## Title

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## Journal

Journal of Vision, 22(10)

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## Publication Date

2022-09-02

## DOI

10.1167/jov.22.10.17

Peer reviewed

# Oculomotor responses of the visual system to an artificial central scotoma may not represent genuine visuomotor adaptation

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**Patients with central vision loss often adopt a location outside their scotoma as the new reference for vision, the preferred retinal locus (PRL). The development of a PRL is important not only for the rehabilitation of patients with central vision loss, but also helps us better understand how the brain adapts to the lack of visual input. Many investigators studied this question using a gaze-contingent display paradigm by imposing an artificial scotoma to simulate central vision loss for normally sighted subjects, with an important assumption that the "PRL" thus developed is the result of visuomotor adaptation, as is the case for people with a real scotoma. In this study, we tested the validity of this assumption. We used a gaze-contingent display combined with an artificial scotoma to first train normally sighted subjects to develop a "PRL" for saccade eye movements. Then, we compared the properties of saccades when the artificial scotoma was randomly turned off or on. When the artificial scotoma was absent, subjects automatically reverted to using their fovea, with a shorter saccade latency. Our findings suggest that the development of a "PRL" in response to an artificial scotoma may represent a strategy, instead of a genuine visuomotor adaptation.**

## Introduction

The brain is a remarkable organ. Not only does it control every single process and activity of a living being, but also it is highly adaptable to changes in the environment. The ability of the brain to adjust itself in response to changes in the environment is attributed to neuroplasticity. In humans, neuroplasticity is critical to, and is responsible for many phases of our lives, such as how infants learn new things, the maturation from infancy to adulthood, and even how we adapt to irreversible disorders or damages to body parts. Over the past several decades, there has been an immense interest on how the brain responds and adapts to disorders and damages to body parts in rehabilitative medicine.

In the domain of vision, it is well known that when the central visual field, including the foveal region that subserves the most acute vision, is damaged due to macular disease, patients with the condition often eventually adopt an alternative retinal location outside the damaged region of the retina as the reference locus for vision. This location is referred to as the preferred retinal locus (PRL; Cummings, Whittaker, Watson, & Budd, 1985; Timberlake, Mainster, Peli, Augliere, Essock, & Arend, 1986). Crossland, Culham, Kabanarou, and Rubin (2005) reported that for a group of 25 individuals who lost their central vision in their better eye due to macular disease, all of them developed a PRL within six months following the onset of the vision loss, even without any specific instructions on how they should shift their gaze in order for them to avoid the central scotoma (blind spot). The fact that individuals could shift their reference locus for vision from the fovea (before the loss of central vision) to an eccentric retinal location (after the loss of central vision) is solid evidence that the brain is adapting to and compensating for the irreversible damages to the macular regions and a permanent loss of central vision.

Given the functional importance of the PRL to people with central vision loss, it is of paramount importance to have a better understanding of the development, or the evolvement of a non-foveal retinal location as the PRL. From a basic science point of view,

Citation: Ağaoğlu, M. N., Fung, W., & Chung, S. T. L. (2022). Oculomotor responses of the visual system to an artificial central scotoma may not represent genuine visuomotor adaptation. *Journal of Vision*, *22*(10):17, 1–20, https://doi.org/10.1167/jov.22.10.17.

https://doi.org/10.1167/jov.22.10.17 Received November 1, 2021; published September 22, 2022 ISSN 1534-7362 

such knowledge might help us better understand the mechanism of neuroplasticity. From a practical point of view, the knowledge might enable rehabilitation professionals to predict the location of the PRL for an individual with bilateral central vision loss, and to institute training to facilitate the adoption of the PRL so as to expedite the visual rehabilitation process. However, to date, our knowledge of the properties of the PRL, how the PRL is used, or the course of development of a PRL and how it is chosen, is very limited. Currently, we know that some patients with macular disease use different preferred retinal loci under different conditions (Lei & Schuchard, 1997), for different tasks (Crossland, Crabb, & Rubin, 2011), or sometimes even for the same task, such as reading (Duret, Issenhuth, & Safran, 1999; Déruaz et al., 2002). We also know that the PRL location does not correspond to the retinal location with the best acuity (Bernard & Chung, 2018) or sensitivity (Fung & Chung, 2019). However, information related to how the PRL is developed is scarce. This is in part due to the fact that the proper way to study how a PRL evolves would be a longitudinal study in which patients who are at high risk of developing bilateral central vision loss will be followed up for a period of time, starting from before they have the vision loss to a period of time after the onset of their vision loss. Clearly, this is not practical. Thus, many research groups turned to the use of an artificial scotoma, combined with a gaze-contingent display paradigm, to simulate central vision loss (e.g. Varsori, Perez-Fornos, Safran, & Whatham, 2004; Aguilar & Castet, 2011; Kwon, Nandy, & Tjan, 2013; Walsh & Liu, 2014; Liu & Kwon, 2016; Rose & Bex, 2017; Chen, Shin, Millin, Song, Kwon, & Tjan, 2019; Prahalad & Coates, 2020; Maniglia, Jogin, Visscher, & Seitz, 2020a). In a nutshell, an eye-tracker is used to continuously record and monitor the gaze positions of subjects with normal vision while these subjects perform a visual task on a computer display. A part of the display that corresponds to a predetermined size of the subject's central visual field is replaced by a patch that does not contain any visual information (the artificial scotoma). Thus, subjects cannot perform the visual task using their central vision. This paradigm forces normally sighted subjects to adopt an alternative location outside the artificial scotoma for seeing.

Using this paradigm, Kwon et al. (2013) showed that after a mere 3-hour free-exploratory training, in which normally sighted subjects were free to explore the use of any location outside an artificial scotoma to visually search for a target or to follow the target when it changed its position on the display, five of their six subjects spontaneously adopted a location in their visual fields immediately outside the artificial scotoma to perform the task. The sixth subject adopted two locations instead of one, with these two locations situated at opposite sides of the artificial scotoma. Further, when these subjects made saccades toward the target, the landing positions of their first saccades were close to the adopted non-foveal locations, although the precision of using these locations for saccades was much worse than that for fixation. After an additional 15 to 25 hours of explicit training of using the non-foveal locations for making saccades, the precision of the landing positions of subjects' first saccades was much improved, and became comparable with that made by the control subjects using their fovea. Rose and Bex (2017) further showed that the improvements in task performance and fixation stability at the training-induced reference locus could be transferred to a nontrained location. Besides an improvement in the oculomotor responses, several studies have shown that performance on perceptual tasks also improved after normally sighted subjects adopted a non-foveal location for seeing. For example, Barraza-Bernal, Rifai, and Wahl (2017) showed that less time was required to read a group of three four-letter words. Liu and Kwon (2016) showed that subjects demonstrated considerable improvements for high-level functions, such as trigram letter-recognition, reading, and spatial attention, but not for low-level functions, such as acuity and contrast sensitivity. In contrast, Maniglia et al. (2020a) found significant improvement in acuity after their subjects have adopted a non-foveal location for seeing. It is unclear why Liu and Kwon (2016) and Maniglia et al. (2020a) found opposite results in relation to acuity, but it is well documented that subjects demonstrated substantial individual variability in response to a simulated scotoma, not only in the location adopted for seeing, but also in terms of the variability of the location, response time, etc. (Maniglia, Visscher, & Setiz, 2020b). In relation to the cortical responses to the presence of a simulated scotoma, Chen et al. (2019) showed that there is a release of response suppression in the visual cortex at the location outside the artificial scotoma that was adopted as the training-induced reference locus, concluding that the visual system is capable of reshaping its oculomotor control and sensory coding to adapt to the loss of central vision, even when the vision loss is intermittent and experimentally induced.

The fact that normally sighted subjects can spontaneously develop a peripheral retinal location as the new reference locus in response to an artificial scotoma in just a few hours and that the brain appears to adapt to this "central vision loss" is encouraging, because we can use this paradigm to create a model in a relatively short amount of time to study the properties of the PRL and to help design and evaluate rehabilitative tools or regimens for patients with real central vision loss. However, as for any model, one must first ask how realistic a model represents the real condition. There are several prominent discrepancies between the findings from normally sighted subjects

adapting to an artificial scotoma and individuals adapting to real central vision loss. First, the time course of the adaptation is very different. Individuals with real central vision loss usually take months to develop a PRL (Crossland et al., 2005). Some are not able to develop a PRL even years after the onset of their vision loss (White & Bedell, 1990). Second, even after years of using their PRLs, most individuals with central vision loss still exhibit much greater fixation instability than people with normal vision (e.g. White & Bedell, 1990; Timberlake, Sharma, Grose, Gobert, Gauch, & Maino, 2005; Tarita-Nistor, González, Markowitz, & Steinbach, 2008; Kumar & Chung, 2014), unlike the findings of Kwon et al. (2013) who showed that fixation stability in the presence of an artificial scotoma could become as good as that for foveal viewing, after merely a few hours of adaptation. Third, White and Bedell (1990) reported that approximately two-thirds of patients with long-standing macular disease who have demonstrated the consistent use of a non-foveal PRL for fixation still made saccades directed toward the nonfunctioning fovea, instead of the non-foveal PRL. These authors concluded that the occurrence of foveating saccades is an indication of an incomplete adaptation to the presence of central vision loss. Considering these discrepancies, in this study, we ask whether or not the observed changes in normal subjects' oculomotor behaviors in response to an artificial scotoma represent a genuine adaptation process, akin to what occurs for people with real central vision loss.

We hypothesize that a genuine adaptation to the use of a non-foveal location as the PRL is associated with the consistent usage of the PRL and that the person should be unaware of doing so. There is substantial reported evidence (consistent with our own experience with clinical patients and research participants) that when asked to "look at" an object, people who have adapted to the use of a non-foveal PRL would automatically place the object at that location, and that these individuals believe they are looking directly at the object (von Noorden & Mackensen, 1962; White & Bedell, 1990). On the contrary, those who have more recent onset of central vision loss and thus have not adapted to the use of a non-foveal PRL would still place the object at the fovea (at least for the first saccade), in other words, they make foveating saccades. It is noteworthy that even after an individual has adopted a non-foveal location as the PRL, it does not necessarily mean that this individual would automatically place objects of regard on this location without conscious awareness of doing so. Crossland et al. (2005) reported that among the individuals who eventually adopt a non-foveal location as the PRL, only 64% of them were unaware of using an eccentric retinal area for seeing. It is possible that with time, people become less aware of using their non-foveal PRL. Most previous reports agree that it is only when someone uses his or her non-foveal PRL consistently and without conscious effort of doing so that the adaptation process can be considered as complete (von Noorden & Mackensen, 1962; White & Bedell, 1990; Crossland et al., 2005).

In this study, we used the artificial scotoma paradigm to first train normally sighted subjects to adopt a location outside the artificial scotoma as their reference locus for performing a visual task. Training ceased when subjects demonstrated a consistent usage of a non-foveal location as their reference locus for fixation and saccades. We then assessed subjects' consistency in using their adopted non-foveal reference locus for making saccades by randomly interleaving trials in which the artificial scotoma was absent (thus allowing foveal vision) and trials in which the artificial scotoma was present (blocking foveal vision). We hypothesized that genuine adaptation would manifest itself as a consistent usage of the adopted non-foveal location for *all* trials, regardless of whether or not the artificial scotoma was present. In contrast, if the adaptation was not a genuine one, then subjects might switch between using the fovea when it was accessible and the non-foveal location when the fovea was covered by the artificial scotoma. Because the testing of our hypothesis depended on subjects making saccades, we needed subjects to have demonstrated a consistent usage of a non-foveal location as the reference location for saccades. As we shall see later, the free exploratory training method (subjects free to use any retinal locations to perform the visual task) adopted in Experiment 1 did not encourage the development of a non-foveal reference location for saccades; therefore, in Experiment 2, we used an explicit training paradigm (Kwon et al., 2013) to train subjects to adopt a non-foveal reference location for making saccades.

Considering that our methods only allow us to measure gaze positions, but not retinal locations,[1] and that the non-foveal location developed in response to an artificial scotoma may not have the same properties as a real PRL in people with central vision loss, in this paper, following Rose and Bex (2017) and Prahalad and Coates (2020), we shall refer to the non-foveal location outside the artificial scotoma that subjects adopt as reference locus as the pseudo-PRL (pPRL).

# Experiment 1

## Methods

### *Participants*

Eleven young adults with normal vision (age = 18–25 years, 8 women) performed a visual search/identification task while the central 8 degrees of their visual field was occluded by a gaze-contingent artificial scotoma for

approximately an hour per day, and for 8 consecutive days. Subjects were recruited from the student population of the University of California, Berkeley campus. All had normal or corrected-to-normal vision (best-corrected visual acuity 20/20 or better in each eye) with no history of any eye disorders or diseases. They all gave written informed consent prior to the commencement of the study. This research was approved by the Institutional Review Board at the University of California, Berkeley, and was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

### *Stimuli and procedure*

We used a gaze-contingent display paradigm to impose an artificial scotoma that occluded the central 8 degrees of the visual field for our subjects. For the first six subjects who participated in the experiment, the artificial scotoma appeared as a visible white disc (150 cd/m$^2$) on a mid-gray background (75 cd/m$^2$) for three of them or a visible black disc (0.09 cd/m$^2$) on the same gray background for the other three. Because there were no discernible differences in the results between white and black artificial scotomas, the black artificial scotoma was used for the subsequent five subjects and also in Experiment 2. To impose the artificial scotoma, subjects' gaze positions were continuously recorded with an infrared video-based eye tracker sampled at 1000 Hz (EyeLink 1000 Plus Binocular Tower Mount Eyetracker; SR Research, Ottawa, Ontario, Canada) with a spatial accuracy typically around 0.25 degrees to 0.50 degrees in our experiment. Before gaze position measurements, we first performed an eye-gaze calibration using the standard nine-point calibration routine supplied by the manufacturer. Subjects, using their fovea, were asked to follow the target (a small dot) that appeared randomly in one of nine positions in sequence. A drift correction immediately followed the calibration, and the drift errors must be smaller than 0.5 degrees before we proceeded with the experiment. The real-time gaze position was used to control the center position of a circular patch (8 degrees diameter rendered as a uniform black or white patch presented against a mid-gray background [luminance = 75.3 cd/m$^2$]) on a 32 inch Display++ LCD monitor (Cambridge Research Systems Ltd., Rochester, UK). The monitor had a resolution of 1920 × 1080 pixels and a refresh rate of 120 Hz (i.e. the position of the artificial scotoma was updated every 8.3 ms). All visual stimuli were generated and controlled with MATLAB (R2016a; MathWorks, Natick, MA, USA) and Psychophysics Toolbox 3 (Brainard, 1997; Pelli, 1997) and its Eyelink extensions (Cornelissen, Peters, & Palmer, 2002). Using the photocell method similar to that described in Bernard, Scherlen, and Castet (2007), our measurement of the delay between the actual gaze measurement and the scotoma location update averaged 12.6 ± 4.4 (SD) ms, comparable with the delays in previous studies (e.g. Cornelissen, Bruin, & Kooijman, 2005; Bernard et al., 2007; Aguilar & Castet, 2011; Kwon et al., 2013; Liu & Kwon, 2016; Maniglia et al., 2020a; Maniglia et al., 2020b). As reported by Aguilar and Castet (2011), transient mismatches between gaze and scotoma locations could arise when eye blinks occur. We minimized the occurrences of these mismatches by turning the screen blank (setting the screen to the gray background) when a blink was detected. The viewing distance was 76 cm. At this viewing distance, each pixel subtended a visual angle of 1.63 arcmin.

### *Determination of target size to be used for training*

Before the commencement of training, we first determined the size of a Tumbling-E stimulus used for training. While the subjects were maintaining stable fixation on a fixation target using their fovea (for this task, the artificial scotoma was not used), a Tumbling-E stimulus was presented at a random location on the display that corresponded to an eccentricity of either 4 degrees or 6 degrees from fixation. The task of the subjects was to indicate the orientation of the E-stimulus (up, down, right, or left) using the four arrow keys on a keyboard. At each eccentricity tested, we used the Method of Constant Stimuli to present seven sizes for the Tumbling-E stimulus, each for five trials, in a random order. We then constructed a psychometric function relating identification accuracy with E-stimulus size, and defined the size threshold as the size of the E-stimulus that corresponded to 62.5% correct (50% after correction for guessing) identification accuracy. The E-stimulus size thresholds derived for the 4 degrees and 6 degrees eccentricities were then averaged, and the averaged value was used as the target size for the training trials. Presumably, this stimulus size would be just large enough for subjects to identify the orientation of the E-stimulus right outside the 8 degrees diameter artificial scotoma.

### *Training*

Before the beginning of each training block, subjects completed the standard nine-point gaze calibration followed by a drift correction with the Eyelink Eyetracker (without any imposed artificial scotoma). Gaze errors must be smaller than 0.5 degrees for the subjects to proceed with training. During training, a Tumbling-E stimulus of the size determined earlier was presented at a random location on the display. Subjects, with the gaze-contingent imposed artificial scotoma, were instructed to identify the orientation of the E-stimulus (up, down, left, or right) and entered their responses using the four arrow keys on a keyboard. Because the size of the E-stimulus was set to the size

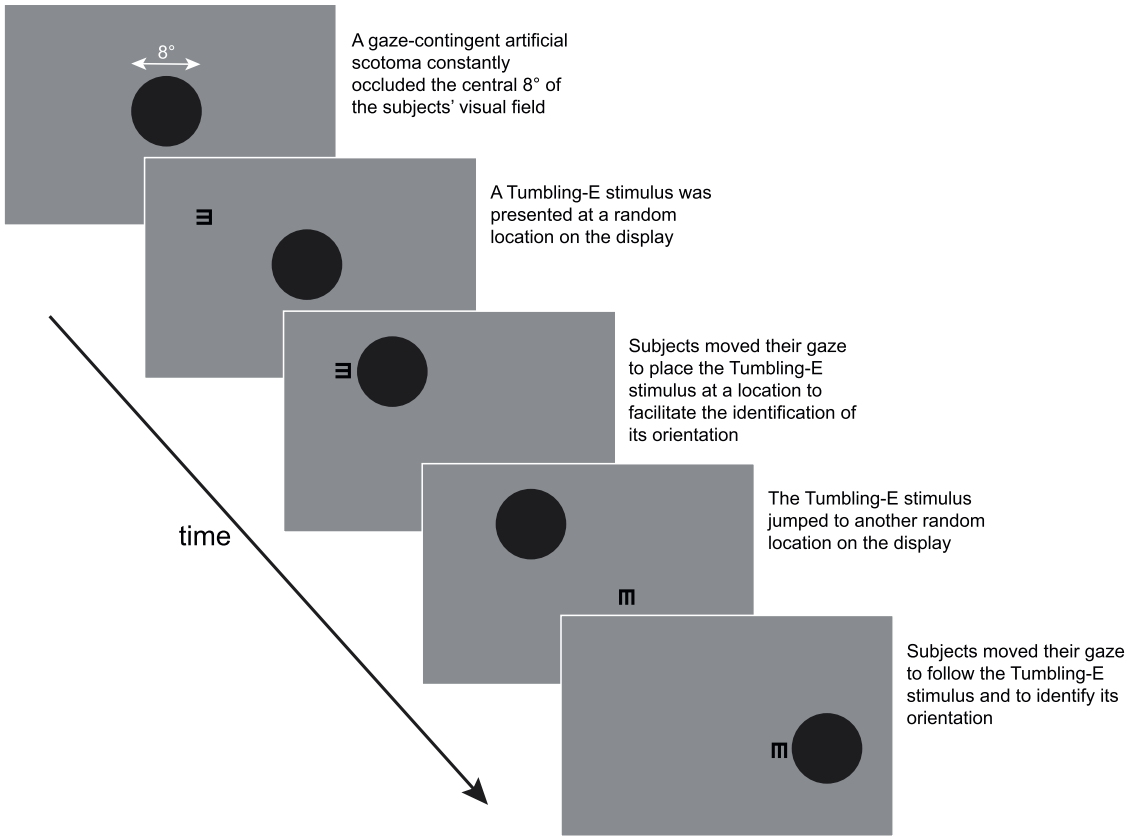


Figure 1. A schematic figure showing the first two trials of a training block in Experiment 1. After a successful nine-point gaze calibration with a drift correction using an Eyelink 1000 Plus Eyetracker, an artificial scotoma was presented on the display that followed closely the eye movements of subjects to constantly occlude the central 8 degrees of the subjects' visual field. On each training trial, a Tumbling E-stimulus (the size of the stimulus was determined earlier for each subject) was presented at a random location on the display and subjects had to make eye movements to place the E-stimulus close to the artificial scotoma so that they could identify the orientation of the E-stimulus. As soon as a response was entered, the E-stimulus jumped to another random location on the display, signaling the beginning of another trial. The artificial scotoma was rendered as black in this figure, but we tested three subjects with a white scotoma and there were very little differences in the results.

threshold for its correct identification at roughly 4 degrees to 6 degrees eccentricity from the fovea, subjects would have to move their eyes (with the artificial scotoma) close enough to the E-stimulus to identify its orientation. The E-stimulus stayed on the display until the subject entered his/her response via a keyboard, before jumping to another random location, signaling the start of another trial (see Figure 1). No specific instructions were given to the subjects as to how to move their eyes in the presence of the artificial scotoma and which gaze positions they should adopt for the identification task. In other words, subjects were free to choose any location(s) to serve as their own pPRL(s). Each block comprised 200 trials and gaze-centering was performed every 20 trials to minimize any positional bias (Kwon et al., 2013). A square box of 8 degrees × 8 degrees was presented at the center of the display and subjects were required to position their artificial scotoma within the box for gaze centering. Each subject completed, on average, 5462 trials (range = 4528 – 6916) over 8 consecutive days (approximately an hour each day).

### *Analyses*

The main parameters of interest were the pPRL location and the variability of the location used for fixation and for making saccades. To quantify the pPRL location and its variability for fixation (fixation stability), we took all the gaze positions for a given subject on a given training day when the subject was not making a saccade (and with all the blinks excluded), then we used kernel density estimation to estimate a probability density function to describe all the gaze positions. The location corresponding to the highest probability of the probability density function represented the location of the pPRL. Fixation stability was quantified as the area enclosed by the contour

line that corresponded to 68% probability of fixation positions, which we termed the "isoline area" (Castet & Crossland, 2012). We used the isoline area to quantify fixation stability instead of the more conventional bivariate contour ellipse area (BCEA; Steinman, Haddad, Skavenski, & Wyman, 1975; Kosnik, Fikre, & Sekuler, 1986; Crossland & Rubin, 2002; Timberlake et al., 2005) because of two main reasons. First, the isoline method does not require the assumption that gaze positions are normally distributed, as the BCEA method does; and, unfortunately, fixation data usually violate the assumption. Second, the BCEA method assumes there is only one peak in the distribution, hence, only one pPRL; but the isoline method does not make that assumption and can identify more than one pPRL. To quantify the pPRL location and its variability for saccades, we used a similar approach, but the data were gathered based on the landing positions of all saccades made when subjects shifted their gaze in response to the appearance of the E-stimulus. Based on the probability density function that described the set of landing positions, we derived the pPRL for saccade (the location corresponding to the highest probability of the probability density function). Its variability was quantified by the isoline area that corresponded to 68% probability of all the saccade landing positions.

## Results

Consistent with several reports showing that normally sighted subjects are able to spontaneously adopt a non-foveal location as their fixational pPRL with only a few hours of training with a gaze-contingent artificial scotoma (Kwon et al., 2013; Walsh & Liu, 2014; Rose & Bex, 2017; Chen et al., 2019; Maniglia et al., 2020a), 10 of our 11 subjects showed that they began to use at least one non-foveal location for fixation after only 2 to 3 hours of training. Those non-foveal locations were subsequently shifted outside the artificial scotoma with additional training (Figure 2). The eleventh subject (S8) did not develop or adopt any location outside the artificial scotoma even after 8 days (approximately 8 hours) of training. We used the isoline area to quantify the stability of using the non-foveal locations for fixation (Castet & Crossland, 2012) to see whether fixation stability improved with training. Although there was an overall general trend of more stable fixation (smaller isoline area) with training (see Figure 2D), a paired *t*-test comparing the log-transformed of the isoline area obtained between the first and the last training day showed no statistical difference (mean difference = 0.23, 95% confidence intervals [CIs] = –0.08, 0.54, t[df = 10] = 1.684, $p$ = 0.123).

When we examined the landing positions of the first saccades made by our subjects when they directed their gaze/artificial scotoma close to the E stimuli, except for one subject, the clusters of saccade landing locations were all close to the fovea (Figure 3D). This finding is in stark contrast to that of Kwon et al. (2013) who showed that the landing positions of the first saccades of their subjects were close to their fixational pPRL. We do not know why our results were so different from theirs, but given that the number of trials, the length of training, the lack of specific instructions to subjects as to how to perform the tasks, and subject characteristics (young adults with normal vision) seemed to be comparable, the only plausible explanation was the difference in the task. It was possible that their object following task, especially the one with a cluttered background, might have encouraged the development of a non-foveal saccade pPRL.

Because we needed our subjects to have a consistent saccade pPRL outside the artificial scotoma before testing whether or not they directed their saccades consistently toward the saccade pPRL location even when the artificial scotoma was absent, we adopted the approach of Kwon et al. (2013) to explicitly train our subjects to adopt their fixation pPRL as their saccade pPRL in Experiment 2.

# Experiment 2

## Methods

### *Participants*

Six of the 11 participants in Experiment 1 (age = 18–25 years, 5 women) returned for further training for a non-foveal saccade pPRL. Five of them have already demonstrated the consistent usage of a non-foveal location outside the artificial scotoma as the fixation pPRL, therefore, our training was targeted at explicitly training these subjects to use the same location as the saccade pPRL. The sixth subject (S7) demonstrated the use of two pPRLs for fixation in Experiment 1, thus, we randomly chose one of these locations for the explicit training. The time gap between the end of Experiment 1 and the beginning of Experiment 2 ranged from a week to 6 months across the six subjects. Interestingly, almost all of them could demonstrate the use of their trained non-foveal fixational pPRL from Experiment 1 immediately upon their return, implying that what they learned could be retained for months even without any additional training.

### *Stimuli and procedure*

This experiment was explicitly targeted at training subjects to use their pPRL for a saccade task. A small cross of 0.5 degrees was constantly presented in close

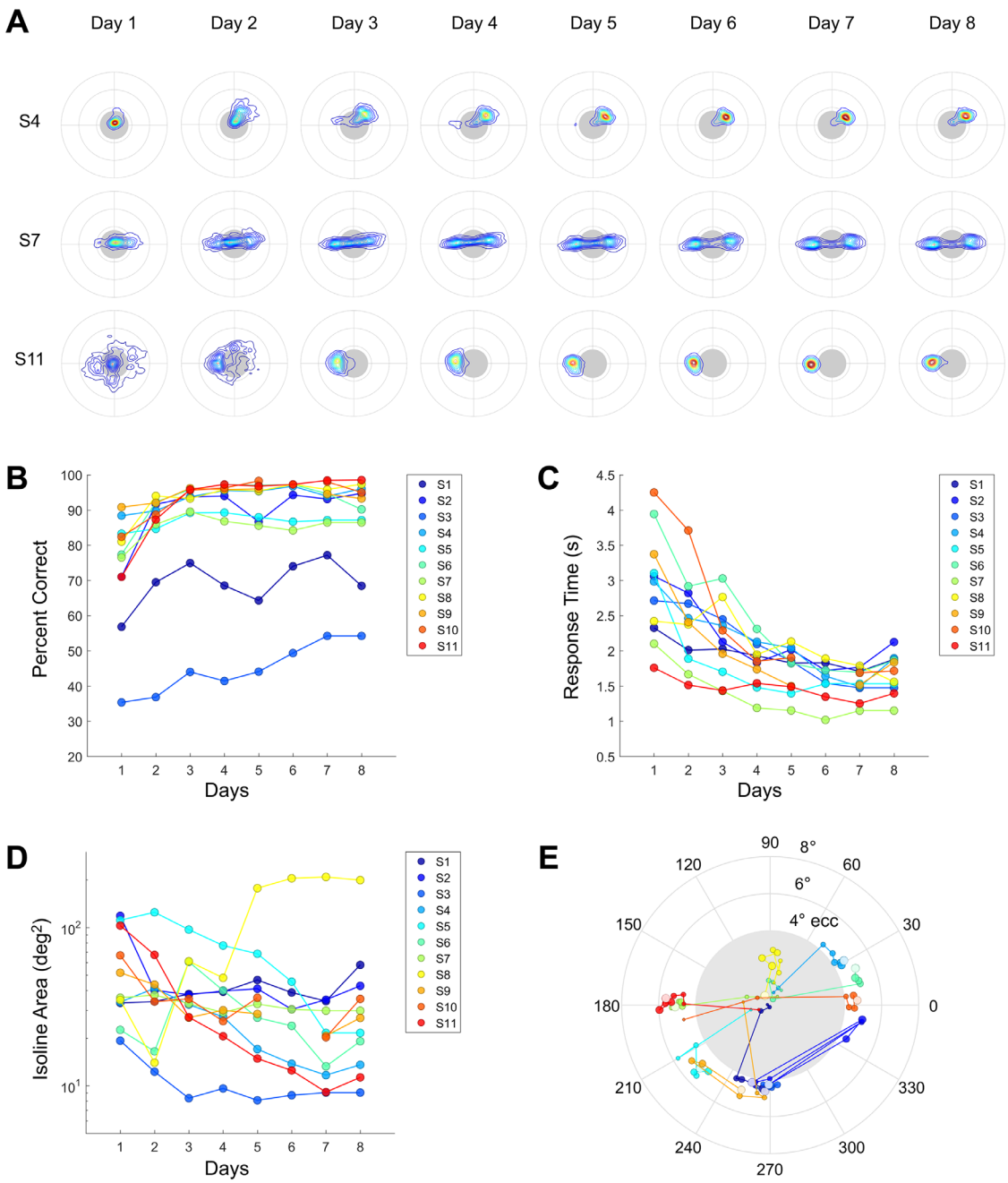


Figure 2. (**A**) Probability density maps describing all the gaze positions relative to the foveal location (center of the polar plot) during fixation are plotted as training progressed (day 1 to day 8) for three subjects (plots for the other subjects are given in the Supplementary Information). The gray circle in each panel represents the 8 degrees diameter artificial scotoma. Subject S4 developed a fixational pPRL at the upper-right location outside the artificial scotoma. S7 developed two pPRLs, straddling the horizontal locations immediately outside the artificial scotoma. S11 developed a pPRL on the left of the artificial scotoma. (**B**) Percent-correct of identifying the orientation of the Tumbling-E stimulus as training progressed. Note that almost all subjects improved in their performance with training, and subsequently reached a plateau (subjects coded by different colors). (**C**) Response time, defined as the time between the onset of the Tumbling-E stimulus and the subject pressing a response key, is plotted as a function of training day. Values plotted represent the values averaged across all the trials of a given training day. (**D**) Fixation stability, quantified by the isoline area that encompassed 68% of the gaze positions after subjects moved their gaze to put the E-stimulus close to the artificial scotoma, is plotted as a function of training day. Fixation stability improved with training for seven of the 11 subjects. (**E**) Fixational pPRL, defined as the location corresponding to the highest probability of each probability distribution map like those shown in **A**, is plotted as training progressed (size of the symbol codes for the training day: smallest one represents day 1, whereas the largest one represents day 8, the pale color symbols represent the pPRL of the last training day). Only S8 (shown in yellow) did not develop a fixational pPRL outside the artificial scotoma with training.

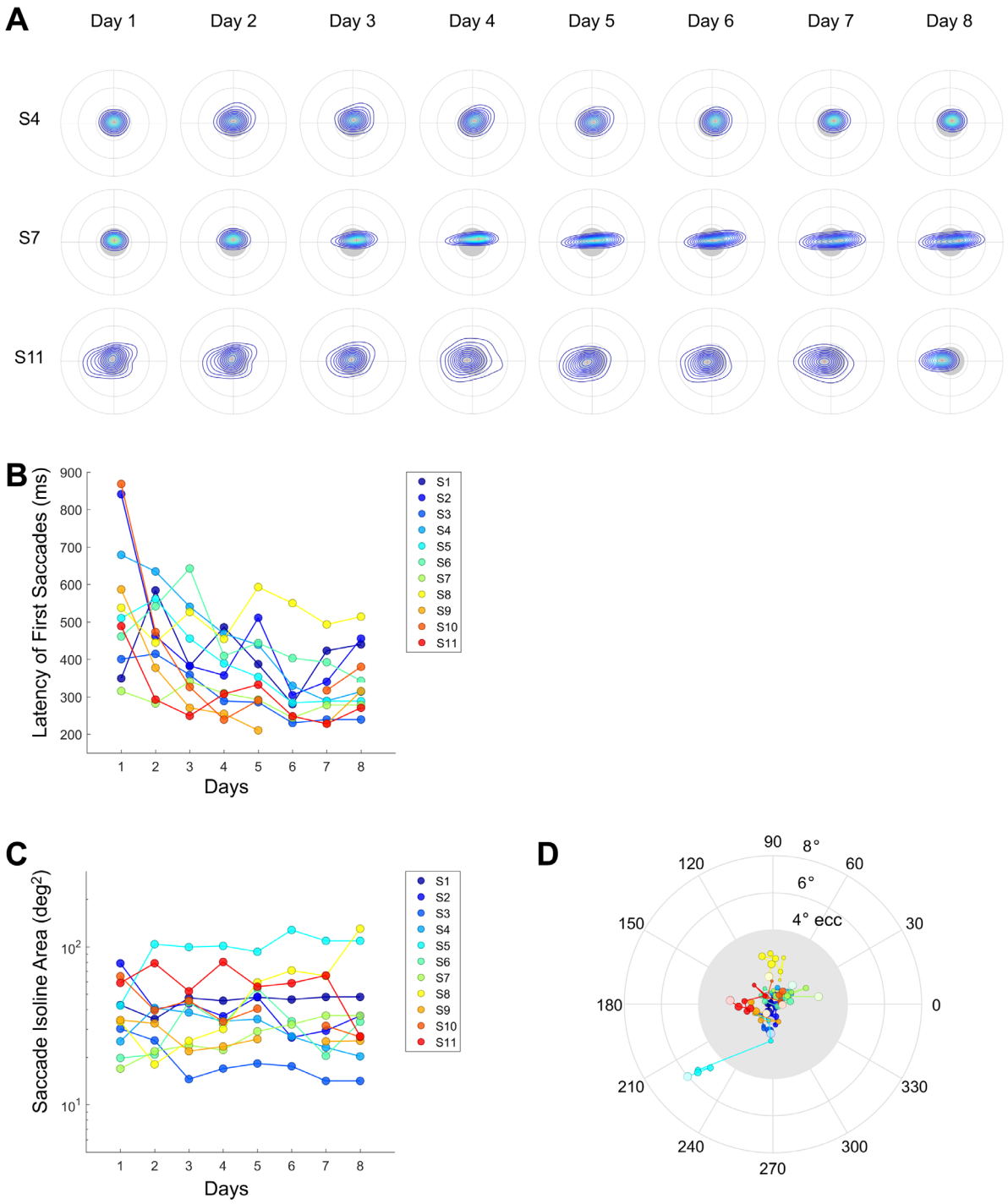


Figure 3. (**A**) Probability density maps describing the landing positions of all the first saccades when subjects made an eye movement to the Tumbling-E stimulus as training progressed (day 1 to day 8), for the same three subjects as those shown in Figure 2 (plots for the other subjects are given in the Supplementary Information). Unlike for fixation (Figure 2), these three subjects continued to reference their saccades to the fovea even after 8 days of training. (**B**) Latency of first saccades improved with training for most of the subjects (subjects coded by different colors). (**C**) Variability of the first saccade landing positions, quantified by the isoline area that encompassed 68% of the landing positions, is plotted as a function of training day. (**D**) The saccade pPRL, defined as the location corresponding to the highest probability of each probability distribution map like those shown in **A**, is plotted as training progressed (size of the symbol codes for the training day: smallest one represents day 1, whereas the largest one represents day 8, the pale color symbols represent the saccade pPRL of the last training day). After training, only S5 (shown in cyan) developed a saccade pPRL outside the artificial scotoma.

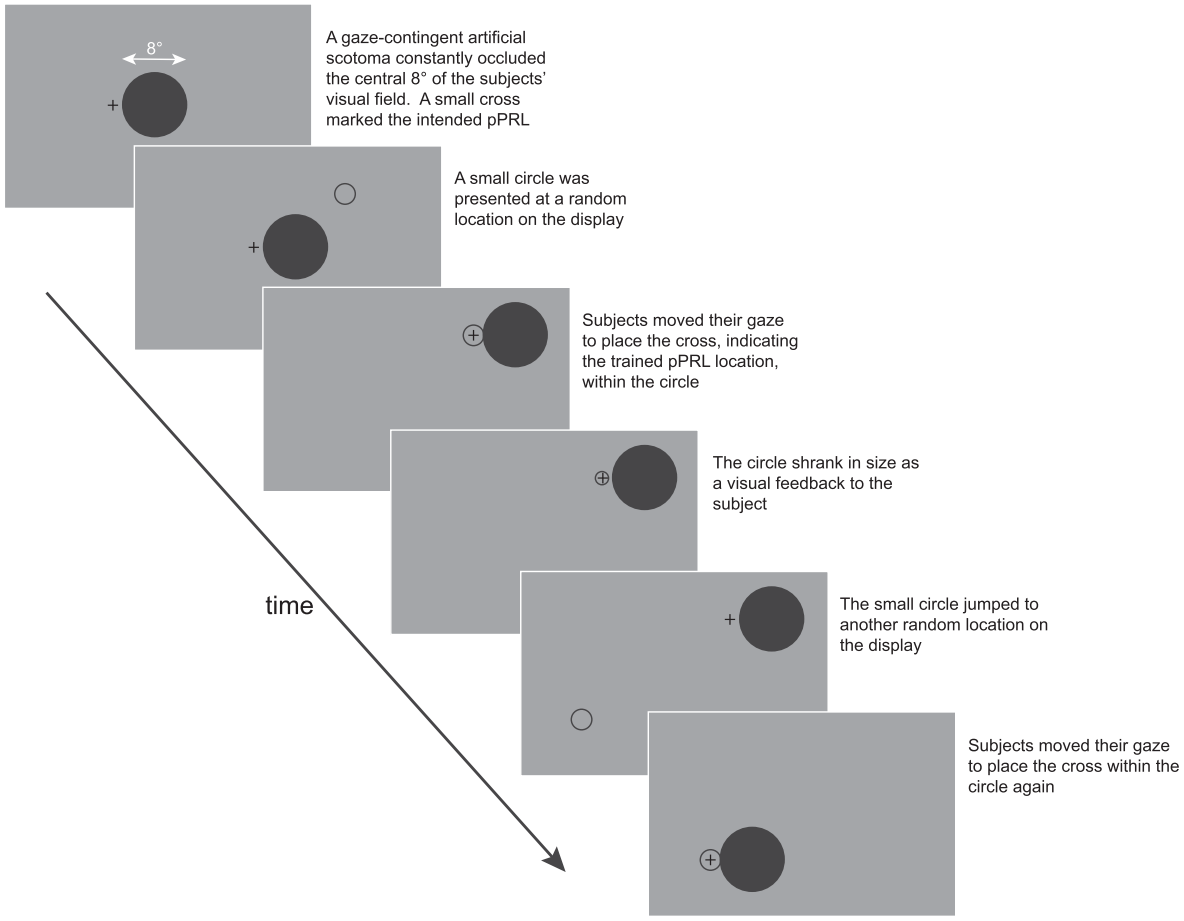


Figure 4. A schematic figure showing the first two trials of a training block in Experiment 2. Similar to Experiment 1, an 8 degrees diameter circular artificial scotoma was presented on the display that followed closely the eye movement of subjects. A small cross (0.5 degrees) was presented next to the artificial scotoma to indicate the pPRL that we hoped to explicitly train. In this figure, the pPRL was to the left of the artificial scotoma, but the location differed for different subjects depending on their own pPRL that was developed in Experiment 1. On each training trial, a 2 degrees circle was presented at a random location on the display and subjects had to make saccadic eye movements to place the cross within the circle. As soon as this was accomplished, the circle shrank in size to serve as visual feedback to the subjects that the trial was successful; before jumping to another random location on the display, signaling the beginning of the next trial.

proximity (Figure 4) to the edge of the artificial scotoma to indicate the location of the non-foveal saccade pPRL that we hoped to train. For five of the six subjects, the saccade pPRL was the same as their fixational pPRL that they adopted in Experiment 1. For the sixth subject (S7) who adopted two pPRLs for fixation, we randomly picked one (on the left of the artificial scotoma) as the target for his/her saccade pPRL.

Each block of training was preceded by an Eyelink calibration routine. Following a successful calibration of gaze positions, a circle of 2 degrees appeared at a random location on the display. The task of the subjects was to make a saccade (with the imposed artificial scotoma) to place the small cross within the circle (see Figure 4). Once the cross was placed within the circle for 200 ms, the circle shrank in size as visual feedback to the subject, and then jumped to another random location on the display as a cue for the subjects to make a saccade toward it. A typical block comprised 100 trials. On average, each subject completed six training blocks in a single session (approximately 1 hour). We continuously monitored several outcome metrics, including fixation stability, response time (the time elapsed between the appearance of the circle on a new location on the display and when the subject placed the small cross within the circle), latency of the first saccades, and the location of the saccade pPRL, during training. Training ended when these outcome metrics all reached a plateau. This took between 14 and 21 sessions, amounting to approximately 64,000 saccades (range = 41,582 – 89,914) made by each subject throughout the course of training. The amount of training time was comparable with that of the explicit training of Kwon et al. (2013).

### *Post-training testing*

Post-training testing followed immediately the last training session. The main purpose of the testing was to determine if subjects consistently used a single non-foveal pPRL for saccade tasks even when the artificial scotoma was randomly removed on half of the trials. In the single testing session, a small white dot appeared at a random location on the display and subjects were instructed to make a saccade to follow the white dot as fast and as accurately as possible. The white dot stayed at any given position and then jumped to a different position, on average, every 1.5 seconds, even if subjects did not make any saccade. There was a total of 100 jumps in a given block. The cross that we used to mark the intended pPRL location during explicit training was not shown. Within a block, the artificial scotoma was randomly removed on half of the trials (the "OFF" trials). We separately analyzed the saccade landing positions, saccade errors, and saccade latencies for the OFF (artificial scotoma absent) and the ON trials (artificial scotoma present). Each subject completed six blocks, or a total of 600 trials.

## Results

The training task in this experiment was explicitly designed to train subjects to reference their saccades to their pPRL. Figure 5 showed that with respect to fixation, most of the oculomotor characteristics remained relatively stable throughout training. What about the characteristics of the saccades? Despite the lengthy duration of training and the apparent plateauing of the outcome metrics, two of the six subjects continued to direct their first saccades toward the fovea, instead of the explicitly marked non-foveal location (S1 and S3, see Figure 6D). As shown in Figure 6B,C, the distribution of the landing positions and the latency of their first saccades did not seem to be able to explain why these two subjects were not able to adopt a non-foveal location as their saccade pPRL. The other four subjects demonstrated that they used the explicitly trained non-foveal location as their saccade pPRL by the end of the training. Previous studies that also used an explicit training paradigm to train normally sighted subjects reported a varied degree of saccade referencing following training. Although some studies showed that 100% of the subjects were able to reference their saccades to a non-foveal location outside the artificial scotoma (six subjects in Kwon et al., 2013, and eight subjects in Liu & Kwon, 2016), other studies, such as Maniglia et al. (2020b) showed that about half of their 19 subjects continued to reference their saccades within the scotoma (and some were very close to the foveal location). Here, we found that 67% (four of six) of our subjects were able to reference their saccades outside the artificial scotoma. The difference in the degree of saccade referencing within and across studies could be due to individual subject variability, but it could also be due to the differences in the training paradigms across studies. Future studies are necessary to understand why some subjects could reference their saccades consistently to a non-foveal location with training whereas others could not, and also how the parameters of the different training paradigms could encourage the adoption of a saccade pPRL.

### *Post-training testing*

Based on our hypothesis, a genuine adaptation to the use of a non-foveal location as the PRL should be associated with a consistent usage of the PRL. In other words, the parameters of saccades should not differ between those made during the ON or the OFF trials. Our comparisons of the parameters of saccades made during the ON and OFF trials focused on the saccade landing positions (representing the saccade pPRL), saccade errors, and saccade latency. Figure 7A shows the distributions of the landing positions of all saccades for all trials for the six subjects. For all subjects, the saccade landing positions clustered around the fovea (0, 0 coordinates) for the OFF trials (scotoma absent = unfilled symbols); whereas the cluster of the landing positions for the ON trials (scotoma present = filled symbols) was shifted away from the fovea, toward the direction of each subject's pPRL. For instance, for subjects S7 and S11, their pPRLs were both located left of the fovea (see Figures 5, 6), and their respective cluster of saccade landing positions were also shifted leftward from the origin (representing the fovea). To illustrate this point more clearly, we plotted the median saccade landing positions in Figure 7B. The cross in each panel represents the pPRL location for a given subject. The smallest circle in each panel represents the median landing position of the primary saccades for a given subject; and increasing sizes of the circles represent the median landing positions of secondary, tertiary, quaternary, and quinary saccades. For the OFF trials (unfilled symbols), the saccade landing positions were all close to the fovea (0, 0 coordinates) for all subjects. There were also very little differences in the landing positions for primary, secondary, tertiary, quaternary, and quinary saccades, meaning that the need to correct for the saccade landing error due to the primary saccades was not high. Indeed, the occurrences of quaternary and quinary saccades for OFF trials were lower than those for ON trials (mean occurrences of tertiary, quaternary, and quinary saccades = 80.4%, 57.6%, and 34.4%, respectively, for OFF trials vs. 91.5%, 78.1%, and 59.2%, respectively, for ON trials). For the ON trials (filled symbols), the saccade landing positions were generally closer to the pPRL location

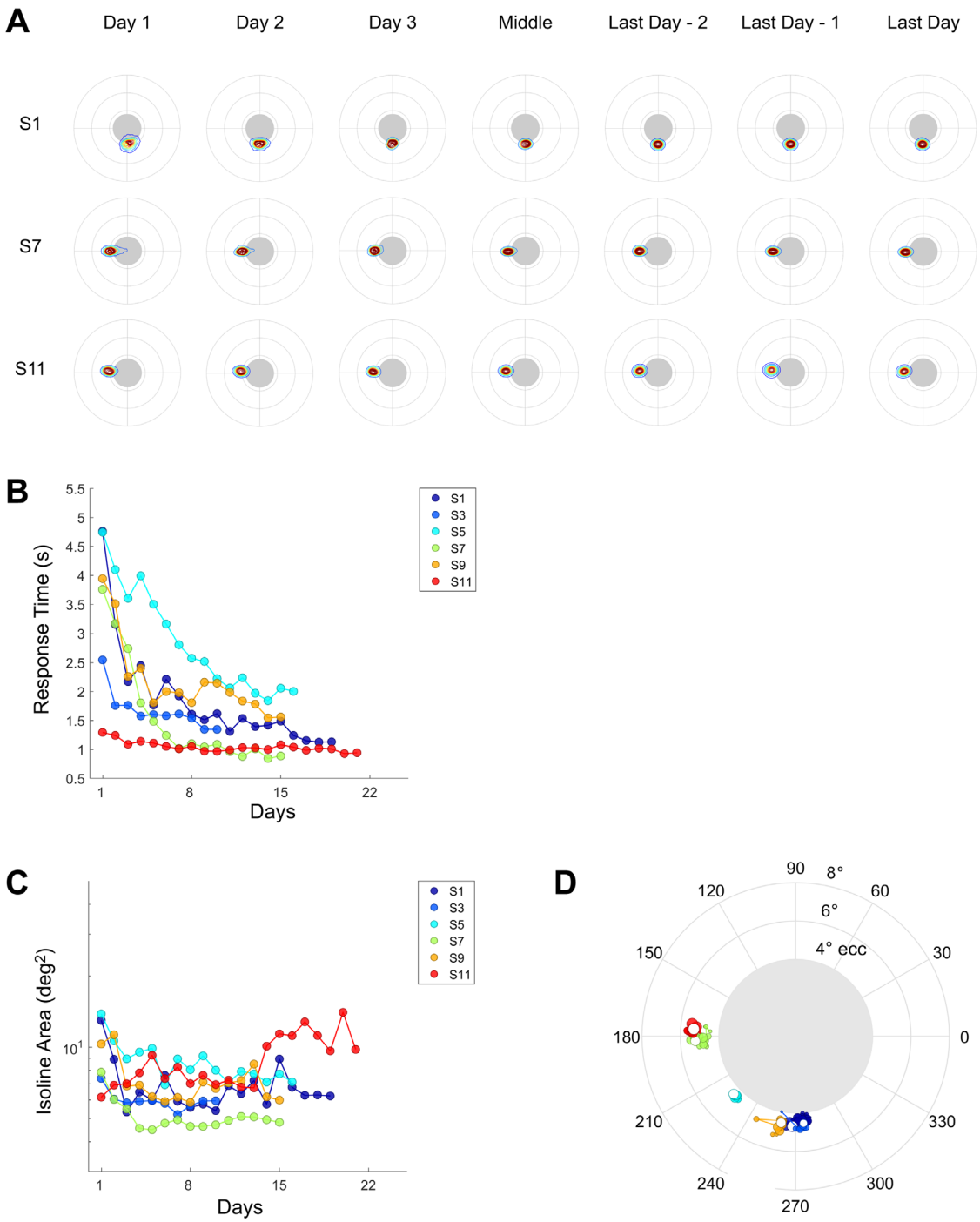


Figure 5. (**A**) Probability density maps describing all the gaze positions during fixation (while subjects held their gazes steady after placing the cross within the circle and while the circle shrank in size) are plotted as training progressed (the first 3 days, in the middle of the training, and the last 3 days) for three subjects in Experiment 2. The gray circle in each panel represents the 8 degrees diameter artificial scotoma. The location of the fixational pPRL was fairly stable throughout training for all subjects. (**B**) Response time, defined as the time between the onset of the 2 degrees circle and the time the subject placed the 0.5 degrees cross within the circle, is plotted as a function of training day. Values plotted represent values averaged across all trials of a given day. (**C**) Fixation stability, quantified by the isoline area that encompassed 68% of the gaze positions during fixation, is plotted as a function of training session. (**D**) The fixational pPRL determined at each training day in Experiment 2. Each subject is represented by a distinct color (see the legend in panels **B** and **C**). For a given color, the size of the circles codes the training process (smallest circle for day 1 with size increases for subsequent training days; unfilled circle represents the location of the fixational pPRL of the last training day). All subjects demonstrated a fixational pPRL outside the artificial scotoma throughout training.

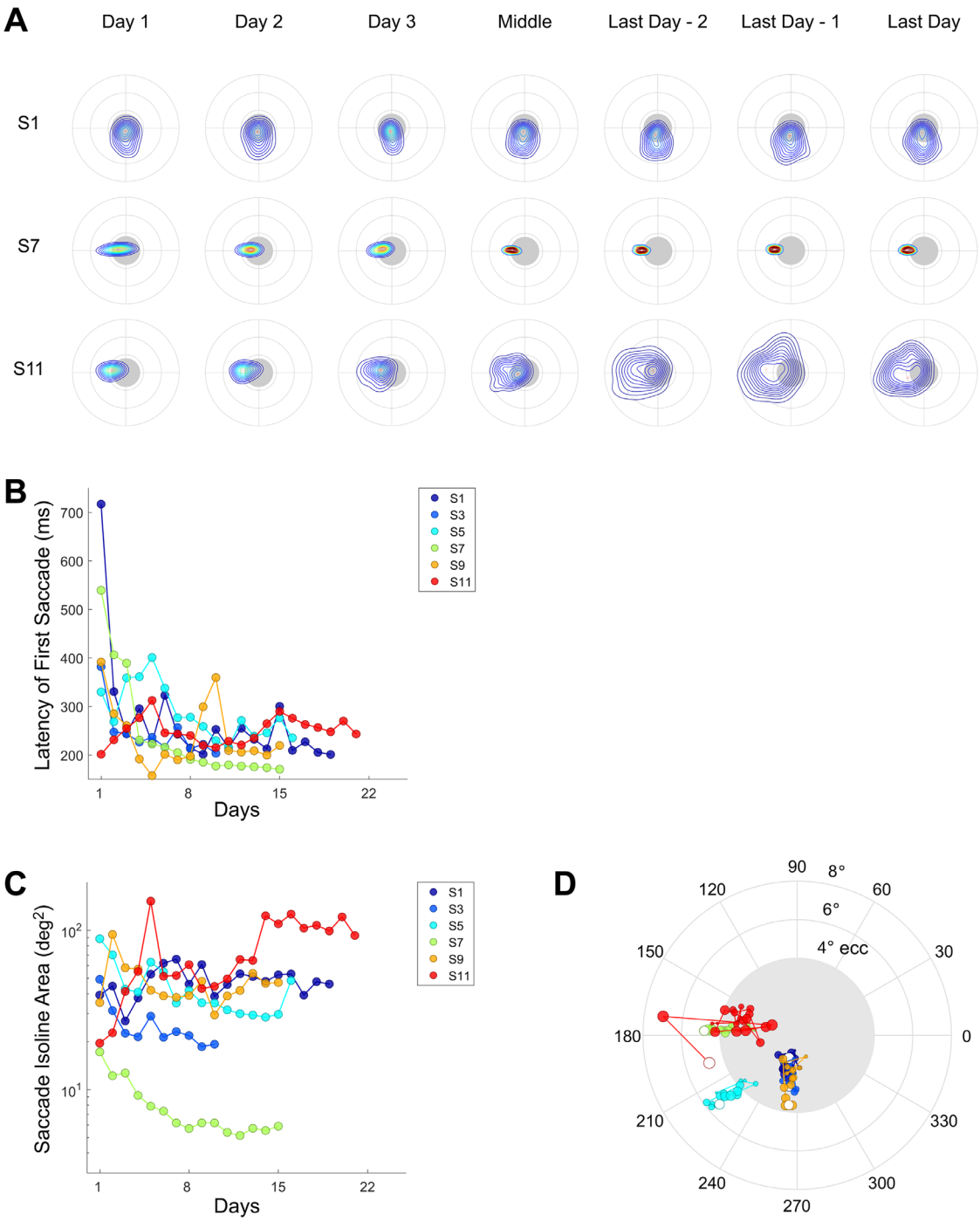


Figure 6. (**A**) Probability density maps describing the landing positions of all the first saccades when subjects made an eye movement to place the cross within the circle, are plotted as training progressed (the first 3 days, in the middle of the training, and the last 3 days) for three subjects in Experiment 2. The gray circle in each panel represents the 8 degrees diameter artificial scotoma. (**B**) Latency of first saccades, defined as the time elapsed since the circle target appeared in a new location on the display and before the eyes moved, are plotted as a function of training day (subjects coded by different colors). (**C**) Variability of the first saccade landing positions, quantified by the isoline area that encompassed 68% of the landing positions, is plotted as a function of training day. (**D**) Saccade pPRL, defined as the location corresponding to the highest probability of each probability distribution map like those shown in **A**, is plotted as training progressed (size of the symbol codes for the training day: smallest one represents day 1 with size increases for subsequent training days; unfilled circle represents the location of the saccade pPRL of the last training day). Despite our explicit training of the pPRL for the saccade task, only four of the six subjects had their saccade pPRL falling outside or close to the edge of the artificial scotoma; the other two subjects (S1 and S3) continued to reference their saccades to locations within the artificial scotoma.

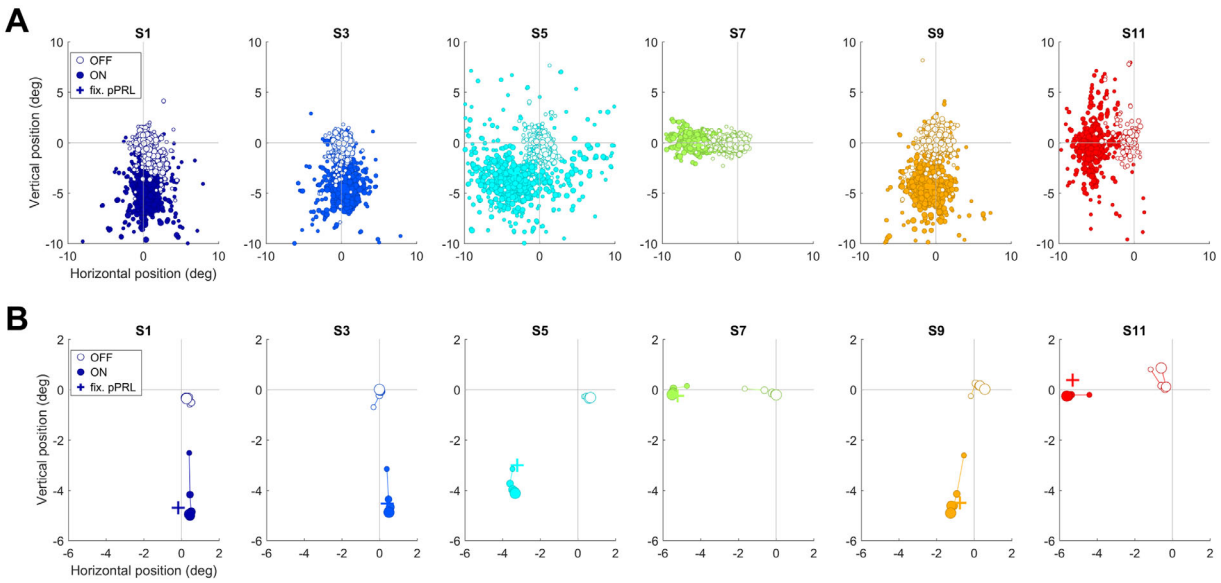


Figure 7. (**A**) Distributions of *all* saccade landing positions, separately plotted for the OFF (unfilled) and ON (filled) trials, for the six subjects (color coded according to our color scheme, see other figures). The origin (0, 0) represents the foveal locations. (**B**) The median saccade landing positions are plotted for the OFF (unfilled) and ON (filled) trials for the six subjects. The size of the symbols codes for the order of the saccades in the sequences (smallest symbols for first saccades, increasing symbol sizes for secondary, tertiary, quaternary, and quinary saccades).

than the fovea, although for some subjects (S1, S3, and S9 in particular), the median landing position of the first saccade was almost halfway between the pPRL location and the fovea, implying a rather large saccade error. The occurrences of subsequent corrective saccades (especially tertiary, quaternary, and quinary saccades) were also higher than for OFF trials. These results showing different saccade pPRLs for the ON and OFF trials, and that there were fewer tertiary, quaternary, and quinary saccades for the OFF trials than for the ON trials are clear evidence that subjects' behaviors were different depending on whether the artificial scotoma was present on a given trial.

Results in Figure 7 strongly suggest that subjects made saccades to different locations (closer to the fovea for OFF trials and closer to the non-foveal pPRL for ON trials) depending on whether or not the artificial scotoma was present on a given trial. One way to quantify if this speculation was indeed correct was to examine the saccade errors. If subjects had adapted to the use of a non-foveal pPRL, then saccade errors with respect to the pPRL should be much smaller than the errors calculated with respect to the fovea. On the contrary, if subjects only used their fovea as the reference locus for saccades, then saccade errors with respect to the fovea should be much smaller than the errors calculated with respect to the pPRL. Figure 8 plots saccade errors calculated with respect to the fovea in panel A, and with respect to the pPRL in panel B. To examine whether the presence of the artificial scotoma on a given trial affected the saccade error, we separately plotted saccade errors according to whether the (current) trial was an ON (blue) or an OFF (orange) trial. Further, we also examined whether the presence of the artificial scotoma in the preceding trial affected the saccade error of the current trial because the starting gaze position or the starting reference locus (the fovea or the pPRL) depended on the presence of the artificial scotoma in the preceding trial. Therefore, in Figure 8, saccade errors are plotted for four categories of trials: the artificial scotoma was present in both the preceding and the current trials (ON -> ON: dark blue), the artificial scotoma was present in the preceding trial but not in the current trial (ON -> OFF: dark orange), the artificial scotoma was absent in the preceding trial but was present in the current trial (OFF -> ON: light blue), and the artificial scotoma was absent in both the preceding and the current trials (OFF -> OFF: light orange). None of the subjects demonstrated a consistent use of either the fovea or the pPRL alone for *all* trials during the post-training testing session. Instead, for all subjects, saccade errors were larger for the ON trials (dark and light blue bars; mean error = 4.52 degrees, CI = 3.66 degrees to 5.38 degrees]) than for the OFF trials (dark and light orange bars; mean error = 1.51 degrees, CI = 1.31 degrees to 1.71 degrees) when calculated with respect to the fovea ($F[1,15] = 84.1$, $p < 0.0001$). However, whether or not the preceding trial was an ON or an OFF trial did not affect the saccade error of the current trial. When

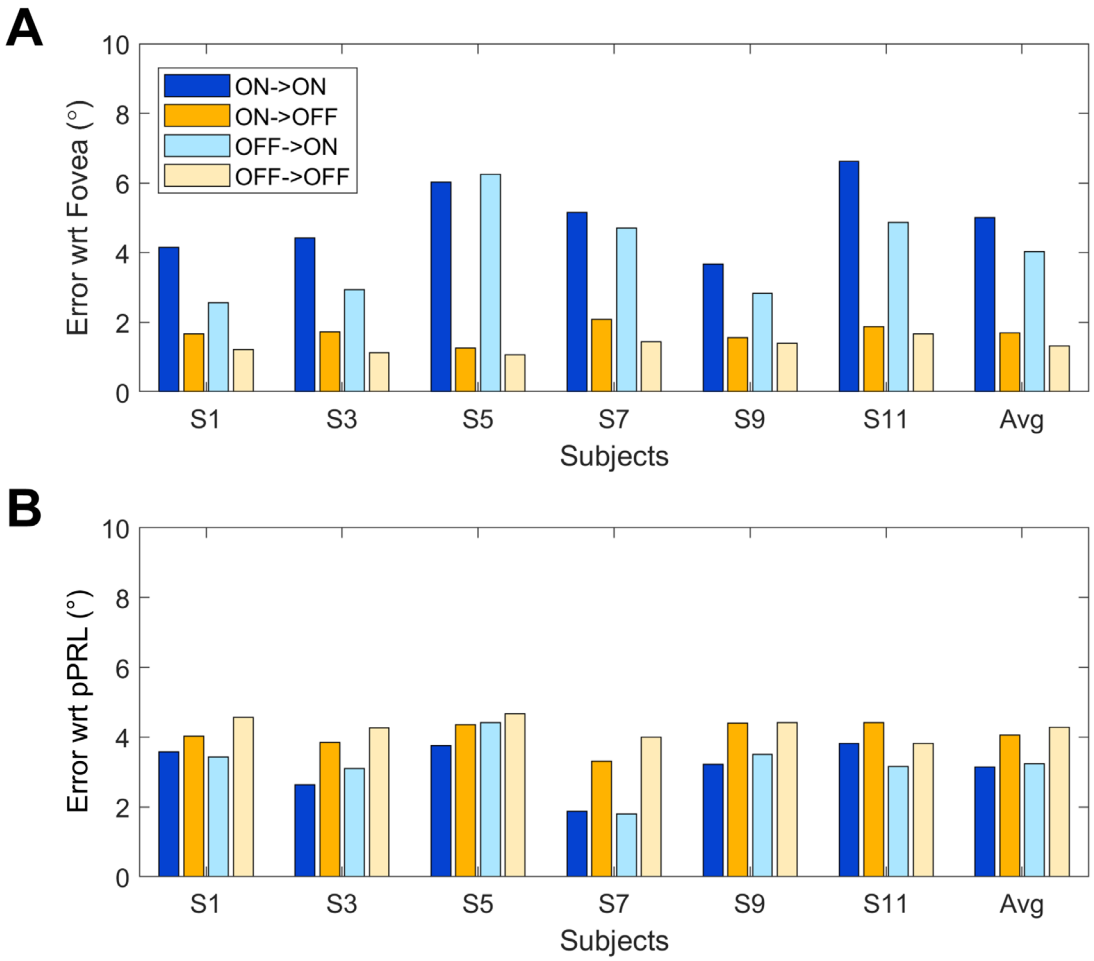


Figure 8. Landing errors of the first saccades made during the testing session following Experiment 2 are plotted for the six subjects (S1 to S11, "Avg" represents the average values). Saccade errors were calculated with respect to the fovea (saccade error represents the vector difference between the saccade landing position and the fovea) in panel **A** and with respect to the pPRL in panel **B**. Saccade errors are plotted separately for the four categories of trials: the artificial scotoma was present in both the preceding and the current trials (ON -> ON: dark blue), the artificial scotoma was present in the preceding trial but not in the current trial (ON -> OFF: dark orange), the artificial scotoma was absent in the preceding trial but was present in the current trial (OFF -> ON: light blue), and the artificial scotoma was absent in both the preceding and the current trials (OFF -> OFF: light orange).

calculated with respect to the pPRL, saccade errors were larger for the OFF trials (dark and light orange bars; mean error = 4.17 degrees, CI = 3.92 degrees to 4.42 degrees) than for the ON trials (dark and light blue bars; mean error = 3.19 degrees, CI = 2.70 degrees to 3.68 degrees; $F[1,15] = 37.2$, $p < 0.0001$). Saccade errors with respect to the pPRL also did not depend on whether the preceding trial was an ON or an OFF trial. These findings are solid evidence that subjects used both the fovea and their pPRL when making saccades during the testing session, and the choice of which one to use as the reference locus for a given trial depended solely on whether the artificial scotoma was present on that trial.

We also compared saccade latencies between the ON and the OFF trials. Across subjects, latencies of the first saccade averaged 263.9 ms (CI = 230.9 ms, to 296.6 ms) and 230.9 ms (CI = 202.4 ms to 259.4 ms) for the ON and the OFF trials, respectively (Figure 9). This difference of 33 ms between the ON and OFF trials was statistically significant ($F[1,15] = 31.1$, $p < 0.0001$) but did not depend on whether or not the artificial scotoma was present in the preceding trial, implying that saccade latency did not depend on the retinal location used at the beginning of a given trial. The longer saccade latency in the presence of an artificial scotoma is consistent with the findings of White and Bedell (1990) who showed that more time is necessary to program saccades that image targets at peripheral retinal locations for people with dysfunctional macula. According to these authors, the added time is needed to cancel or inhibit foveating saccades, similar to the increased in saccade latency reported for making anti-saccades (Hallett, 1978).

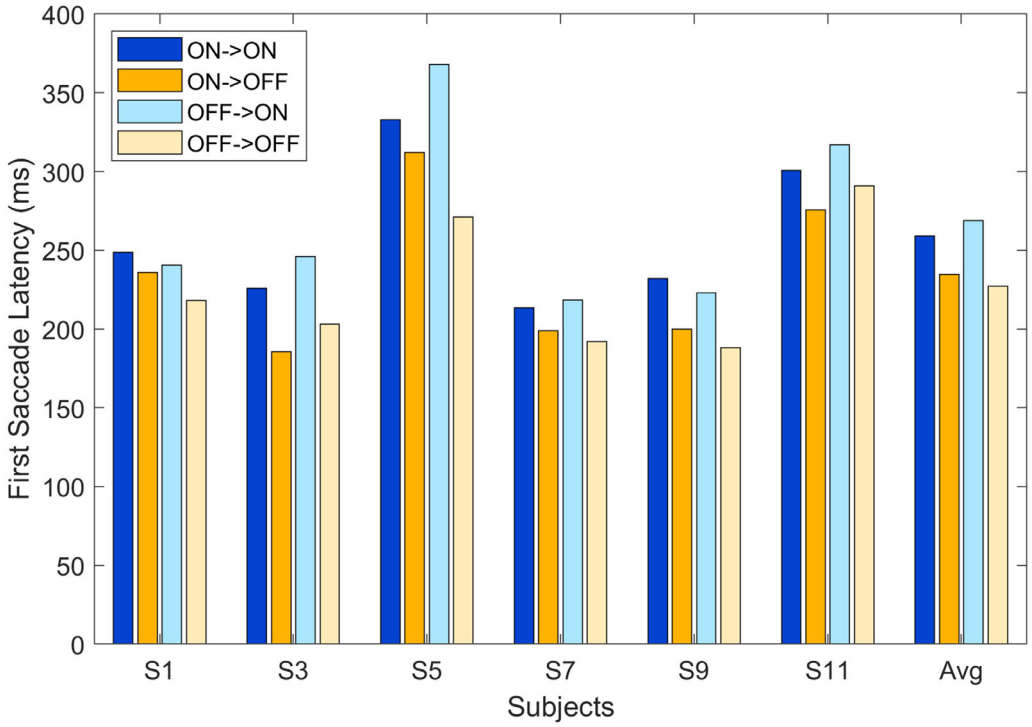


Figure 9. Latency of the first saccades (ms) made by the six subjects (S1 to S11, "Avg" represents the average values) during the testing session following Experiment 2. Saccade latencies are plotted separately for the four categories of trials: the artificial scotoma was present in both the preceding and the current trials (ON -> ON: dark blue), the artificial scotoma was present in the preceding trial but not in the current trial (ON -> OFF: dark orange), the artificial scotoma was absent in the preceding trial but was present in the current trial (OFF -> ON: light blue), and the artificial scotoma was absent in both the preceding and the current trials (OFF -> OFF: light orange).

## Summary of key oculomotor measurements across experiments

Table 1 summarizes the response time and several key oculomotor measurements, specifically, latency of the first saccades, eccentricity and variability of the fixation and saccade pPRLs, at the beginning and end of training in Experiments 1 and 2, as well as for the testing phase that followed Experiment 2. For the testing phase, latency of first saccades and the eccentricity and variability of the saccade pPRLs are also separately reported for the ON and OFF trials. Interpretation of these data should consider that the training tasks used in experiments 1 and 2 were different and thus different oculomotor responses might be more prone to changes due to the specific training task.

## Discussion

Even after subjects have demonstrated the consistent usage of a non-foveal location as their saccade pPRL in the presence of an artificial scotoma with extensive training, they reverted to using the fovea as soon as the fovea became "functional" when the artificial scotoma was removed. This conclusion was drawn based on the findings that when the artificial scotoma was absent, subjects made saccades that landed closer to the fovea; but when the artificial scotoma was present, subjects made saccades that landed closer to the non-foveal pPRL and usually with a larger initial saccade error and a longer saccade latency. These behaviors were consistent across the six subjects who participated in Experiment 2 and strongly implied that the use of whichever retinal location as the pPRL depended primarily on the resources available to the subjects on a given trial, specifically, whether or not foveal information was accessible to the subjects.

White and Bedell (1990) postulated that a complete adaptation to the use of a non-foveal location as the PRL means that saccades are made to place the object of regard on the non-foveal PRL location, instead of placing the object at the fovea. Using their rather strict criterion (subjects could not show a foveating saccade), they found that only seven of their 21 subjects with macular disease demonstrated a complete adaptation to the use of a non-foveal location as their PRL, despite

| **All subjects** | Experiment 1 training | |
|---|---|---|
| | First session | Last session |
| Response time, s | 2.91 ± 0.76 (1.76, 4.25) | 1.68 ± 0.28 (1.15, 2.12) |
| Latency of first saccades, ms | 548.95 ± 183.10 (315.36, 868.52) | 348.86 ± 87.80 (239.33, 513.87) |
| Fixation pPRL eccentricity, degrees | 1.87 ± 1.77 (0.15, 4.71) | 4.43 ± 1.33 (0.59, 5.62) |
| Fixation ISOA, degree$^2$ | 57.32 ± 36.85 (19.25, 118.42) | 42.41 ± 54.02 (9.04, 199.23) |
| Saccade pPRL eccentricity, degrees | 0.81 ± 0.34 (0.38, 1.36) | 1.70 ± 1.59 (0.51, 6.02) |
| Saccade ISOA, degree$^2$ | 40.72 ± 19.54 (16.90, 78.59) | 46.17 ± 37.72 (14.14, 130.17) |

| **Subjects S1, S3, S5, S7, S9, S11** | Experiment 1 training | | Experiment 2 training | | Post-training testing | |
|---|---|---|---|---|---|---|
| | First session | Last session | First session | Last session | | |
| Response time, s | 2.56 ± 0.61 (1.76, 3.37) | 1.55 ± 0.28 (1.15, 1.88) | 3.51 ± 1.36 (1.29, 4.76) | 1.31 ± 0.42 (0.88, 2.00) | | 1.51 ± 0.01 (1.50, 1.52) |
| Latency of first saccades, ms | 441.78 ± 104.02 (315.36, 586.65) | 305.24 ± 70.45 (239.33, 439.98) | 426.82 ± 179.17 (201.37, 717.17) | 212.12 ± 26.46 (170.44, 243.16) | | 281.24 ± 54.63 (222.99, 361.93) |
| Fixation pPRL eccentricity, degrees | 1.41 ± 1.58 (0.15, 4.52) | 4.93 ± 0.46 (4.28, 5.62) | 4.57 ± 0.39 (4.00, 5.00) | 4.79 ± 0.38 (4.41, 5.31) | | 1.28 ± 2.03 (0.32, 5.42) |
| Fixation ISOA, degree$^2$ | 59.07 ± 38.65 (19.25, 111.20) | 26.08 ± 17.68 (9.04, 58.00) | 9.74 ± 3.14 (6.15, 13.80) | 6.64 ± 1.70 (4.81, 9.77) | | 9.09 ± 2.84 (4.92, 12.62) |
| Saccade pPRL eccentricity, degrees | 0.81 ± 0.24 (0.54, 1.13) | 2.26 ± 2.02 (0.52, 6.02) | 2.58 ± 1.70 (0.80, 5.13) | 3.77 ± 1.56 (1.26, 5.39) | | 1.11 ± 0.80 (0.42, 2.38) |
| Saccade ISOA, degree$^2$ | 37.63 ± 14.16 (16.90, 59.03) | 43.42 ± 34.14 (14.14, 109.08) | 41.44 ± 25.99 (17.21, 88.41) | 43.16 ± 29.87 (5.88, 92.65) | | 24.95 ± 14.53 (8.74, 47.51) |
| | | | | | ON trials first saccade Latency, ms | 263.88 ± 53.45 (216.00, 350.50) |
| | | | | | ON trials first saccade pPRL eccentricity, degrees | 2.55 ± 1.81 (0.87, 5.69) |
| | | | | | ON trials first saccade ISOA, degree$^2$ | 34.74 ± 19.55 (9.50, 64.03) |
| | | | | | OFF trials first saccade Latency, ms | 230.92 ± 45.58 (194.00, 291.50) |
| | | | | | OFF trials first saccade pPRL eccentricity, degrees | 0.74 ± 0.41 (0.47, 1.44) |
| | | | | | OFF trials first saccade ISOA, degree$^2$ | 9.89 ± 4.80 (4.61, 18.11) |

Table 1. Mean ± standard deviation (minimum and maximum given in parentheses) of various oculomotor characteristics for the different experiments.

the fact that the other 14 subjects all had vision loss ranging between 1 and 29 years. This finding suggests that for people with real central vision loss, their full adaptation to using a non-foveal location as the PRL could take a long time, or, in some cases, may never happen. Thus, it is amazing that normally sighted subjects can make saccades consistently toward a non-foveal location in the presence of an imposed artificial scotoma after 15 to 25 hours of intermittent training to use that non-foveal location (Kwon et al., 2013, also see our data). Kwon et al. (2013) interpreted their finding as evidence that the oculomotor system develops a motor plan in response to the artificial scotoma that opts for simplicity over optimality with respect to saccade amplitude and accuracy. The result is that the oculomotor system uses a single non-foveal location as the pPRL in response to the presence of the artificial scotoma, and that this amounts to adding a constant vector offset to the existing oculomotor control. They further postulated that once learned (probably learning the magnitude and the direction of the vector offset), the motor plan can be retained without continuous practice, explaining their retention effect. In our study, there was a 3- to 6-month gap between the end of Experiment 1 and the beginning of Experiment 2 for three of the participants; yet these subjects still remembered where their non-foveal pPRL should be. If the use of a non-foveal location as the pPRL is indeed due to the plasticity of the oculomotor system, one may wonder why the oculomotor system did not "relearn" to return that non-foveal pPRL location to the "baseline" condition (i.e. fovea) when there was no training and subjects were free to use their fovea.

Recently, Chen et al. (2019) showed that following an explicit training in the presence of an artificial scotoma, as used by Kwon et al. (2013), there was a reduction of crowding (the adverse effect of a nearby flanker on the recognition of a target) at the non-foveal pPRL location along the direction that connect the non-foveal location with the fovea. These authors suggested that the reduction in crowding was a consequence of the adoption of the non-foveal location as the pPRL. Based on the original theory of Nandy and Tjan (2012), crowding arises mainly in the periphery because the image statistics at any given non-foveal retinal location is confounded by saccadic eye movements (based on the assumption that in normal vision, saccades are directed toward the fovea). This theory predicts that when saccades are re-referenced to a non-foveal location, the image statistics would no longer be confounded by eye movements at that location, leading to a reduction of crowding. This prediction is consistent with the report that the extent of crowding is indeed smaller at the non-foveal PRL location of people with a real central scotoma when compared with the extent of crowding at the same eccentricity in the normal periphery (Chung, 2013), especially along the radial direction (the direction of saccades). At the core of all these predictions and theories, is that the oculomotor system can learn to make saccades to a different reference location and that the visual system can learn the new and updated image statistics. In the study of Chen et al. (2019), when their normally sighted subjects were not in the laboratory and thus did not have an imposed artificial scotoma, they were free to use their fovea and made saccades directed toward the fovea, which amounted to approximately 15 hours of the day (assuming 8 hours of sleep and 1 hour of testing with an artificial scotoma in the laboratory). In this case, it is difficult, if not impossible, to explain why when these subjects made saccades referenced to the fovea during most of their daily lives, the image statistics at their non-foveal pPRL would not be updated to include the confounds due to saccadic eye movements. Therefore, Chen et al.'s finding of a reduction in crowding at the pPRL location of normally sighted subjects is unlikely to be solely due to the intermittent use (only in the laboratory) of the pPRL as a saccade reference location. Instead, their finding could be attributed to simply perceptual learning, a potential factor that the authors did not address or rule out. All these raise the questions of what the visual and oculomotor systems really learn during training with an imposed artificial scotoma, what an artificial scotoma really simulates, and what is the underlying basis of normally sighted subjects' "adaptations" to an imposed artificial scotoma.

We postulate that what normally sighted subjects learn during the implicit or explicit training using an imposed artificial scotoma is the strategy to deal with the occlusion of their central field. Potentially, all subjects need to learn is the magnitude and direction of the vector offset from the fovea. Take, for example, subject S7 of our study, his non-foveal pPRL is at the left edge of the artificial scotoma, therefore his vector offset should be approximately 4 degrees (radius of the artificial scotoma) with the direction of the offset toward the left. This information seems to be just as easy to learn, if not easier, as what previous researchers claimed to be motor learning or a true adoption of another non-foveal location as the pPRL. Our explanation is also more consistent with how automatic subjects switched from using the fovea for the OFF trials to using the non-foveal location for the ON trials. Had a motor adaptation process (similar to saccadic adaptation to smaller or larger amplitudes) taken place for developing the pPRL for saccades after a prolonged training with an artificial scotoma, we would expect that remapping of saccade vectors from pPRL back to the fovea would not happen at the very first saccade after the artificial scotoma was no longer present. This is because the saccadic adaptation literature indicates that it takes dozens (if not hundreds) of saccades to recalibrate the saccade amplitude back to normal after

adapting to smaller or larger saccades (e.g. McLaughlin, 1967; Miller, Anstis, & Templeton, 1981; Semmlow, Gauthier, & Vercher, 1989; Hopp & Fuchs, 2004).

An analogy to phantom limb can be made here to clarify what is meant by a genuine neural plasticity or adaptation. Just as patients who undergo unilateral major limb amputation need to use their intact limb for daily tasks, patients with central vision loss need to use an intact part of their retina (albeit at a lower resolution) to visually perceive their environment. It is now well established that patients suffering from phantom limb syndrome might feel pain in their amputated limbs or hands with tactile stimulation to face (e.g. Pons, Garraghty, Ommaya, Kaas, Taub, & Mishkin, 1991; Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001; Collins, McKean, Huff, Tommerdahl, Favorov, Waters, & Tsao, 2017), which is a piece of direct evidence of some neural plasticity taking place in the brain (e.g. face area is expanding to hand/arm area in the somatosensory cortex). For patients with central vision loss, an analogous neural rewiring (functional or structural) for remapping saccades from the fovea to the PRL, especially in saccade target selection and saccade execution circuitry (e.g. superior colliculus and frontal eye field), would have resulted in a shift in the retinotopic maps, which would have, in turn, led to automatic oculomotor behavior (i.e. no added latency for first saccades directed toward the PRL). If the artificial scotoma is a good model for real central vision loss, then we would also expect a shift in the retinotopic maps and the automatic oculomotor behavior, such that for our subjects with normal vision, there should be no additional latency for the first saccades for the ON trials (the artificial scotoma was present) when compared with those made for the OFF trials (the artificial scotoma was absent).

As stated in the Introduction, patients with macular disease might use multiple PRLs under different conditions (Lei & Schuchard, 1997), for different tasks (Crossland, Crabb, & Rubin, 2011), or for the same task (Duret, Issenhuth, & Safran, 1999; Déruaz et al., 2002). Recently, also using an artificial scotoma method to induce pPRLs in normally sighted subjects, Maniglia, Visscher, and Seitz (2021) found that some of their subjects adopted consistent looking strategies (probably referred to the use of the same pPRL) whereas others used different pPRLs for different (perceptual) tasks. Their results, like ours, demonstrate substantial individual responses to the presence of induced central vision loss, even though we induced or reinforced the use of a single pPRL for saccadic eye movements in Experiment 2, whereas Maniglia et al. allowed the use of multiple pPRLs and evaluated different perceptual tasks. The important question, therefore, is what could account for the variable individual responses. Future studies are necessary to answer this important question.

In summary, our findings that subjects with normal vision reverted back to the use of the fovea and making saccades toward the fovea as soon as the artificial scotoma was removed imply that what subjects learned during our training tasks (primarily oculomotor in nature) was simply a strategy to deal with the presence of the artificial scotoma, instead of a genuine neural or oculomotor adaptation as what people with real central vision loss show, or a genuine sensory adaptation. We acknowledge that the use of an artificial scotoma has been used to study perceptual tasks in relation to central vision loss, for example, reading (e.g. Bernard, Scherlen, & Castet, 2007; Liu & Kwon, 2016; Barraza-Bernal et al., 2017; Bernard, Aguilar, & Castet, 2016; Gupta, Mesik, Engel, Smith, Schatza, Calabrèse, van Kuijk, Erdman, & Legge, 2018; Prahalad & Coates, 2020), face recognition (Tsank & Eckstein, 2015), acuity (Liu & Kwon, 2016; Maniglia et al., 2020a), and visual search (Cornelissen et al., 2005; Walsh & Liu, 2014), suggesting that the artificial scotoma paradigm might have the potential of facilitating our understanding of how to improve visual functions in peripheral vision. The artificial scotoma paradigm even presents itself a valuable tool for the development of novel visual aids (Aguilar & Castet, 2017). Considering that the current study focused on the oculomotor responses of subjects when faced with an artificial scotoma, our conclusion may thus only apply to the adaptation processes observed in oculomotor tasks. Whether our conclusion also applies to perceptual tasks remains to be tested in future studies. Nevertheless, we suggest that the use of the artificial scotoma paradigm must be treated with caution if the ultimate purpose is to draw conclusions that would be applied to people with real central vision loss.

*Keywords: central vision loss, artificial scotoma, preferred retinal locus, saccade, visuomotor adaptation*

## Acknowledgments

Supported in part by a UC Berkeley Summer Undergraduate Research Fellowship from the Rose Hills Foundation (to W.F.), UC Berkeley Regents' and Chancellor's Scholars' Research Fellowship (to W.F.), NIH Short-term Training Grant T35-EY007138 (to W.F.), and NIH Research Grants R01-EY012810 and R21-EY030253 (S.T.L.C.).

Commercial relationships: none.
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## Footnote

[1]For normally sighted subjects with a good calibration and assuming that subjects use the center of their fovea, retinal location could be inferred from the gaze positions. Here, we adopt a strict definition for retinal location — if we cannot see the retina, we would rather not refer to any inferred locations as retinal locations.

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