeded in training a new retinal locus rather than only improving fixation at the existing location (Chung, 2020). It is necessary to consider the influence of this change when drawing conclusions about the importance of fixation stability alone in improving outcomes.

In nature, the eye is regularly completing visual search and smooth pursuit movements, therefore training that targets multiple forms of oculomotor control better simulates the real-world learning experience for persons living with bilateral central vision loss. In the present study, we have demonstrated that saccadic precision has a moderate association with accuracy and can be learned almost simultaneously with fixation stability when training utilizes a method that requires more than just static eye gaze. Given the importance of saccadic eye movements in reading and visual search, clinical interventions that focus on fixation stability should also include opportunities for developing saccadic precision to improve performance.

References

- Agaoglu MN, & Chung STL (2020). Exploration of functional consequences of fixational eye movements in the absence of a fovea. *Journal of Vision*, 20(2):12, 1–15. 10.1167/jov.20.2.12
- Amore FM, Fasciani R, Silvestri V, Crossland MD, de Waure C, Cruciani F, & Reibaldi A (2013). Relationship between fixation stability measured with MP-1 and reading performance. *Ophthalmic & Physiological Optics*, 33(5), 611–617. 10.1111/opo.12048 [PubMed: 23489240]
- Astle AT, Blighe AJ, Webb BS, & McGraw PV (2015). The effect of normal aging and age-related macular degeneration on perceptual learning. *Journal of Vision*, 15(10):16. 10.1167/15.10.16
- Barraza-Bernal MJ, Rifai K, & Wahl S (2017). Transfer of an induced preferred retinal locus of fixation to everyday life visual tasks. *Journal of Vision*, 17(14):2, 1–16. 10.1167/17.14.2
- Bernard J, & Chung S (2018). Visual acuity is not the best at the preferred retinal locus in people with macular disease. *Optometry & Visual Science*, 95(9), 829–836. 10.1097/OPX.0000000000001229
- Bullimore MA, Bailey IL, & Wacker RT (1991). Face recognition in age-related maculopathy. *Investigative Ophthalmology and Visual Science*, 32(7), 2020–2029. [PubMed: 2055696]
- Chen N, Shin K, Million R, Song Y, Kwon M, & Tjan B (2019). Cortical reorganization of peripheral vision induced by simulated central vision loss. *Journal of Neuroscience*, 39(18), 3529–3536. 10.1523/JNEUROSCI.2126-18.2019 [PubMed: 30814310]
- Chung S (2011). Improving reading speed for people with central vision loss through perceptual learning. *Investigative Ophthalmology & Visual Science*, 52(2), 1164–1170. 10.1167/iovs.10-6034 [PubMed: 21087972]
- Chung S (2020). Reading in the presence of macular disease: a mini-review. *Ophthalmic & Physiological Optics*, 40(2), 171–186. 10.1111/opo.12664 [PubMed: 31925832]
- Crossland MD, Culham LE, & Rubin GS (2004). Fixation stability and reading speed in patients with newly developed macular disease. *Ophthalmic & Physiological Optics*, 24(4), 327–333. 10.1111/j.1475-1313.2004.00213.x

- Crossland MD, Sims M, Galbraith RF, & Rubin GS (2004). Evaluation of a new quantitative technique to assess the number and extent of preferred retinal loci in macular disease. *Vision Research*, 44(13), 1537–1546. 10.1016/j.visres.2004.01.006 [PubMed: 15126063]
- Crossland MD, Cullham LE, Kabanarou SA, & Rubin GS (2005). Preferred retinal locus development in patients with macular disease. *Ophthalmology*, 112(9), 1579–1585. 10.1016/j.opthta.2005.03.027 [PubMed: 16087239]
- Dimitrov PN, Robman LD, Varsamidis M, Aung KZ, Makeyeva GA, Guymer RH, & Vingrys AJ (2011). Visual function tests as potential biomarkers in age-related macular degeneration. *Investigative Ophthalmology & Visual Science*, 52(13), 9457–9469. 10.1167/iovs.10-7043 [PubMed: 22003115]
- Elliot DB, Trukolo-Illic M, Strong JG, Pace R, Plotkin A, & Bevers P (1997). Demographic characteristics of the vision-disabled elderly. *Investigative Ophthalmology and Visual Science*, 38(12), 2566–2575. [PubMed: 9375576]
- Erbezi M, & Ozturk T (2018). Preferred retinal locus locations in macular degeneration. *Retina*, 38(12), 2372–2378. 10.1097/IAE.0000000000001897 [PubMed: 29065012]
- Falkenberg HK, Rubin GS, & Bex PJ (2007). Acuity, crowding, reading, and fixation stability. *Vision Research*, 47(1), 126–135. 10.1016/j.visres.2006.09.014 [PubMed: 17078991]
- Fletcher DC & Schuchard RA (1997). Preferred retinal loci relationship to macular scotomas in a low-vision population. *Ophthalmology*, 104, 632–638. 10.1016/s0161-6420(97)30260-7 [PubMed: 9111255]
- Foulsham T (2015). Eye movements and their functions in everyday tasks. *Eye*, 29, 196–199. 10.1038/eye.2014.275 [PubMed: 25397783]
- Gancarz G & Grossberg S (1999). A neural model of saccadic eye movement control explains task-specific adaptation. *Vision Research*, 39(18), 3123–3143. 10.1016/S0042-6989(99)00049-8 [PubMed: 10664809]
- Hooper P, Jutai JW, Strong G, & Russell-Minda E (2008). Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Canadian Journal of Ophthalmology*, 43(2), 180–187. 10.3129/i08-001 [PubMed: 18347620]
- Janssen CP & Verghese P (2016). Training eye movements in visual search in individuals with macular degeneration. *Journal of Vision*, 16(15):29. 10.1167/16.15.29
- Kaltenegger K, Kuester S, Altpeter-Ott E, Eschweiler GW, Cordey A, Ivanov IV, Martus P Knipp C, & Trauzettel-Klosinski. (2019). Effects of home reading training on reading and quality of life in AMD - a randomized and controlled study. *Graefe's Archives for Clinical and Experimental Ophthalmology*, 257(7), 1499–1512. 10.1007/s00417-019-04328-9
- Klein ML, Ferris III FL, Armstrong J, Hwang TS, Chew EY, Bressler SB, Chandra SR, & AREDS Group. (2008). Retinal precursors and the development of geographic atrophy in age-related macular degeneration. *Ophthalmology*, 115(6), 1026–1031. 10.1016/j.opthta.2007.08.030 [PubMed: 17981333]
- Krauzlis RJ, Goffart L, & Hafed ZM (2017). Neuronal control of fixation and fixational eye movements. *Philosophical Transactions of the Royal Society B*, 372: 20160205. 10.1098/rstb.2016.0205
- Kumar G, & Chung STL (2014). Characteristics of fixational eye movements in people with macular disease. *Investigative Ophthalmology & Visual Science*, 55(8), 5125–5133. 10.1167/iovs.14-14608 [PubMed: 25074769]
- Kwon M, Nandy AS, & Bosco ST (2013). Rapid and persistent adaptability of human oculomotor control in response to simulated central vision loss. *Current Biology*, 23(17), 1663–1669. 10.1016/j.cub.2013.06.056 [PubMed: 23954427]
- Legge GE, & Chung ST (2016). Low vision and plasticity: implications for rehabilitation. *Annual Review of Vision Science*, 2, 321–343. 10.1146/annurev-vision-111815-114344
- Leigh RJ & Kennard C (2003). Using saccades as a research tool in the clinical neurosciences. *Brain*, 127(3), 460–477. 10.1093/brain/awh035 [PubMed: 14607787]
- Leigh RJ & Zee DS (2015). *Functional Classes of Eye Movements*. In *The neurology of eye movements* (5th ed.). Oxford University Press.

- Linblad AS, Lloyd PC, Clemons TE, Gensler GR, Ferris III FL, Klein ML, Armstrong JR, & AREDS Group. (2009). Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Archives of Ophthalmology*, 127(9), 1168–1174. 10.1001/archophthalmol.2009.198 [PubMed: 19752426]
- Liu R & Kwon M (2016). Integrating oculomotor and perceptual training to induce a pseudofovea: A model system for studying central vision loss. *Journal of Vision*, 16(6):10, 1–21. 10.1167/16.6.10
- McMahon TT, Hansen M, & Viana M (1991). Fixation characteristics in macular disease: Relationship between saccadic frequency and reading rate. *Investigative Ophthalmology & Visual Science*, 32(3), 567–574. [PubMed: 2001931]
- Mandelcorn MS, Podbielski DW, & Mandelcorn ED. (2013). Fixation stability as a goal in the treatment of macular disease. *Canadian Journal of Ophthalmology*, 48(5), 364–367. 10.1016/j.jcjo.2013.05.006 [PubMed: 24093181]
- Maniglia M & Seitz AR (2018). Towards a whole brain model of perceptual learning. *Current Opinion in Behavioral Science*, 20, 47–55. 10.1016/j.cobeha.2017.10.004
- Maniglia M, Jogin R, Visscher KM, & Seitz AR (2020). We don't all look the same; detailed examination of peripheral looking strategies after simulated central vision loss. *Journal of Vision*, 20(13):5. 10.1167/jov.20.13.5
- Maniglia M, Soler V, & Trotter Y (2020). Combining fixation and lateral masking training enhances perceptual learning effects in patients with macular degeneration. *Journal of Vision*, 20(10):19. 10.1167/jov.20.10.19
- Maniglia M, Visscher KM, & Seitz AR (2020). A method to characterize compensatory oculomotor strategies following simulated central vision loss. *Journal of Vision*, 20(15), 1–18. 10.1167/jov.20.9.15
- Matin E (1974). Saccadic suppression: A review and an analysis. *Psychological Bulletin*, 81(12), 899–917. 10.1037/h0037368 [PubMed: 4612577]
- Midena E, Vujosevic S, & Convento E (2007). Microperimetry and fundus autofluorescence in patients with early age-related macular degeneration. *British Journal of Ophthalmology*, 91, 1499–1503. 10.1136/bjo.2007.119685 [PubMed: 17504849]
- Mirpour K, Bolandnazar Z, & Bisley JW (2018). Suppression of frontal eye field neuronal responses with maintained fixation. *Proceedings of the National Academy of Sciences (PNAS)*, 115(4), 804–809. 10.1073/pnas.1716315115
- Morales MU, Saker S, Wilde C, Rubinstein M, Limoli P, & Amoaku WM (2020). Biofeedback fixation training method for improving eccentric vision in patients with loss of foveal function secondary to different maculopathies. *International Ophthalmology*, 40: 305–312. 10.1007/s10792-019-01180-y [PubMed: 31583549]
- Pijnacker J, Verstraten P, van Damme W, Vandermeulen J, & Steenbergen B (2011). Rehabilitation of reading in older individuals with macular degeneration: A review of effective training programs. *Aging, Neuropsychology, and Cognition*, 18(6), 708–732. 10.1080/13825585.2011.613451
- Ramachandran VS & Gregory RL (1991) Perceptual filling in of artificially induced scotomas in human vision. *Nature*, 350, 699–702. 10.1038/350699a0 [PubMed: 2023631]
- Rayner K (1998). Eye movements in reading and information processing: 20 years of research. *Psychological Bulletin*, 124(3), 372–422. 10.1037/0033-2909.124.3.372 [PubMed: 9849112]
- Renninger L, Dang L, Verghese P, & Fletcher D (2008). Effect of central scotoma on eye movement behavior [Abstract]. *Journal of Vision*, 8(6), 641. 10.1167/8.6.641
- Rohrschneider K, Gluck R, Blankenagel A, & Volker HE (1997). Fixation behavior in Stargardt disease. *Fundus-controlled studies. Ophthalmologie*, 94, 624–628. 10.1007/s003470050171 [PubMed: 9410227]
- Rose D & Bex P (2017). Peripheral oculomotor training in individuals with healthy visual systems: Effects of training and training transfer. *Vision Research*, 133, 95–99. [PubMed: 28192092]
- Rubin GS & Feely M (2009). The role of eye movements during reading in patients with age-related macular degeneration (AMD). *Neuro-Ophthalmology*, 33(3), 120–126. 10.1080/01658100902998732
- Schuchard RA (1993). Validity and interpretation of Amsler grid reports. *Archives of Ophthalmology*, 11(6), 776–780. 10.1001/archophth.1993.01090060064024

- Schucard RA (1995). Adaptation to macular scotomas in persons with low vision. *American Journal of Occupational Therapy*, 49(9), 870–876. 10.5014/ajot.49.9.870
- Shima N, Markowitz SN, & Reyes SV (2010). Concept of a functional retinal locus in age-related macular degeneration. *Canadian Journal of Ophthalmology*, 45(1), 62–66. 10.3129/i09-236 [PubMed: 20130713]
- Seiple W, Szlyk JP, McMahon T, Pulido J, & Fishman GA (2005). Eye-movement training for reading in patients with age-related macular degeneration. *Investigative Ophthalmology & Visual Science*, 46(8), 2886–2896. 10.1167/iovs.04-1296 [PubMed: 16043863]
- Steinman R (1965). Effect of target size, luminance, and color on monocular fixation. *Journal of the Optical Society of America*, 55(9), 1158–1164. 10.1364/JOSA.55.001158
- Stewart E, Valsecchi M, & Schutz A (2020). A review of interactions between peripheral and foveal vision. *Journal of Vision*, 20(12):2. 10.1167/jov.20.12.2
- Sunness JS, Applegate CA, Haselwood D, & Rubin GS (1996). Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology*, 103, 1458–1466. 10.1016/s0161-6420(96)30483-1 [PubMed: 8841306]
- Sunness JS, Rubin GS, Applegate CA, Bressler NM, Marsh MJ, Hawkins BS, & Haselwood D (1997). Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*, 104(10), 1677–1691. 10.1016/s0161-6420(97)30079-7 [PubMed: 9331210]
- Takahashi M, Sugiuchi Y, Na J, & Shinoda Y (2022). Brainstem circuits triggering saccades and fixation. *Journal of Neuroscience*, 42(5), 789–803. 10.1523/JNEUROSCI.1731-21.2021 [PubMed: 34880121]
- Tarita-Nistor L, Gonzalez EG, Markowitz SN, & Steinbach MJ (2009). Plasticity of fixation in patients with central vision loss. *Visual Neuroscience*, 26(5–6), 487–494. 10.1017/S0952523809990265 [PubMed: 20003597]
- Van der Stigchel S, Bethlehem RAI, Klein BP, Berendschot TTJM, Nijboer TCW, & Domoulin SO (2013). Macular degeneration affects eye movement behavior during visual search. *Frontiers in Psychology*, 4(579), 1–9. 10.3389/fpsyg.2013.00579 [PubMed: 23382719]
- Vingolo EM, Napolitano G, & Fragiotta S (2018). Microperimetric biofeedback training: fundamentals, strategies, and perspectives. *Frontiers in Bioscience*, 10, 48–64.
- Vukicevic M, Le A, & Baglin J (2012). A simplified method of identifying the trained retinal locus for training eccentric viewing. *Journal of Visual Impairment & Blindness*, 106(9), 555–561. 10.2741/s500
- Walsh D & Liu L (2014). Adaptation to a simulated central scotoma during visual search training. *Vision Research*, 96, 75–86. 10.1016/j.visres.2014.01.005 [PubMed: 24456805]
- Whitaker SG, Cummings RW, & Swieson LR (1991). Saccade control without a fovea. *Vision Research*, 31(12), 2209–2218. 10.1016/0042-6989(91)90173-3 [PubMed: 1771800]
- Whitaker SG, Budd J, & Cummings RW (1988). Eccentric fixation with macular scotoma. *Investigative Ophthalmology & Visual Science*, 29(2), 268–278. [PubMed: 3338884]
- White JM, & Bedell HE (1990). The oculomotor reference in humans with bilateral macular disease. *Investigative Ophthalmology & Visual Science*, 31(6), 1149–1161. [PubMed: 2354915]
- Wong WL, Su X, Li X, Cheung CMG, Klein R, & Cheng CY (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *The Lancet Global Health*, 2, e106–e116. 10.1016/S2214-109X(13)70145-1 [PubMed: 25104651]
- Xie X, Liu L, & Yu C (2020). A new perceptual training strategy to improve vision impaired by central vision loss. *Vision Research*, 174, 69–76. 10.1016/j.visres.2020.05.010 [PubMed: 32615458]

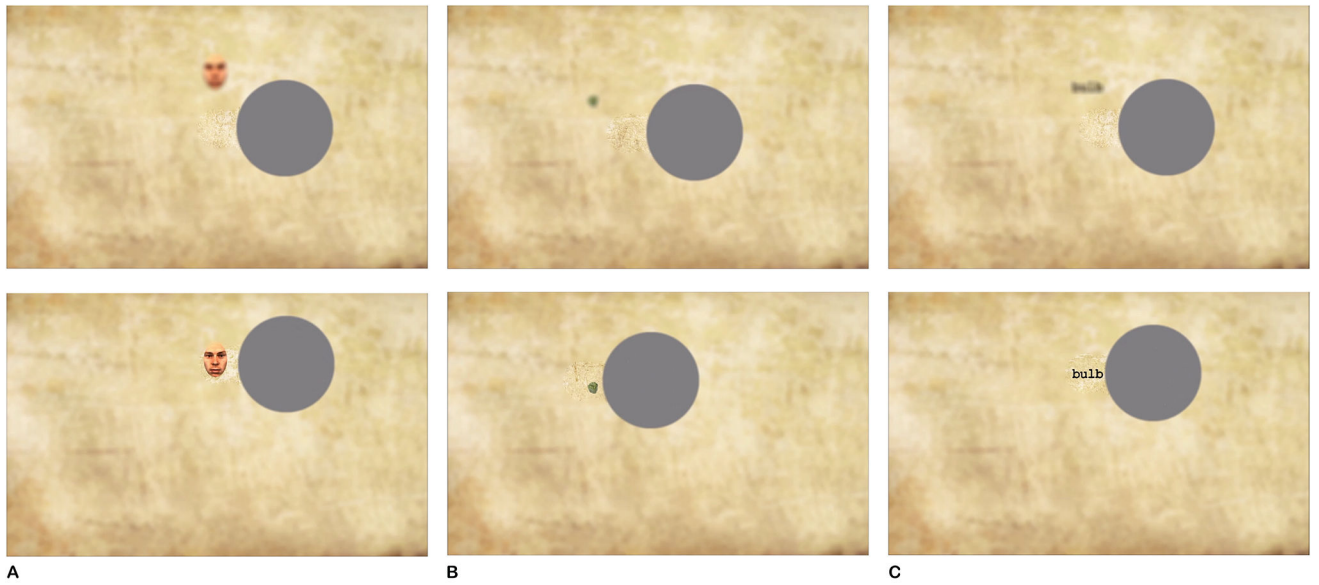


Figure 1. Training task used in the study.

Participants were asked to recognize a target as it changed location and identity by directing the TRL clear window (located in this example to the left of the simulated scotoma) onto the target. This was performed under three conditions: **A.** Face Recognition, **B.** Object Recognition, and **C.** Word Recognition. In each case, the target was obscured (top image) until revealed (bottom image) by directing the trained TRL over the target. In A, a face is shown. In B, a bell pepper is shown. In C, the word “bulb” is shown.

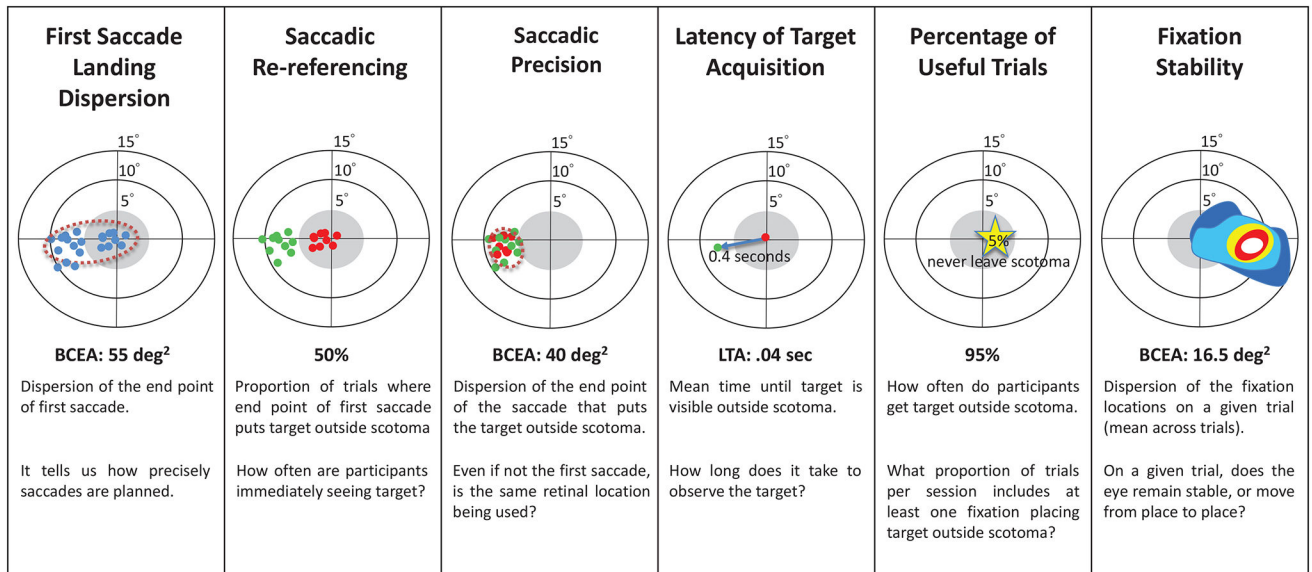


Figure 2. Overview of the oculomotor metrics used in the study (adapted from Maniglia, Visscher and Seitz, 2020).

These metrics were extracted from the eye movement data collected during each training block. First saccade landing dispersion: blue dots represent the end points of absolute first saccades during each trial of a training block. The BCEA is represented by a red ellipse and encompasses 68% of total eye positions. Saccadic re-referencing: green dots represent ‘absolute’ first fixations of a trial that place the target outside of the scotoma, red dots are ‘absolute’ first fixations of a trial that place the target within the scotoma. Saccadic precision: dots represent the end points of saccades that first place the target outside of the scotoma. A green dot means the saccade was an ‘absolute’ first saccade (same as Saccadic re-referencing), whereas a red dot means that location was from a second or later saccade. Latency of target acquisition: reflects how long it takes to make a saccade which places the target in a visible location. Percentage of useful trials: indicates what percentage of trials include at least one saccade placing the target in a visible location. Fixation stability: a within-trial measure of dispersion after the first saccade of each trial, normalized to center each trial starting point to the average across-trial TRL location. It is visually represented using a kernel density estimator (KDE).

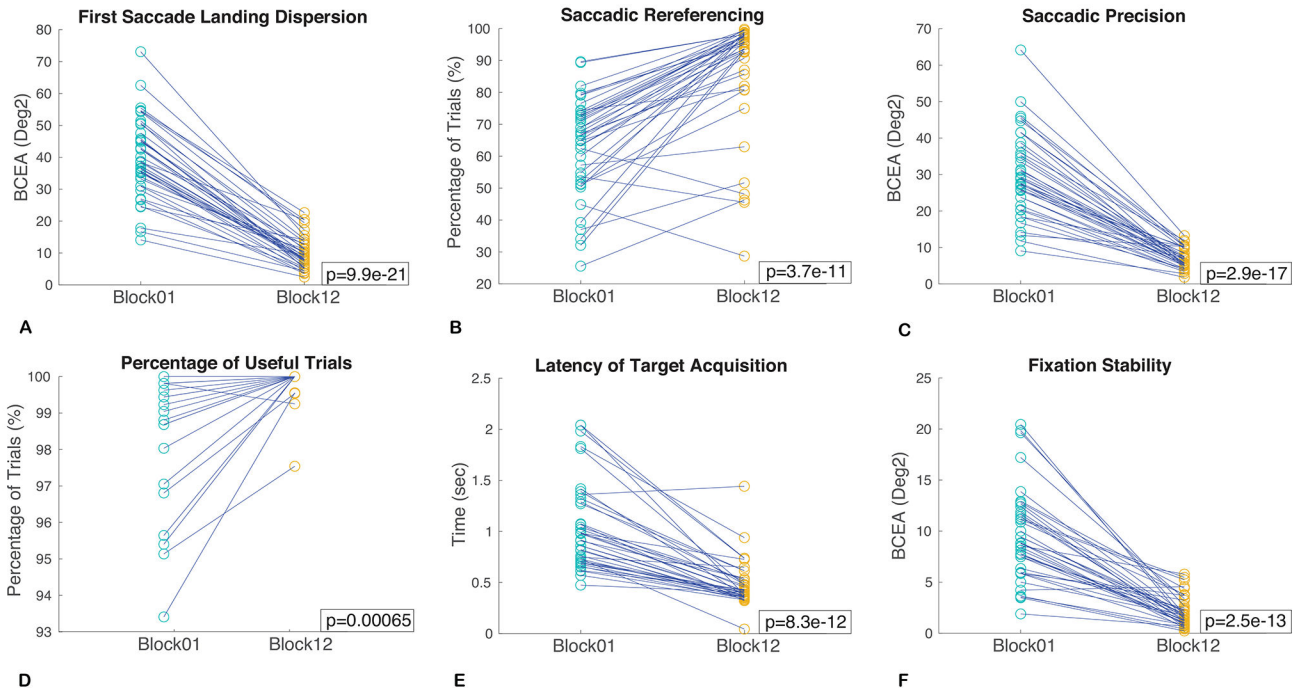


Figure 3. Oculomotor changes with training.

Block average of metrics scores for each of the six oculomotor metrics as a function of training (comparison between the first training session (Block 1) and the last training session (Block 12)).

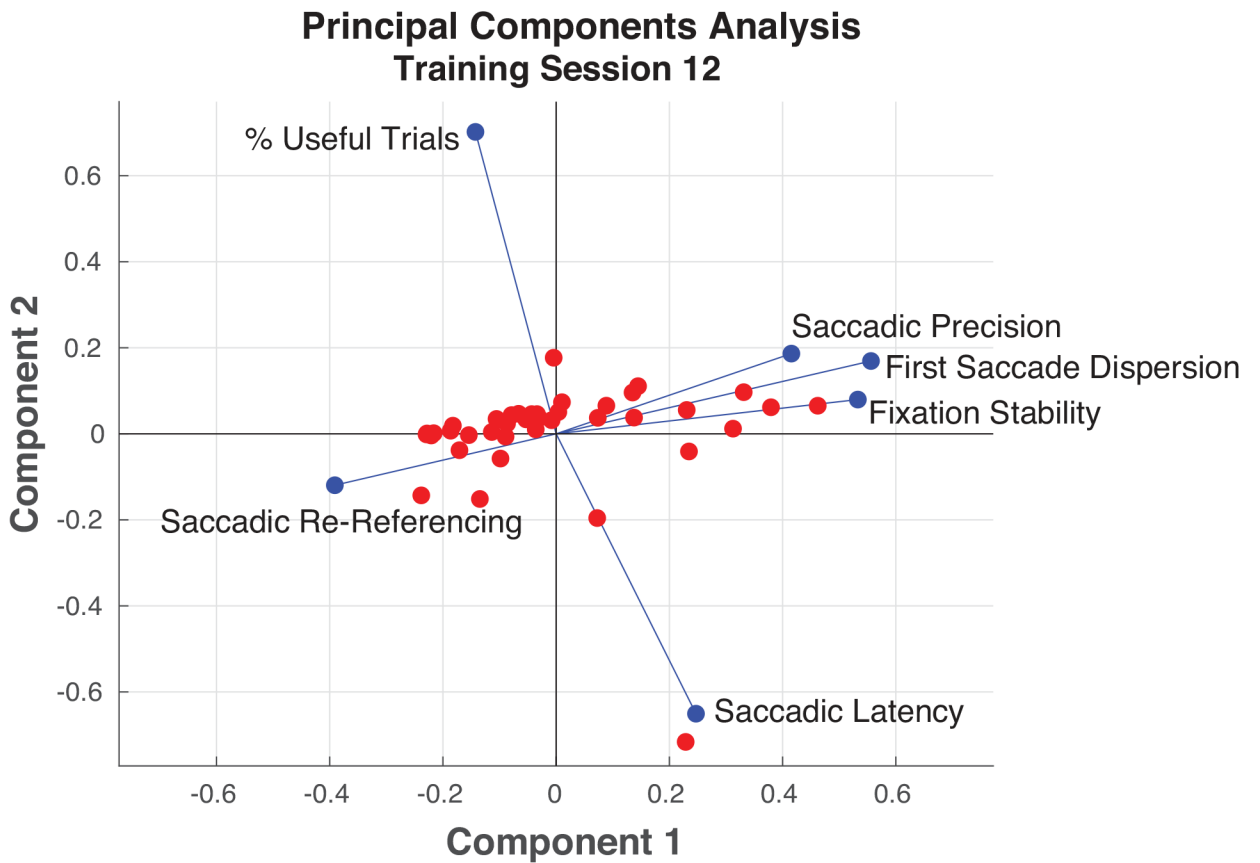


Figure 4. Principal components analysis on the oculomotor metric scores.

Plot of the two principal components; red dots represent scores for individual participants and blue dots represent the weighting of each metric. Principal Component 1 weighs heavily on a cluster of three metrics that are highly correlated with each other: fixation stability, saccadic precision, and first saccade landing dispersion.

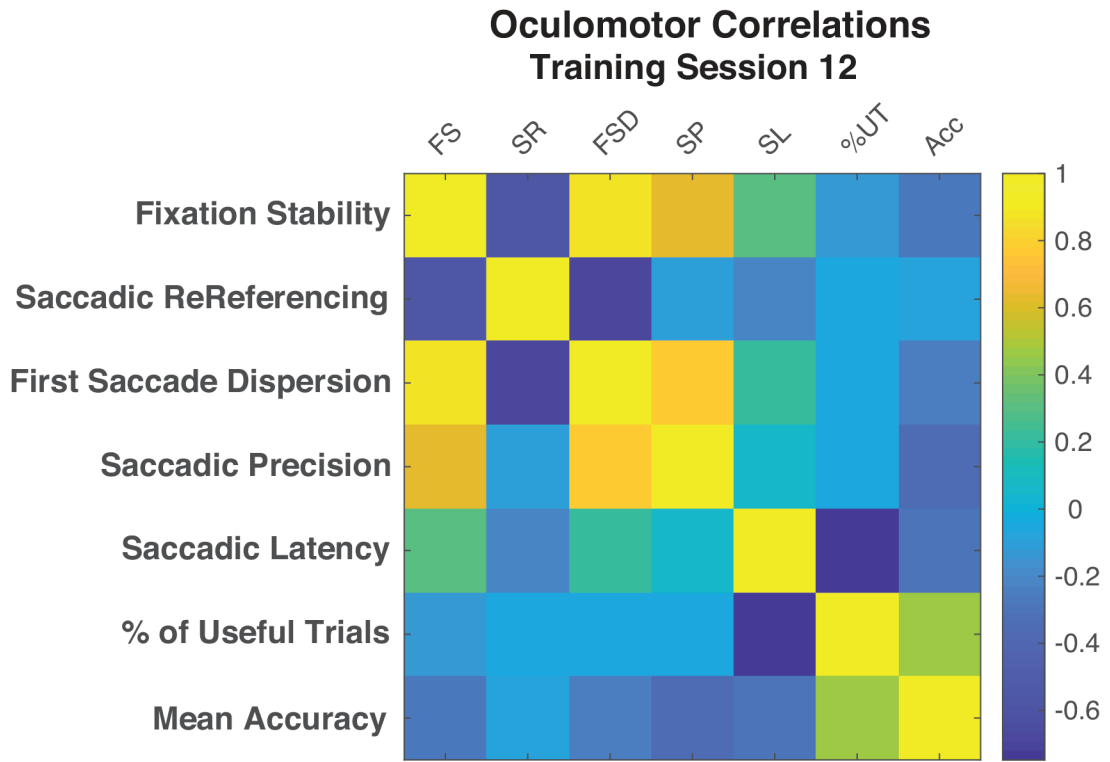


Figure 5. Correlation matrix of oculomotor metrics and mean accuracy.
 A correlation analysis was completed to measure the strength and direction of association between the oculomotor metrics at the last training session and the overall mean accuracy between the three tasks. Colors indicate Pearson’s R.

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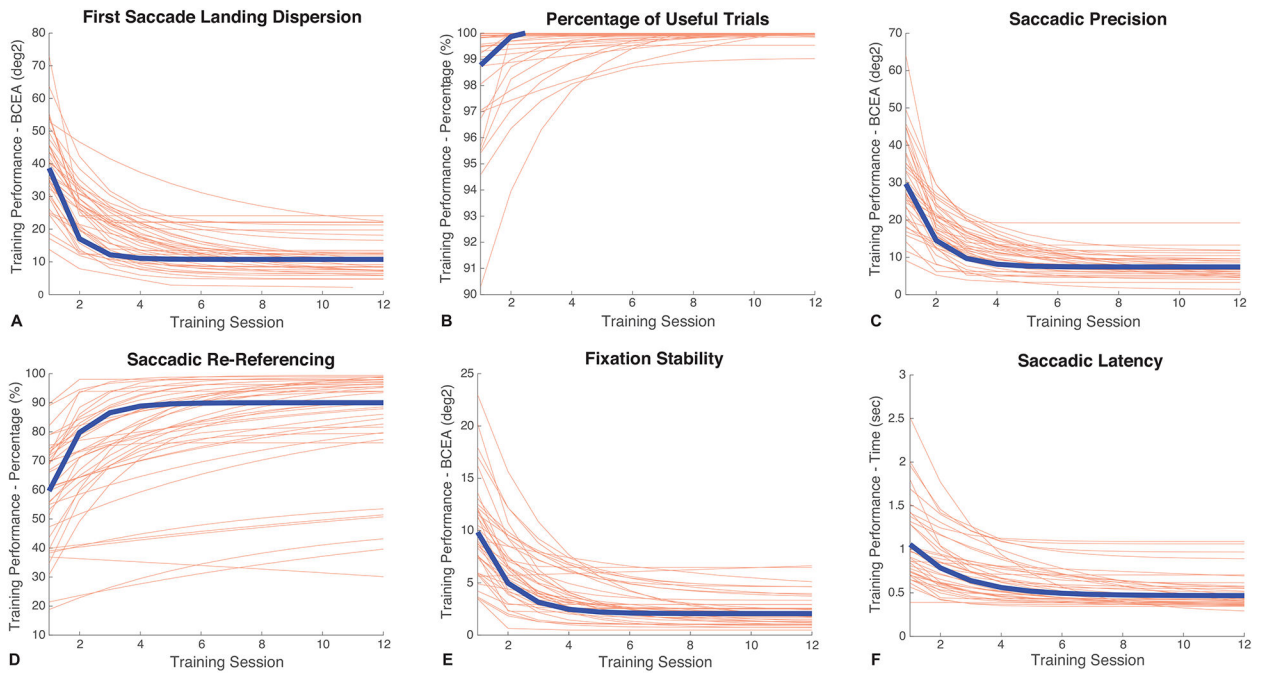


Figure 6. Learning curves of the six oculomotor metrics.

The blue line represents the mean value of a given metric as a function of training session.

Orange lines represent the learning curves for each participant (fit to Equation 1). **A.**

First saccade landing dispersion, **B.** Percentage of useful trials, **C.** Saccadic Precision, **D.**

Saccadic re-referencing, **E.** Fixation stability, and **F.** Saccadic latency.

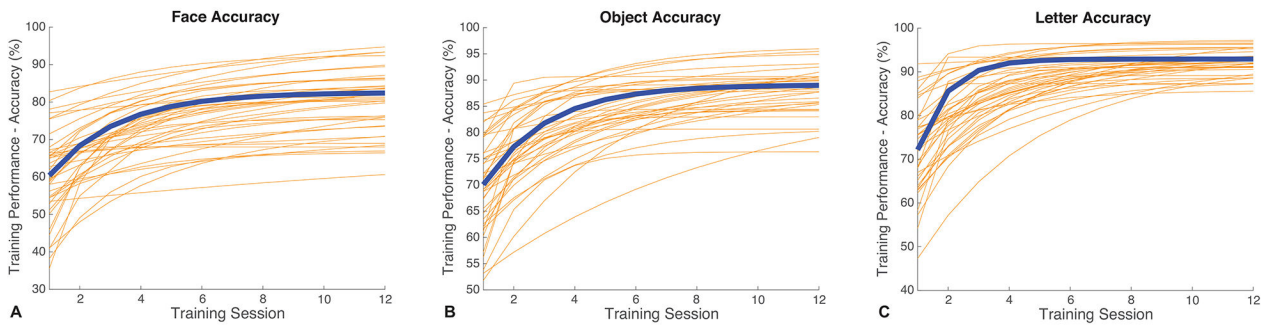


Figure 7. Learning curves of the three behavioral tasks. The blue line represents the mean accuracy value of a given behavioral task as a function of training session. Orange lines represent the learning curves for each participant (fit to Equation 1). **A.** Face accuracy, **B.** Object accuracy, **C.** Letter accuracy.

Table 1.**Mean changes in accuracy.**

Comparison of the mean change in accuracy between the first and last training sessions (Block01 vs. Block12). Accuracy is expressed as percentage of correct trials, with higher accuracy indicating better performance.

Mean Changes in Accuracy				
	Block01 (%)	Block12 (%)	Mean Change (%)	<i>p</i> -value
Letter Task	72.45	92.23	19.78	1.0×10^{-15}
Object Task	69.93	88.20	18.38	4.2×10^{-16}
Face Task	59.85	80.73	20.88	9.3×10^{-15}

Table 2.**Differences in learning rates.**

Comparison of the differences in learning rates between each of the behavioral tasks (face, object, letter) and each of the eye movement metrics. P-values reflect a within-subject t-test comparing the eye metric learning rate to the behavioral test learning rate.

Eye Metric	<i>k</i>	Difference from face rate (<i>k</i> = 0.45)	Difference from object rate (<i>k</i> = 0.48)	Difference from letter rate (<i>k</i> = 1.04)
First saccade landing dispersion	1.49	$k = -1.04, p = 0.07$	$k = -1.01, p = 0.06$	$k = -0.45, p = 0.50$
Percentage of useful trials	1.33	$k = -0.88, p = 0.08$	$k = -0.85, p = 0.07$	$k = -0.29, p = 0.60$
Saccadic precision	1.14	$k = -0.69, p = 0.06$	$k = -0.66, p = 0.06$	$k = -0.10, p = 0.84$
Saccadic re-referencing	1.07	$k = -0.62, p = 0.24$	$k = -0.59, p = 0.24$	$k = -0.03, p = 0.94$
Fixation stability	0.99	$k = -0.54, p = 0.01$	$k = -0.51, p = 0.03$	$k = 0.05, p = 0.90$
Saccadic latency	0.61	$k = -0.16, p = 0.32$	$k = -0.13, p = 0.19$	$k = 0.43, p = 0.28$