# Successful visually guided eye movements following sight restoration after congenital cataracts

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**Sensitive periods have previously been identified for several human visual system functions. Yet, it is unknown to what degree the development of visually guided oculomotor control depends on early visual experience—for example, whether and to what degree humans whose sight was restored after a transient period of congenital visual deprivation are able to conduct visually guided eye movements. In the present study, we developed new calibration and analysis techniques for eye tracking data contaminated with pervasive nystagmus, which is typical for this population. We investigated visually guided eye movements in sight recovery individuals with long periods of visual pattern deprivation (3–36 years) following birth due to congenital, dense, total, bilateral cataracts. As controls we assessed (1) individuals with nystagmus due to causes other than cataracts, (2) individuals with developmental cataracts after cataract removal, and (3) individuals with normal vision. Congenital cataract reversal individuals were able to perform visually guided gaze shifts, even when their blindness had lasted for decades. The typical extensive nystagmus of this group distorted eye movement trajectories, but measures of latency and accuracy were as expected from their prevailing nystagmus—that is, not worse than in the nystagmus control group. To the best of our knowledge, the present quantitative study is the first to investigate the characteristics of oculomotor control in congenital cataract reversal individuals, and it indicates a remarkable effectiveness of visually guided eye movements despite long-lasting periods of visual deprivation.**

## Introduction

Gaze orienting is crucial for visual perception. Eye movements allow us to foveate relevant events in the world and require a precise and efficient oculomotor system. Humans are not born with a fully functional oculomotor system, which is characterized by a protracted development (Luna, Velanova, & Geier, 2008). Although visually guided saccades have been reported to occur as early as within the first month of life (Aslin & Salapatek, 1975), infants and children had less stable fixations, longer latencies, and shorter saccade amplitudes than adults (Alahyane, Lemoine-Lardennois, Tailhefer, Collins, Fagard, & Doré-Mazars, 2016; Aslin & Salapatek, 1975; Cohen & Ross, 1978; Harris, Jacobs, Shawkat, & Taylor, 1993;

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Irving, González, Lillakas, Wareham, & McCarthy, 2011; Munoz, Broughton, Goldring, & Armstrong, 1998; Ross, Radant, Hommer, & Young, 1994). Eye movement studies in blind humans have demonstrated that, although many late-blind individuals were able to voluntarily orient their eyes even after several years of blindness, congenitally blind adults with intact eyes were not (Hall, Gordon, Hainline, Abramov, & Engber, 2000; Kämpf & Pieper, 1987; Leigh & Zee, 1980; Schneider, Thurtell, Eisele, Lincoff, Bala, & Leigh, 2013). These results suggest that the human oculomotor system does not properly develop in the total absence of visual input. However, it is yet unclear whether and to what degree eye movement control is possible in humans whose sight can be restored—that is, whether there is a sensitive period for the development of visually guided eye movements.

Individuals born with congenital, dense, total, bilateral cataracts provide a unique opportunity for research into the experience-dependent development of the human visual system as several of them do not receive patterned visual input until the cataracts are removed. Although some visual system functions appear to develop normally after sight is restored, such as color perception (Brenner, Cornelissen, & Nuboer, 1990; McKyton, Ben-Zion, Doron, & Zohary, 2015; Pitchaimuthu, Sourav, Bottari, Banerjee, Shareef, Kekunnaya, & Röder, 2019), retinotopy (Sourav, Bottari, Kekunnaya, & Röder, 2018), and biological motion detection (Bottari, Troje, Ley, Hense, Kekunnaya, & Röder, 2015; Hadad, Maurer, & Lewis, 2012), others do not, leading to lasting impairments such as reduced visual acuity (Ellemberg, Lewis, Maurer, Hong Lui, & Brent, 1999; Kalia et al., 2014), impaired face processing (Le Grand, Mondloch, Maurer, & Brent, 2001; Putzar, Hötting, & Röder, 2010), reduced global motion perception (Bottari, Kekunnaya, Hense, Troje, Sourav, & Röder, 2018; Hadad et al., 2012), and compromised multisensory speech perception (Putzar, Hötting, Rösler, & Röder, 2007; Putzar et al., 2010). It could be hypothesized that these impairments stem from an impaired oculomotor control, preventing these individuals from systematically scanning the visual environment. However, the ability to perform visually guided eye movements after congenital visual deprivation has not yet been quantitatively investigated; that is, a systematic assessment of visually guided oculomotor control in cataract reversal individuals with visual deprivation periods extending beyond the typical range of sensitive periods for development of visual system functions is missing. Studies on the effects of transient binocular visual deprivation in macaque monkeys (Carlson, 1990; Harwerth, Smith, Paul, Crawford, & Von Noorden, 1991; Hyvärinen, Hyvärinen, & Linnankoski, 1981; Regal, Boothe, Teller, 1976; Tusa, Mustari, Burrows, & Fuchs, 2001) reported that after sight restoration the animals were able to visually orient their head and eyes to follow light and objects but did not analyze oculomotor control in detail. The main reason for a lack of detailed data on eye movement control in cataract reversal individuals most likely is the extensive and permanent nystagmus these individuals develop if surgery was not performed within the first weeks of life. These involuntary oscillations of the eyes render the estimation of gaze position extremely difficult.

The present study developed a new approach to assess eye movements in cataract reversal individuals despite their prevailing extensive nystagmus, and it investigated to what extent human oculomotor control develops after a long period of congenital blindness. Eye tracking was performed in a reactive saccade task, and eye movement characteristics including (1) latency, (2) duration, (3) endpoint error, (4) saccade peak velocity, and (5) saccade amplitude were assessed. The data of congenital cataract reversal individuals were compared to three control groups comprised of developmental cataract reversal individuals to assess the effects of age at visual deprivation onset, individuals with nystagmus due to reasons other than cataracts to estimate the effects of nystagmus on visually guided eye movements, and normally sighted controls.

# Methods

## Participants

All participants were recruited and tested between November 2018 and February 2019 at the LV Prasad Eye Institute in Hyderabad, India. None of the participants had impairments in sensory systems other than vision nor any known neurological disorder. One additional nystagmus control individual (see below) was excluded for excessive eye tracking signal artifacts due to partially closed eyes.

The cataract reversal group (CC) consisted of nine subjects (three females; mean age, 22.8 years; range, 8–44 years) with a history of congenital, dense, total, bilateral cataracts that were surgically removed earliest at the age of 3 years (mean, 15.8 years; range, 3–36 years). The history of congenital, dense, total, bilateral cataracts was confirmed by medical records. In addition to the clinical diagnosis, factors such as vision loss, density of the lenticular opacity, strabismus, presence of nystagmus, absence of fundus view prior to surgery, and positive family history aided in the classification of CC participants. Presurgical visual acuity assessments were available in six of the nine cases. Three CC individuals with presurgery visual acuity between 1.4 and 1.48 logMAR units (see Table 1) had partially absorbed cataracts, which are regularly observed in congenital cataract patients. A visual acuity of 1.4

| Participant | Age, y | Gender | Age at surgery, y | Visual experience, mo | Presurgical visual acuity | Postsurgical visual acuity |
|---|---|---|---|---|---|---|
| CC-a | 36 | Male | 23 | 161 | Unknown | 1.30 |
| CC-b | 17 | Male | 16 | 12 | 1.40* | 0.80 |
| CC-c | 16 | Female | 15 | 12 | 1.48* | 1.10 |
| CC-d | 13 | Female | 3 | 120 | Unsteady fixation at light | 0.40 |
| CC-e | 44 | Male | 36 | 102 | Unknown | 1.20 |
| CC-f | 8 | Female | 4 | 48 | CF 0.5 m | 0.70 |
| CC-g | 22 | Male | 17 | 58 | CF 0.5 m | 0.90 |
| CC-h | 32 | Male | 13 | 226 | Unknown | 1.00 |
| CC-i | 16 | Male | 15 | 15 | 1.48* | 1.10 |

Table 1. Characteristics of the CC individuals. *Notes*: Visual acuity is expressed in logMAR units and refers to the better eye. CF represents those able to count fingers; equivalence with logMAR acuity has been reported to be 1.7 to 2.0 at 30 cm (Schulze-Bonsel, Feltgen, Burau, Hansen, & Bach, 2006). *Subjects with documented absorbed cataracts in the latter part of their childhood.

logMAR is considered to be severe blindness according to the ICD-10 (World Health Organization, 2004). CC individuals were tested at least 1 year after cataract removal surgery (mean, 7.0 years; range, 1–19 years). Mean postsurgical visual acuity was 0.94 logMAR (range, 0.40–1.30). All CC individuals suffered extensive nystagmus. Table 1 provides a detailed description of the CC individuals.

The nystagmus control group (NC) group consisted of 13 individuals with infantile nystagmus syndrome due to reasons other than cataracts and without a period of blindness. These individuals enabled a dissociation of the influence of nystagmus and early visual experience (three females; mean age, 12.5 years [range, 7–28 years]; mean visual acuity, 0.50 logMAR [range, 0.10–0.90]).

The developmental cataract group (DC) consisted of 16 individuals (six females; mean age, 15.3 years; range, 9–32 years). All DC individuals had a history of a transient period of bilateral cataracts later in life and had undergone the same surgical procedure as the CC individuals. They were tested at least 1 year after cataract removal surgery (mean, 9.0 years; range, 1–19 years). Mean postsurgical visual acuity was 0.20 logMAR (range, 0.00–1.00).

The sighted control group (SC) consisted of 13 individuals (three females; mean age, 14.6 years; range, 10–18 years) with normal or corrected-to-normal vision. This group allowed us to establish typical eye movement parameters for healthy individuals.

Expenses associated with taking part in the study were reimbursed. Minors received a small present. The participants and/or their legal guardians provided written informed consent for taking part in the study. Participants and/or their legal guardians were informed about the study and received the instructions in one of the languages they were able to understand. The study was approved by the local ethics board of the Faculty of Psychology and Human Movement Science (University of Hamburg, Germany) and the institutional ethics board of the LV Prasad Eye Institute (Hyderabad, India).

## Setup

Eye movements were recorded binocularly at 500 Hz using an EyeLink 1000 Plus Eye Tracker (SR Research Ltd., Kanata, ON, Canada). Subjects were seated in a darkened room and head constrained so that their eyes were at a distance of 60 cm from the screen. Stimuli were generated in MATLAB (MathWorks, Natick, MA) using Psychtoolbox 3 (Brainard, 1997; Kleiner, Brainard, Pelli, Ingling, Murray, & Broussard, 2007) on a Windows 7 PC (Microsoft, Redmond, WA) and presented on an Eizo FG2421 LCD monitor (Ishikawa, Japan) at a resolution of 1920 × 1080 at 120 Hz.

## Experimental design

After the subjects were given instructions and eye tracker calibration was performed, a gray dot (diameter = 1° of visual angle) was shown on a black screen. After 2 to 4 seconds (uniform random sample) the dot jumped to a new location at a distance of 5° to 15° (uniform random sample) in a random direction from the previous dot location. Targets could appear in a subsection of the screen spanning 39° × 22°. Subjects were instructed to always fixate the dot and to follow the target when it changed position. Thus, the saccade target of a trial always became the fixation target of the next trial. To prevent fatigue and to minimize blinking, after every 10 trials (dot position changes) the dot disappeared. Subjects were instructed to close their eyes and after a few seconds to open them again. After the experimenter pressed a key, the dot reappeared at the same location from which it had disappeared and after 2 seconds jumped to the next location. After 99 dot jumps, the experiment terminated.

## Online eye-tracker calibration

The extensive nystagmus present in many of the subjects prohibited the use of default calibration

procedures. Each subject was initially calibrated manually by selecting gaze samples from raw data recordings while a target was presented at one of following five locations: screen center, 15° right and left of the center, and 8.5° above and below the center. The mapping was determined by fitting the medians of the selected samples to the corresponding calibration targets using a second-order polynomial function (Stampe, 1993).

## Offline calibration and endpoint error

Optimal calibration coefficients were determined offline by minimizing median endpoint error. Beginning with the initial online manual calibration, eye movement endpoints were computed by the procedure described in the section Detection of visually guided eye movements below. For each subject, the calibration coefficients that resulted in the lowest mean Euclidian endpoint error across all trials were determined by an implementation of the Nelder–Mead simplex optimization algorithm. These calibration coefficients were then used to recalibrate the raw gaze position data, from which new endpoints were computed. This procedure was repeated 30 times, from which the set of coefficients with the lowest resulting endpoint error were determined and used to calibrate the raw gaze position data for the analysis. Due to the random distribution of saccade targets across the screen, this method generated an optimal mapping function to minimize calibration error. This offline calibration method would however be insensitive to directionally systematic endpoint errors, such as, for example, always looking to the left of a target dot. Such constant errors were not of interest in the present study and do not affect the interpretation of the extracted eye movement parameters.

The calibration procedure was 11-fold cross-validated within the dataset by using a portion of the experimental trials to estimate calibration coefficients and measuring the resulting endpoint error in the remaining trials. Data were partitioned into 11 subsamples of nine trials; endpoint errors were calculated for each subsample using calibration coefficients computed from the other 10 subsamples. Because we calibrated gaze samples using the same locations that served as targets and we used the entire dataset, subjects' endpoint errors described in the Results section are equivalent to their calibration error.

Eye blinks were detected and removed according to the method suggested by Mathôt (2013); recording epochs of 50 ms before and after a pupil size change velocity of greater than an empirically defined value ($3.5 \times 10^4$ arbitrary units) were disregarded.

Saccades were defined by the EyeLink saccade detection algorithm (SR Research, 2017) with default thresholds of 35°/s velocity and 9500°/s$^2$ acceleration. A subset of the detected saccades in each group was visually inspected to confirm that saccades were correctly detected. The better eye was used for each subject—that is, the eye with the lowest median endpoint error.

## Detection of visually guided eye movements

Typical eye movement analysis is based on an alternating pattern of fixation and saccades. By contrast, in individuals with nystagmus, the eyes are almost never at rest; fixation periods are difficult to define, and voluntary saccades are difficult to differentiate from the fast phase of the nystagmus. In addition, a pattern of alternating slow drifts and saccades was often observed (e.g., Worfolk & Abadi, 1991). The idiosyncratic pattern of these eye movements required a new definition of the start and end of a visually guided eye movement applicable to both typical and atypical eye movements.

Visually guided eye movements can be described by the distance between gaze and targets (Figures 1C, 1D). During a gaze shift from a fixation target to the saccade target, the distance of gaze to the fixation target increases ($\bar{F}$, black line), whereas the distance to the saccade target decreases ($\bar{T}$, red line). Subtracting $\bar{F}$ from $\bar{T}$ produces a singular measure of gaze position relative to the two targets: $\Delta FT$ (Figures 1E, 1F, 1I). As soon as a gaze shift takes place, $\Delta FT$ moves from positive values to negative values. A value of zero ($\Delta FT = 0$) indicates that gaze is equidistant from the fixation target and the saccade target ($\bar{F} = \bar{T}$). Before this zero point (further referred to here as *midpoint*) gaze is closer to the fixation target, and after the midpoint gaze is closer to the saccade target. The midpoint can unambiguously be detected in both typical eye movements and in eye movements superimposed by nystagmus, provided that a gaze shift from the fixation target toward the saccade target took place.

If a midpoint was detected ($\Delta FT = 0$) within 1.5 seconds after target onset, we defined the startpoint of a visually guided eye movement as the point in time at which gaze had reached 7.5% of the total $\Delta FT$ displacement. Correspondingly, the time point when the gaze passed 92.5% of the total $\Delta FT$ displacement was used as endpoint measure (Figures 1E, 1F). When $\Delta FT$ never crossed the midpoint, the trial was considered a failed gaze shift. Importantly, the same analysis approach was used for all subjects in the present study.

The pattern of results reported in the result section did not change considerably, with cutoff values ranging from 1% to 10% in steps of 0.5% (see Figures A.1 to A.3 in the Appendix). The cutoff values of 7.5% and 92.5% of the $\Delta FT$ displacement were chosen based on a validation done in the SC group. For SC individuals,

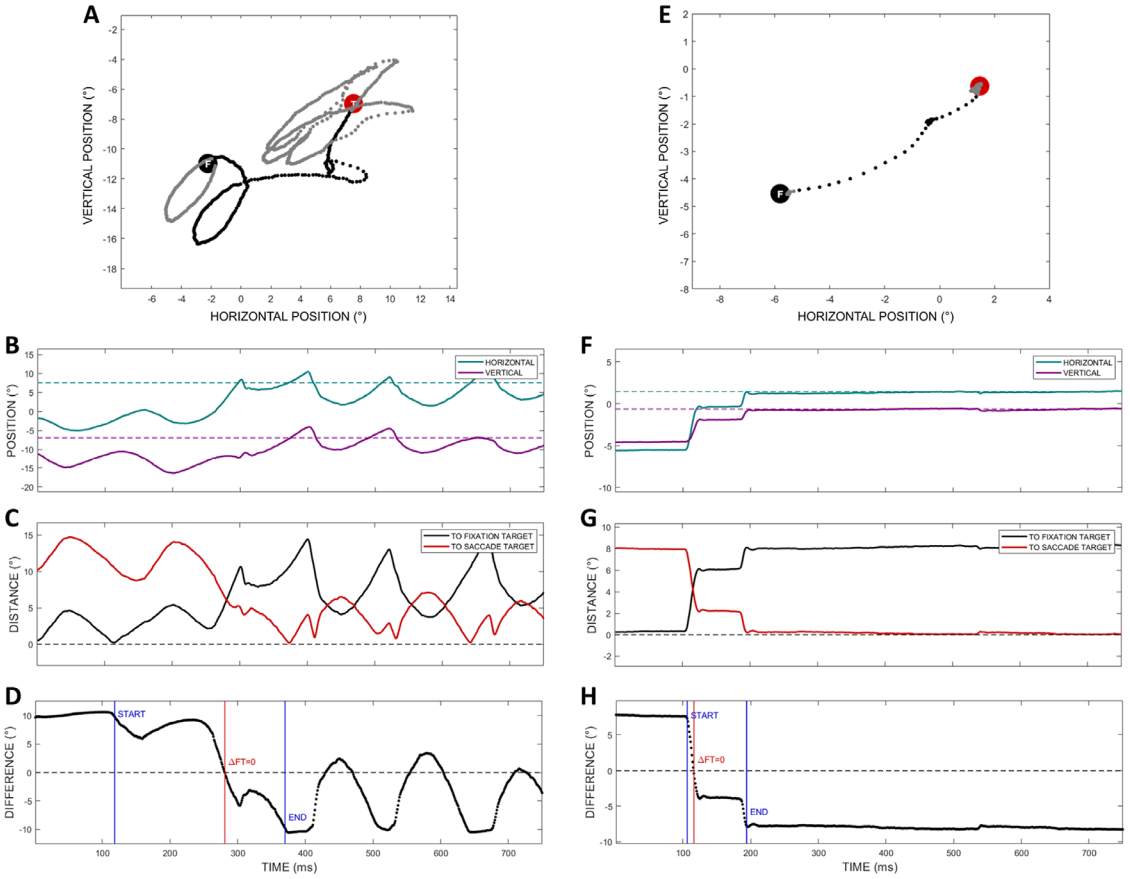


Figure 1. Illustration of the eye movement classification algorithm on two example trials. (A–D) Single trial of eye movement data from a congenital cataract reversal individual. (E–H) Single trial of eye movement data from a normal sighted control. A and E show 2D plots of the eye movement traces. *Black dots* indicate samples classified as the visually target guided portion of the eye movement trace and *gray dots* represent other samples. B and F display a horizontal (*cyan line*) and vertical (*magenta line*) eye movement trace. The dashed *cyan* and *magenta lines* indicate the horizontal and vertical target position. Position 0° represents the center of the screen. C and G show the distance of gaze from fixation target (*black line*) and target position (*red line*), respectively. In D and H, the *black lines* indicate the difference between the distance of gaze from fixation target and saccade target. $\Delta FT = 0$ represents the eye movement midpoint, where gaze is equidistant from the fixation target and saccade target, with positive values indicating gaze being closer to the fixation target and negative values indicating gaze being closer to the saccade target position.

start- and endpoint classification as defined by the described new method was compared to the values provided by the eye-tracker parser at the different cutoff values. Normally sighted individuals typically reached the targets within two saccades. Thus, in order to be able to directly compare the new and the eye tracker-derived parameters, the endpoint of the gaze shift was defined as the end of the second saccade, if more than one saccade was detected. Next we computed the difference between the estimates of the new and eye tracker-based methods. The smallest difference was observed for a cutoff value of 7.5%/92.5% (see Figure A.4 in the Appendix). The new method estimated startpoints as on average 6.8 ms later (range of individual subjects, 6–8 ms) and endpoints as on average 7 ms earlier (range for individual subjects, 0–18 ms). These results provide a convincing evaluation of our new method and demonstrate that gaze start- and endpoints were reliably evaluated by the newly introduced method.

## Visually guided eye movement measures

### Successful eye movements

We considered an eye movement as successful when the gaze position was shifted toward the target within the first 1.5 seconds of its onset (i.e., the trial contained a midpoint), irrespective of whether the gaze shift was achieved by one or multiples drifts or saccades or a combination of both. In this case, a midpoint was defined while otherwise the trial was considered a failed

visually guided eye movement. To quantify whether a successful eye movement contained a saccade, we examined whether the SR saccade detection algorithm had detected a saccade of at least 2° in amplitude within 200 ms before and 200 ms after the midpoint. We assessed the proportions of successful eye movement trials and the proportion of successful trials containing a saccade. The remaining analyses were performed only for successful eye movement trials. Saccade velocity, amplitude, and latency were only assessed for saccades with peak velocities below 1000°/s. The percentages of trials discarded from successful trials containing saccades were as follows: CC group, 4% (subject range, 0%–9%); NC group, 2% (subject range, 0%–10%); DC group, 1% (subject range, 0%–5%); and SC group, 1% (subject range, 0%–1%). The cutoff value of 1000°/s was chosen, slightly above normal saccade peak velocities, which in humans typically reach up to 900°/s (Bahill, Clark, & Stark, 1975), to allow for the inclusion of possible abnormally fast saccades in individuals with nystagmus. For each analysis of the remaining eye movement parameters, we report the percentage of discarded trials relative to the number of trials containing a midpoint (successful trials).

## Latency and duration of visually guided eye movements

The latency of a visually guided eye movement was defined as the time interval between target onset and the start of a gaze shift (see above). Trials with latencies below 50 ms and above 1000 ms were not analyzed for latency and duration (trials discarded: CC group, 22% [subject range, 8%–33%]; NC group, 21% [subject range, 13%–42%]; DC group, 6% [subject range, 0%–20%]; SC group, 3% [subject range, 0%–9%]). The relatively low cutoff value of 50 ms was chosen just below the minimal latency of typical express saccades in humans (around 75–85 ms) (Biscaldi, Fischer, & Stuhr, 1996; Fischer & Ramsperger, 1984), in order to include potentially fast latencies due to an atypical release of cortical inhibition as expected for CC individuals. The upper cutoff value of 1000 ms was applied to exclude gaze shifts that began long after target onset and very likely reflect lapses of concentration. The latency of visually guided eye movements was calculated with the new detection method. Thus, latencies of gaze shifts initiated with a drift and the latencies of gaze shifts initiated with a saccade are not distinguished. Therefore, we additionally report *saccade latencies*, which were defined exclusively as the time interval between target onset and the beginning of detected saccades.

The duration of a visually guided eye movement was defined as the time interval between the start and the end of a gaze shift. In the present study, this duration might be comprised of drifts, one or multiple saccades, or a combination of drifts and saccades. Thus, the eye movement duration does not necessarily reflect the duration of a single drift or saccade, as is usually reported in the eye movement literature. The duration of eye movements as reported in the present study indicates the time efficiency of eye movements from fixation to the visual target when they had been initiated.

## Saccade peak velocity

In order to obtain eye movement velocity, we used a moving window technique. A second-order polynomial was fitted to the gaze position data (in this case, to seven samples, with three to the left and three to the right of the central sample). The parameters of the fitted function allowed us to compute the velocity for the central point of the window (see Smeets & Hooge, 2003). *Saccade peak velocity* describes the largest instantaneous velocity within a saccade. If more than one saccade was detected in a trial, the saccade with the largest amplitude was chosen. *Saccade amplitude* refers to the Euclidean distance between the start- and endpoint of a detected saccade.

## Statistical analysis

Statistics were computed in R (R Core Team, 2020). To be able to quantify evidence for or against the two alternative hypotheses (difference between groups vs. no difference between groups) a Bayesian approach was adopted. The mean and variance of the mean for each variable in each group were estimated by a random intercept model fitted with the R package brms (Bürkner, 2017) and the probabilistic programming language Stan (Carpenter et al., 2017), using default brms estimation priors. Endpoint error, fixation stability, latency, duration, saccade peak velocity, amplitude, main sequence slope, and intercept were modeled as Student's *t*-distribution with variance and shape as free parameters. Values of eye movement success and saccade success were modeled as binomial distributions. Values of endpoint error, fixation stability, latency, and duration were log transformed prior to analysis. Posterior distributions are reported in terms of their mean and 95% highest density interval (HDI). Bayesian correlation analyses were performed in JASP (JASP Team, 2019), using default priors.

Hypothesis tests were performed by the R package bain (Gu, Hoijtink, Mulder, & van Lissa, 2019), which computes Bayes factors through the Savage–Dickey ratio by using a fraction of the information in the posterior distribution estimated in brms to specify the variance of the prior distribution (O'Hagan, 1995; Gu, Mulder, & Hoijtink, 2018). Unless otherwise described, hypothesis test results are reported as Bayes

| Parameter (unit) | Group | Mean estimate | 95% HDI | *BF* | ln(*BF*) |
|---|---|---|---|---|---|
| Eye movement success, % | CC | 0.84 | (0.74, 0.91) | — | — |
| | NC | 0.87 | (0.8, 0.92) | 0.17 | –1.772 |
| | DC | 0.93 | (0.89, 0.96) | 1.66 | 0.507 |
| | SC | 0.95 | (0.92, 0.97) | 14 | 2.629 |
| Saccade success, % | CC | 0.79 | (0.68, 0.88) | — | — |
| | NC | 0.87 | (0.81, 0.92) | 0.44 | –0.821 |
| | DC | 0.94 | (0.91, 0.96) | 95 | 4.556 |
| | SC | 0.97 | (0.95, 0.98) | $4.2 \times 10^4$ | 10.645 |
| Latency, ms | CC | 220 | (199, 244) | — | — |
| | NC | 224 | (206, 244) | 0.15 | –1.897 |
| | DC | 250 | (232, 268) | 1.05 | 0.049 |
| | SC | 213 | (197, 230) | 0.17 | –1.772 |
| Saccade latency, ms | CC | 298 | (267, 333) | | |
| | NC | 272 | (248, 298) | 0.33 | –1.109 |
| | DC | 256 | (236, 277) | 1.59 | 0.464 |
| | SC | 208 | (189, 226) | $4.6 \times 10^4$ | 10.728 |
| Duration, ms | CC | 325 | (268, 385) | — | — |
| | NC | 296 | (249, 346) | 0.19 | –1.661 |
| | DC | 168 | (126, 212) | $1.0 \times 10^3$ | 6.914 |
| | SC | 152 | (105, 199) | $4.0 \times 10^3$ | 8.302 |
| Endpoint error, ° | CC | 1.44 | (1.12, 1.84) | — | — |
| | NC | 1.22 | (0.98, 1.5) | 0.24 | –1.427 |
| | DC | 0.75 | (0.63, 0.89) | 913 | 6.817 |
| | SC | 0.65 | (0.53, 0.78) | $4.1 \times 10^4$ | 10.628 |
| Saccade peak velocity, °/s | CC | 256 | (224, 288) | — | — |
| | NC | 339 | (312, 366) | 302 | 5.71 |
| | DC | 324 | (301, 347) | 48 | 3.865 |
| | SC | 367 | (341, 392) | $2.5 \times 10^5$ | 12.409 |
| Saccade amplitude, ° | CC | 7.99 | (7.33, 8.62) | — | — |
| | NC | 8.69 | (8.16, 9.21) | 0.6 | –0.511 |
| | DC | 9.6 | (9.17, 10.04) | 630 | 6.445 |
| | SC | 9.54 | (9.07, 10.01) | 217 | 5.378 |

Table 2. Statistical results and parameter estimates. *Notes*: *BF*s indicate evidence in favor of a difference between groups relative to no difference between groups. *BF*s reflect comparisons of the CC group with each of the other three groups. HDI represents the 95% highest density interval of the posterior distribution of group means.

factors (*BF*s) in favor of the undirected hypothesis of a difference between groups. Bayes factors here indicate how much more probable it is that there is a difference between groups than that there is none, given the observed data. $BF < 1$ indicates that it is more probable that there is no difference between the groups, and $BF > 1$ indicates that it is more probable that there is a difference between groups.

In line with Jeffreys (1961), we evaluated *BF*s greater than 3 as evidence worth considering for a relevant group difference, and *BF*s smaller than 0.33 as evidence for no group difference; we refer to comparisons with a *BF* between 0.33 and 3 as inconclusive marginal evidence, and indicate the direction of the trend. *BF*s > 10 were rounded to the nearest digit. In addition, *BF*s were reported in ln(*BF*), the natural logarithm of the Bayes factor in Table 2.

All data, analysis, and stimulus scripts will be made available on reasonable request by the corresponding author.

# Results

## Success and accuracy of visually guided eye movements

All subjects in all groups were able to perform visually guided eye movements, albeit with considerable differences in eye movement trajectory. Figure 1 displays

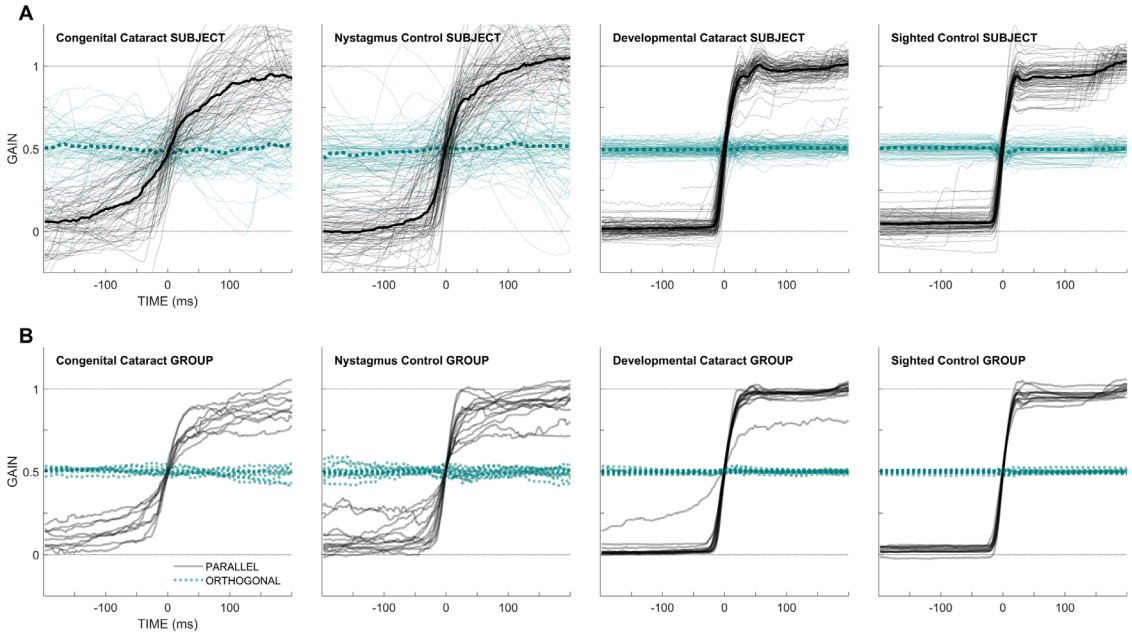


Figure 2. Eye movement traces in the congenital cataract reversal group, the developmental cataract reversal group, a group of participants with nystagmus, and in normally sighted controls. Eye movement traces start 200 ms before and end 200 ms after a detected midpoint in a trial and indicate gaze position after transformation into two components: displacement parallel (*gray solid lines*) and orthogonal (*cyan dotted lines*) to the axis between the fixation and the saccade target. Traces were normalized to the distance between the fixation and the saccade target, which are marked with dotted lines at positions 0 and 1, respectively. (A) Examples of data recorded in one individual subject of each group. Individual plots show position traces for all trials with a detectable midpoint (*thin lines*) and the corresponding median trace of a participant (median position at each time point; *thick lines*). Individual subject plots for each participant can be found in the Appendix (Figures A.5 to A.8). (B) Median eye position traces for each subject and component per group.

two example trials, one from a CC individual (Figures 1A–1D) and one from a SC individual (Figures 1E–1H) starting at the time point at which the target jumped from its previous position (the fixation target) to a new target position (the saccade target). SC individuals and all but one DC individuals consistently made typical rapid eye movements (saccades) to the saccade target (Figure 3B, 3F). In contrast, eye movement trajectories in the CC and NC individuals were comprised, as expected, of saccades and slow drifts toward the target. Extensive nystagmus during task performance emerged in all CC individuals but in only one of 16 individuals in the DC group.

The eye movement signal can be transformed into two components: displacement parallel to the axis between fixation target and saccade target and displacement orthogonal to this axis. Plots of the parallel (gray solid lines in Figure 2) and orthogonal (cyan dotted lines in Figure 2) component traces 200 ms before until 200 ms after the eye movement midpoint (see Detection of visually guided eye movements section) are displayed in Figure 2A for one example subject from each group and in Figure 2B for all subjects from each group. All subjects predominantly made eye movements along the parallel axis, indicating that they all were able to systematically perform eye movements from the fixation target to the saccade target, albeit with considerably variable trajectories in the CC and NC groups. The variability in the orthogonal component in the CC and NC groups reflects eye movements unrelated to the intended gaze shift, such as nystagmus.

CC individuals performed successful visually guided eye movements in 84% of the trials (95% HDI, 74–91; range, 60–94), which was lower compared to both the success rate of the SC group ($BF = 14$; see Table 2 for detailed statistical estimates of this and following measures). The comparison to the DC group was inconclusive, with marginal evidence indicating a lower success rate in the CC group ($BF = 1.66$). Importantly, the success rate of the CC group was, however, similar to that of the NC group ($BF = 0.14$). Of these successful visually guided eye movements, 79% contained at least one saccade in the CC group (95% HDI, 68–88; range, 66–91) (Figure 3B), which was a lower rate than found in the SC group ($BF = 4.2 \times 10^4$) and the DC group ($BF = 95$). The comparison to the NC group was inconclusive, with marginal evidence indicating that the proportion of saccades in successful visually guided eye movements was similar between the CC group and the NC group ($BF = 0.44$). Correlations in the CC group

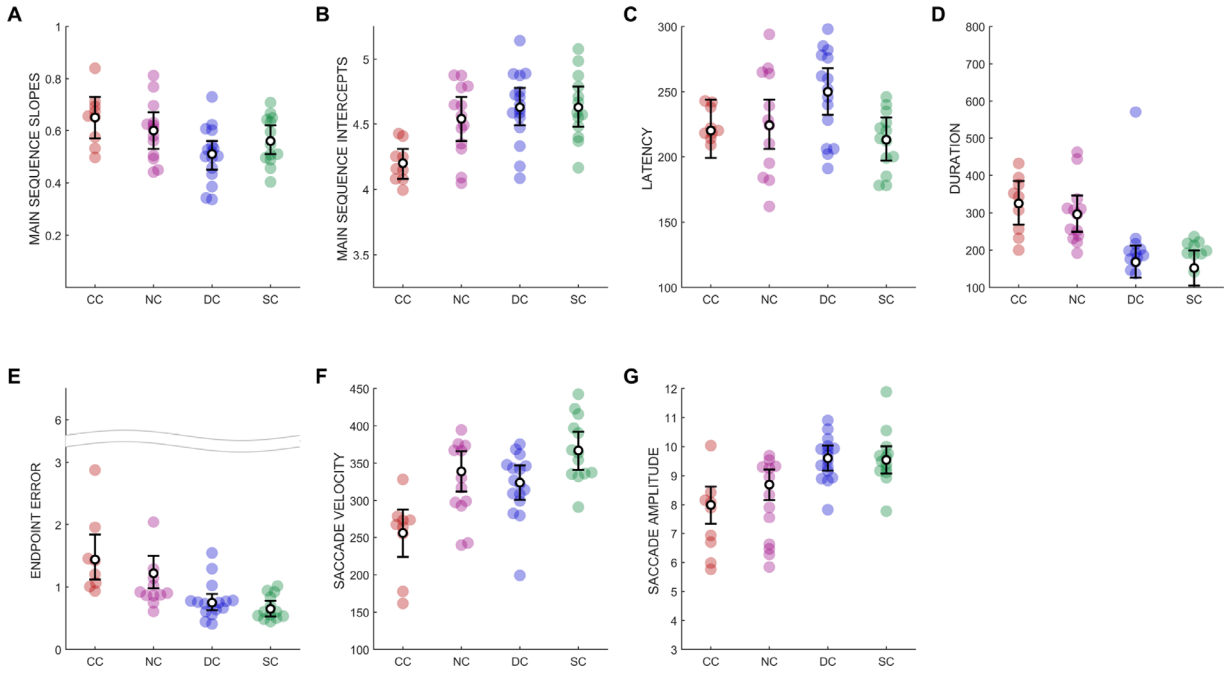


Figure 3. Eye movement characteristics for all groups. *Colored, filled circles* represent individual subject medians; *black, open circles* represent estimated posterior distribution means per group, and bars represent 95% HDIs. (A) Percentage of successful visually guided eye movements. (B) Percentage of successful eye movements containing a saccade. (C) Eye movement latencies. (D) Eye movement durations. (E) Endpoint errors. (F) Saccade peak velocities. (G) Saccade amplitudes.

between the proportion of successful visually guided eye movements and duration of blindness ($r = 0.24$, $BF = 0.49$) or duration of visual experience since surgery ($r = –0.25$, $BF = 0.49$) were inconclusive with marginal evidence pointing towards an absence of a correlation (see Figure A.10 in the Appendix).

The accuracy of visually guided eye movements was assessed as endpoint error, which represents the position of gaze at the end of an eye movement. The final endpoint error of successful visually guided eye movements in the CC group was 1.44 visual degrees on average (95% HDI, 1.12–1.84) and similar to the average endpoint error of the NC group ($BF = 0.24$; see Table 2 for detailed statistical results). The average endpoint error of the CC group was larger than in the SC group ($BF = 4.1 \times 10^4$) and in the DC group ($BF = 913$) (Figure 3E). Correlations in the CC group between endpoint error and duration of blindness ($r = 0.33$, $BF = 0.41$) or duration of visual experience since surgery ($r = –0.03$, $BF = 0.56$) were inconclusive, with marginal evidence pointing toward an absence of a correlation.

In summary, CC individuals were able to successfully perform visually guided eye movements and achieved an astonishing accuracy. Lower success rates and lower eye movement accuracy in this group could be accounted for by the pathological nystagmus characterizing eye movements in CC individuals.

## Latency, duration, and velocity of visually guided movements

Next we evaluated the timing (initiation time, duration, and velocity) of visually guided eye movements in CC individuals. The latency to initiate an eye movement indicates the processing time required to disengage from the current fixation target, program an eye movement, and initiate the motor commands. The duration of a visually guided eye movement evaluates the time efficiency of movement execution. For example, the duration of eye movements is expected to be longer, if less efficient movements, such as drifts, emerge or when pathological eye movements, such as nystagmus, superimpose the visually guided eye movement. Finally, the peak velocity of saccades (when present) was compared across groups.

In the CC group, the latency to initiate a visually guided eye movement was on average 220 ms (95% HDI, 199–244; see Figure 3C and Table 2) and was similar to the average latencies in the NC group ($BF = 0.15$) and the SC group ($BF = 0.17$). A comparison of latencies between the CC and DC groups was inconclusive ($BF = 1.05$). The latencies analyzed here included both visually guided eye movements starting with a saccade and visually guided eye movements starting with a drift. For a better comparison to previous studies (Dunn, Margrain, Woodhouse, & Erichsen, 2015;

Huurneman, Boonstra, & Goossens, 2016; Worfolk & Abadi, 1991) we additionally computed the latency to the first saccade within a visually guided movement (when present). In the CC group, the latency to initiate a visually guided saccade was on average 298 ms (95% HDI, 267–333; see Table 2 for all groups estimates), which was longer than the average saccade latency in the SC group ($BF = 4.6 \times 10^4$). The comparison of the CC group with the DC group ($BF = 1.59$) was inconclusive, with marginal evidence indicating lower saccade latencies in the CC group. Saccade latencies were similar between the CC and NC groups ($BF = 0.33$).

The duration of visually guided eye movements was longer in the CC group than in the SC group ($BF = 4.0 \times 10^3$) and in the DC group ($BF = 1.0 \times 10^3$) but was similar between the CC and NC groups ($BF = 0.19$) (Figure 3D).

Saccade peak velocities in the CC group were lower than in all other groups (Figure 3G); that is, they were lower than in the SC group ($BF = 2.5 \times 10^5$), the DC group ($BF = 48$), and the NC group ($BF = 302$). As saccade peak velocity depends on the amplitude of a saccade, lower saccade peak velocities might be a consequence of hypometric saccades in CC individuals. In fact, saccade amplitude was lower in the CC group than in the SC group ($BF = 217$) and in the DC group ($BF = 630$) (Figure 3H). The comparison of average saccade amplitudes between the CC and NC groups was inconclusive, with marginal evidence indicating no difference between these groups ($BF = 0.6$). To further clarify this result, we analyzed the saccade main sequence (Bahill et al., 1975). Because log–log space saccade amplitude and saccade peak velocities are typically linearly related, we fitted linear regression lines relating saccade amplitude and peak velocity for each subject in the CC and NC groups. The mean of the slope coefficients was similar in the CC and NC groups ($BF = 0.23$), but the mean of the intercept coefficients was lower in the CC group than in the NC group ($BF = 39$). Thus, lower saccade velocities in the CC group cannot be accounted for by lower saccade amplitudes overall, as peak velocities were lower for the entire range of amplitudes (see also Figure A.9 in the Appendix).

In summary, CC individuals were able to initiate and complete eye movements to visual targets as fast as NC and SC controls. By contrast, the peak velocity of saccades (when present) in the CC group was lower than in all other groups, including the NC group.

## Discussion

In the present study, we investigated the presence and characteristics of visually guided eye movements in individuals with a history of congenital, dense, total, bilateral cataracts (CC group) which were later removed at different times in their lives. Visually guided eye movements in CC individuals were compared to those of normally sighted controls (SC group) and to eye movements of a group of developmental cataract individuals (DC group). An additional group of individuals who suffered nystagmus but who did not have a history of congenital loss of pattern vision was tested as an additional control group (NC group) to control for the nystagmus prevalent in all individuals with a history of congenital cataracts. All CC individuals were able to execute visually guided eye movements. Except for a lower saccade velocity, differences between the CC and the SC groups in eye movement success, latency, duration, endpoint error, and saccade amplitude could be accounted for by the nystagmus superimposing visually guided eye movements. To the best of our knowledge, the present data provide the first quantitative description of visually guided eye movements following long-lasting visual deprivation (more than 3 years) from birth and demonstrate a remarkable ability to perform visually guided movements in this group. This result contrasts with the often extensive and prevailing visual deficits in CC individuals. These findings suggest that visual impairments are likely not predominantly linked to aberrant basic visually guided eye movements.

Commonly used calibration and analysis routines designed for normally sighted individuals are not well suited for individuals with nystagmus. In infantile nystagmus, drift and saccades alternate in a highly heterogeneous fashion and often vary extensively both within and between individuals. Recently, a calibration method has been suggested based on the automatic extraction of foveation periods according to relative velocity within the nystagmus slow phase periods, outlier correction, and waveform shape comparison (Dunn, Harris, Ennis, Margrain, Woodhouse, McIlreavy, & Erichsen, 2019; Rosengren, Nyström, Hammar, & Stridh, 2020). In the present study, we propose a different approach, one that defines the eye movements' start- and endpoints independent of the shape and uniformity of nystagmus waveforms. Based on this definition and using a cross-validation approach, calibration coefficients were iteratively optimized to minimize the endpoint error over the full set of experimental data, rather than relying on a short, initial calibration procedure. Our method resulted in a mean deviation of endpoint error estimates of no more than 1° of visual angle. Moreover, we successfully adjusted and validated the new method in the SC group by comparing the classification of start- and endpoints of the new and the standard method offered by the eye tracker software.

Previous studies have not systematically assessed individual eye movement characteristics of visually guided eye movements in CC individuals. Some qualitative reports described gaze following behavior in a child after cataract surgery (Chen et al., 2016).

Moreover, clinical studies investigating eye movements in CC individuals have exclusively focused on a description of nystagmus waveform characteristics (Abadi, 2002; Abadi, Forster, & Lloyd, 2006; Birch, Wang, Felius, Stager, & Hertle, 2012), without assessing the presence or quantitative characteristics of visually guided eye movements. For NC individuals, it has been shown that nystagmus does not prevent visually guided eye movements (e.g., Collewijn, Apkarian, & Spekreijse, 1985; Kommerell, 1986; Yee, Wong, Baloh, & Honrubia, 1976). However, only a few studies have reported quantitative metrics such as saccade latency and amplitude (Dunn et al., 2015; Huurneman et al., 2016; Worfolk & Abadi, 1991) in individuals with nystagmus. Two of these studies found longer saccade latencies in NC individuals compared to healthy controls (Dunn et al., 2015; Huurneman et al., 2016). The present study replicated this finding for individuals of the NC group and extended it to CC individuals. Importantly, it has been shown that individuals with infantile nystagmus seem to be able to strategically adapt their nystagmus slow and fast phases, using saccades when targets were located in the direction of the nystagmus quick phase and using drifts when the target was located in the opposite direction (Kommerell, 1986; Worfolk & Abadi, 1991). This pattern of eye movements implies that drifts need to be considered as a crucial element of visually guided eye movements in individuals with infantile nystagmus. Therefore, we suggest that an estimate of latency must take into account any type of eye movement in the direction of the target in order to be a valid estimate of eye movement initiation time for individuals with nystagmus. With such a latency measure we did not find a difference between the NC and SC groups, nor did we find evidence for a difference between the CC and SC groups, suggesting that visually guided eye movements in CC individuals were programmed as fast as in normally sighted individuals despite their nystagmus.

We demonstrated further that visually guided eye movements in CC individuals were remarkably accurate, despite their nystagmus and their overall low visual acuity. The endpoint error of the CC group was indistinguishable from the endpoint error of the NC group, and on average only 0.79° larger than in normally sighted controls. This present observation in CC individuals is in agreement with a previous report indicating that individuals with nystagmus can accurately fixate visual targets (Dell'Osso, Van der Steen, Steinman, & Coleewijn, 1992).

CC individuals were investigated between 1 and 19 years after surgery. In order to maximize the likelihood that CC individuals indeed suffered a complete loss of pattern vision at birth, we employed multiple inclusion criteria, which were only met by a subgroup of the congenital cataract individuals treated at the LV Prasad Eye Institute. These criteria included family history and reports, lack of fundus visibility, strabismus, the presence of nystagmus, partially absorbed cataracts, and the results of the presurgery vision assessment. Moreover, all CC individuals still suffered marked visual impairments after cataract removal surgery. A limitation of studies in congenital cataract reversal individuals is that, although highly likely, there is no absolute guarantee that all participants had dense and total cataracts at birth. Thus, the most conservative conclusion would be that visually guided eye movements depend less on good visual capacities at birth than on a number of other visual functions (Ganesh, Arora, Sethi, Gandhi, Kalia, Chatterjee, & Sinha, 2014; Lewis & Maurer, 2005).

We can only speculate on how CC individuals achieve the impressive ability to execute visually guided eye movements. Multiple, parallel, subcortical, and cortical pathways are involved in oculomotor control (Lynch & Tian, 2006; Pierrot-Deseilligny, Milea, & Müri, 2004). Thus, visually guided eye movements of CC individuals could be mediated by an experience-independent development or recovery of either subcortical and/or cortical pathways. Overt orienting to visual stimuli as measured in the present study can be subcortically generated through the retinocollicular pathway. In fact, the subcortical pathway has for a long time been considered to be sufficient for the generation of visually guided saccades, as non-human animal studies have observed visually guided eye movements even after damaging occipital, parietal and frontal cortex (Humphrey, 1974; Schiller, True, & Conway, 1980; Schneider, 1969; Sprague, 1966; Trevathe, 1968). Moreover, the retinocortical pathway of primates is known to be highly mature at birth (Stein, 1984; Qu, Zhou, Zhu, Cheng, Ashwell, & Lu, 2006; Wallace, McHaffie, & Stein, 1997). It has been hypothesized that in human infants, during the first months of life, visually guided orienting is largely subcortically mediated. By contrast, cortical systems have a more protracted development and are thought to begin guiding visual behavior only later (Bronson, 1974; Johnson, 1990). In human adults, only lesions in the parietal eye field or of parietal projections to the superior colliculus have consistently been associated with deficits in the production of visually guided eye movements (Gaymard, Lynch, Ploner, Condy, & Rivaud-Péchoux, 2003; Müri & Nyffeler, 2008; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991). Electrophysiological recordings in visually deprived monkeys' Brodmann area 7 did not find a considerable recovery of visual responses at the end and 1 year after the end of the visual deprivation (Carlson, Pertovaara, & Tanila, 1987; Hyvärinen et al., 1981). Area 7 in monkeys is a multisensory parietal region adjacent to the lateral intraparietal area, which is thought to be the homolog of the human parietal eye field. Therefore, we speculate that the CC individuals' visually guided

eye movements might be predominantly mediated by retinocollicular mechanisms. In fact, other tasks that have been associated with the superior colliculus, such as multisensory redundancy effects in simple target detection tasks, have been found to be unimpaired in CC individuals (de Heering, Dormal, Pelland, Lewis, Maurer, & Collignon, 2016; Putzar, Gondan, & Röder, 2012). Future studies must implement more complex active vision tasks in order to isolate the functionality of cortical eye movement related pathways.

Despite the finding of unimpaired (compared the NC individuals) major parameters of visually guided eye movements, the peak velocity of saccades was found to be lower in the CC group than in the NC group; that is, the lower velocity could not be explained by nystagmus. It has been demonstrated that, in agreement with the dual coding hypothesis (Sparks & Mays, 1990), both saccade trajectories and eye movement kinematics such as velocity are coded by the superior colliculus (Goossens & van Opstal, 2006; Goossens & van Opstal, 2012; Smalianchuk, Jagadisan, & Gandhi, 2018). Studies in visually deprived cats observed a lower number of visually responsive cells and a lower response rate of visual neurons (Rauschecker & Harris, 1983). Thus, it might be speculated that the lower velocity of the visually guided eye movements of CC individuals might be related to changes in the response rate of visual collicular neurons, whereas the high accuracy of their visually guided eye movements might be related to the activation of a preserved topological organization of the visually responsive neurons. In fact, non-human animal studies have found a typical topography and typical receptive field sizes in the superior colliculus of visually deprived animals at the end of the deprivation period (King & Carlile, 1993; Vidyasagar, 1978). In accord with this finding a recent study found a retinotopic organization and typical latency of the first visual response (Sourav et al., 2018).

In summary, the present study demonstrated a remarkable ability of cataract reversal individuals with a history of long-lasting loss of pattern vision from birth to execute visually guided eye movements despite suffering nystagmus.

*Keywords: eye movements, sight recovery, developmental neuroplasticity, sensitive periods*

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# Appendix

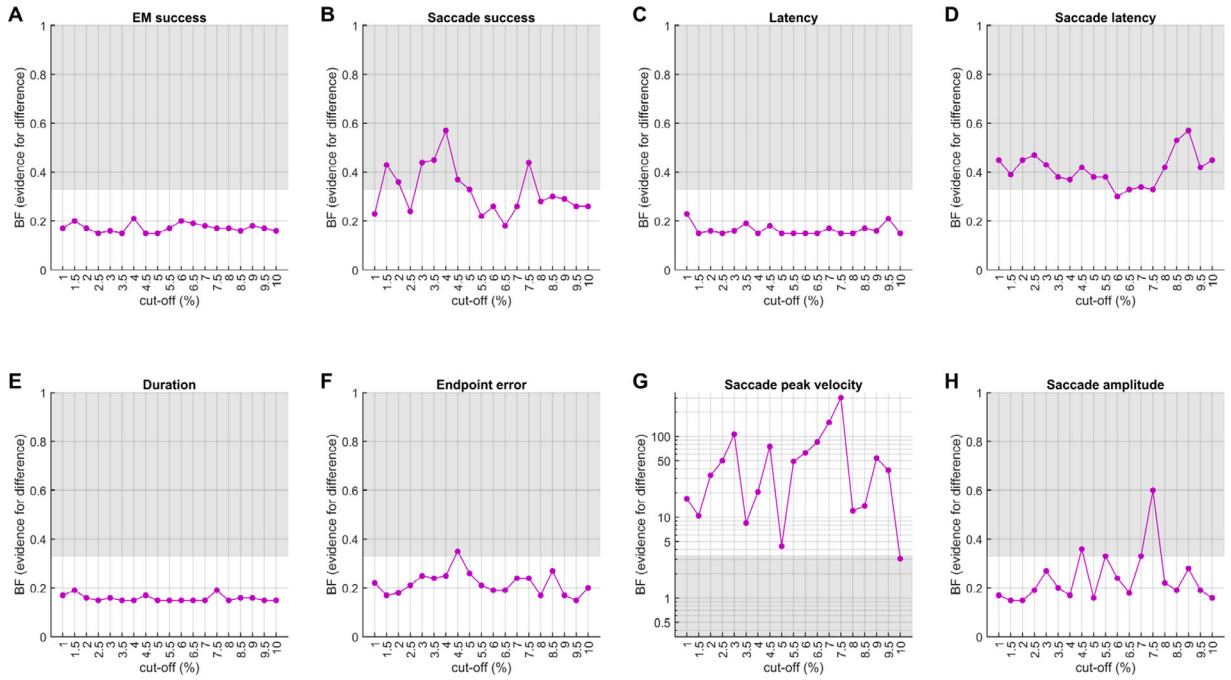


Figure A.1. *BF*s indicating evidence for a difference in eye movement characteristics (see Figure 3) between the CC and NC groups for 19 different cutoff values implemented in the classification algorithm (see Methods section). *Gray shaded areas* indicate *BF*s between 0.33 and 3, which represent inconclusive evidence.

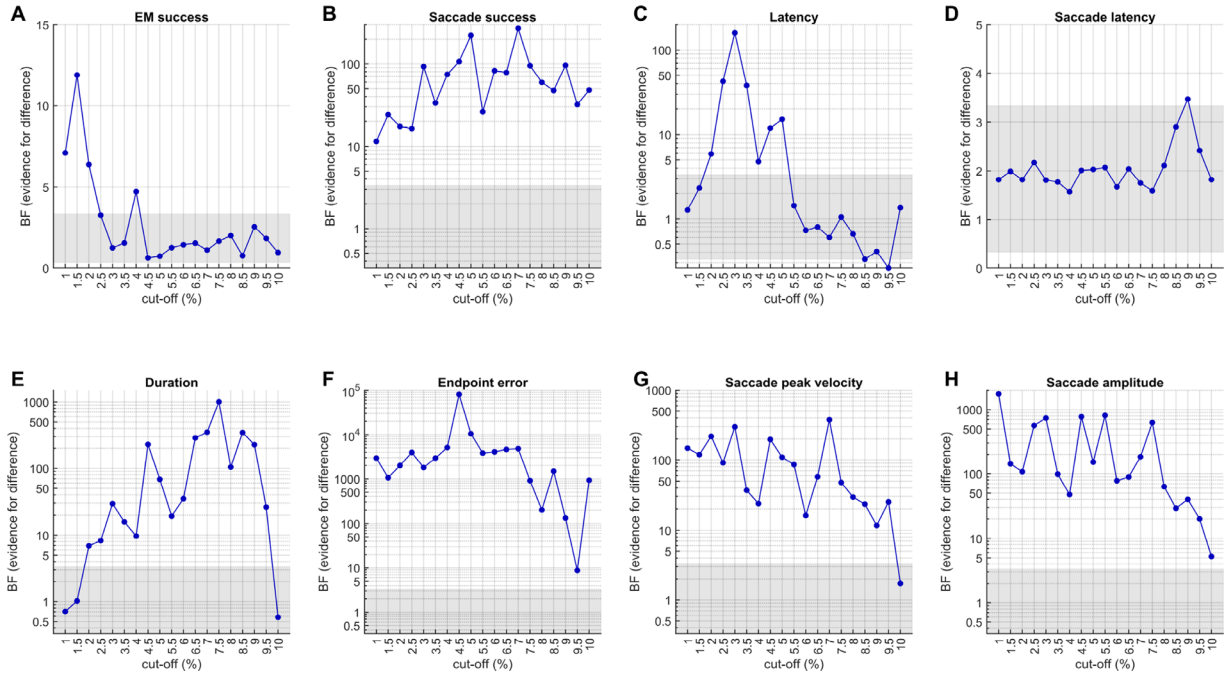


Figure A.2. *BF*s indicating evidence for a difference in eye movement characteristics (see Figure 3) between the CC and DC groups for 19 different cutoff values underlying the classification algorithm (see Methods section). *Gray shaded areas* indicate *BF*s between 0.33 and 3, which represent insufficient evidence.

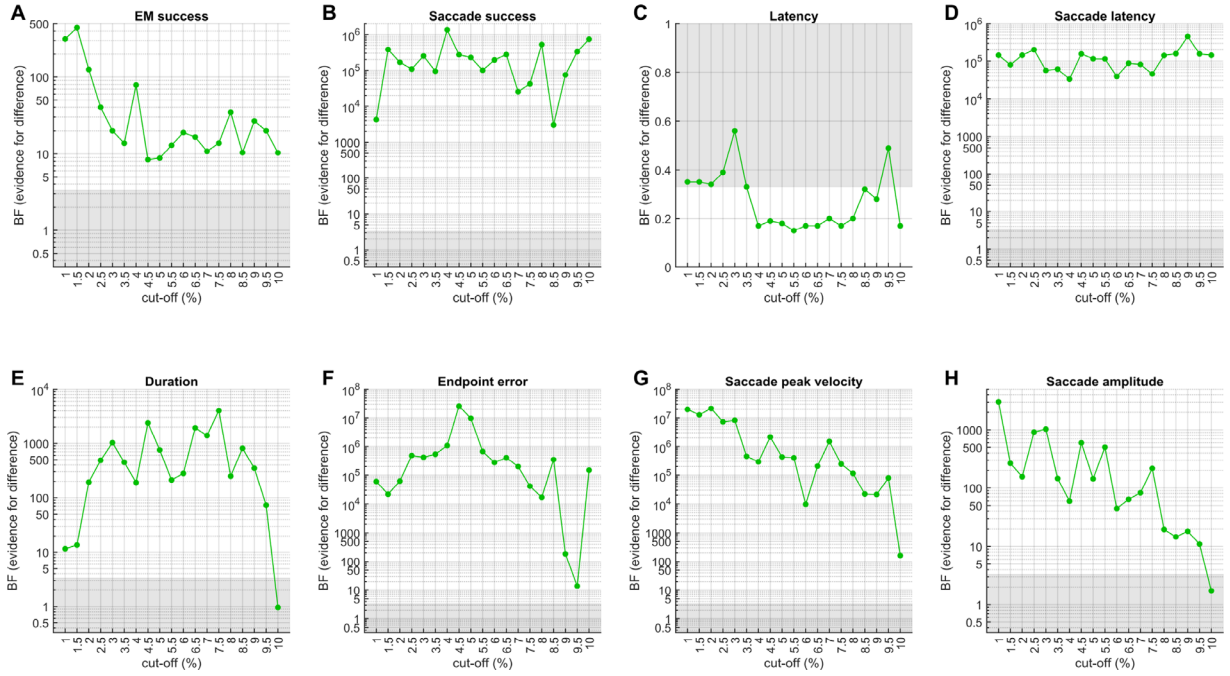


Figure A.3. *BF*s indicating evidence for a difference in eye movement characteristics (see Figure 3) between the CC and SC groups for 19 different cutoff values underlying the classification algorithm (see Methods section). *Gray shaded areas* indicate *BF*s between 0.33 and 3, which represent insufficient evidence.

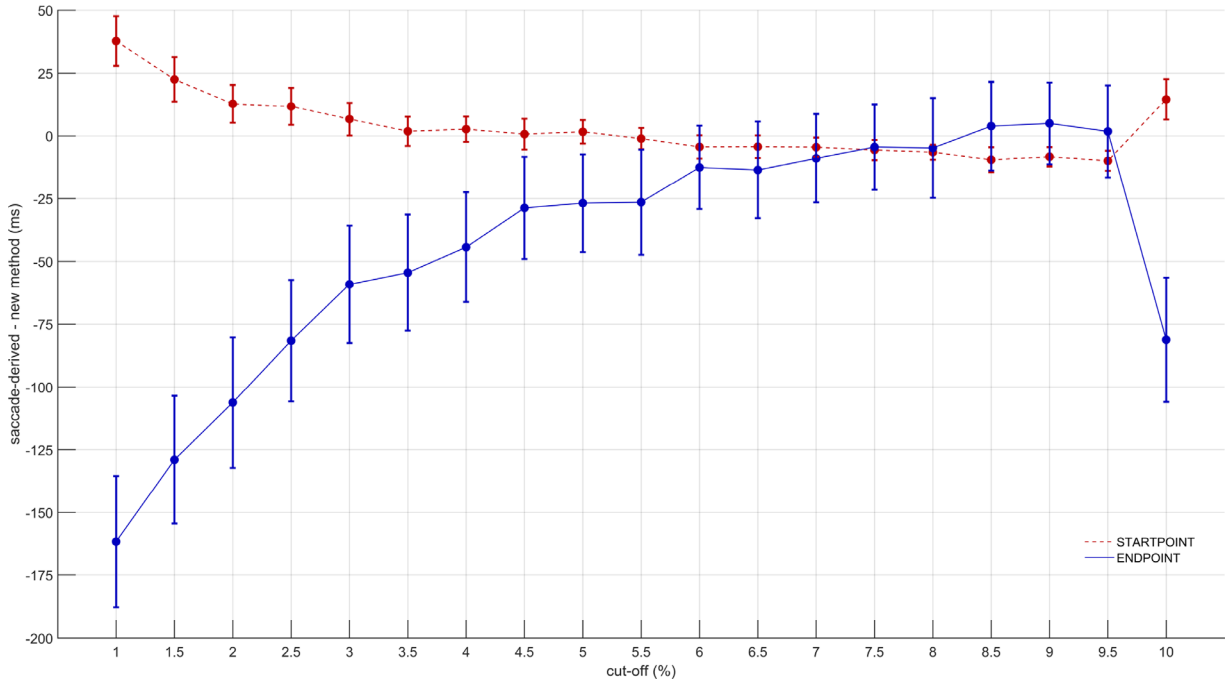


Figure A.4. Differences between start- and endpoints defined by the eye tracker-based method (saccade-derived method) versus the newly suggested method in the sighted control group for 19 different cutoff values underlying the classification algorithm (see Methods section). Positive values indicate that the new method estimated start- and endpoints earlier than the saccade-derived method. Error bars indicate SEM. At a cutoff value of 7.5%, the standard and new methods matched best.

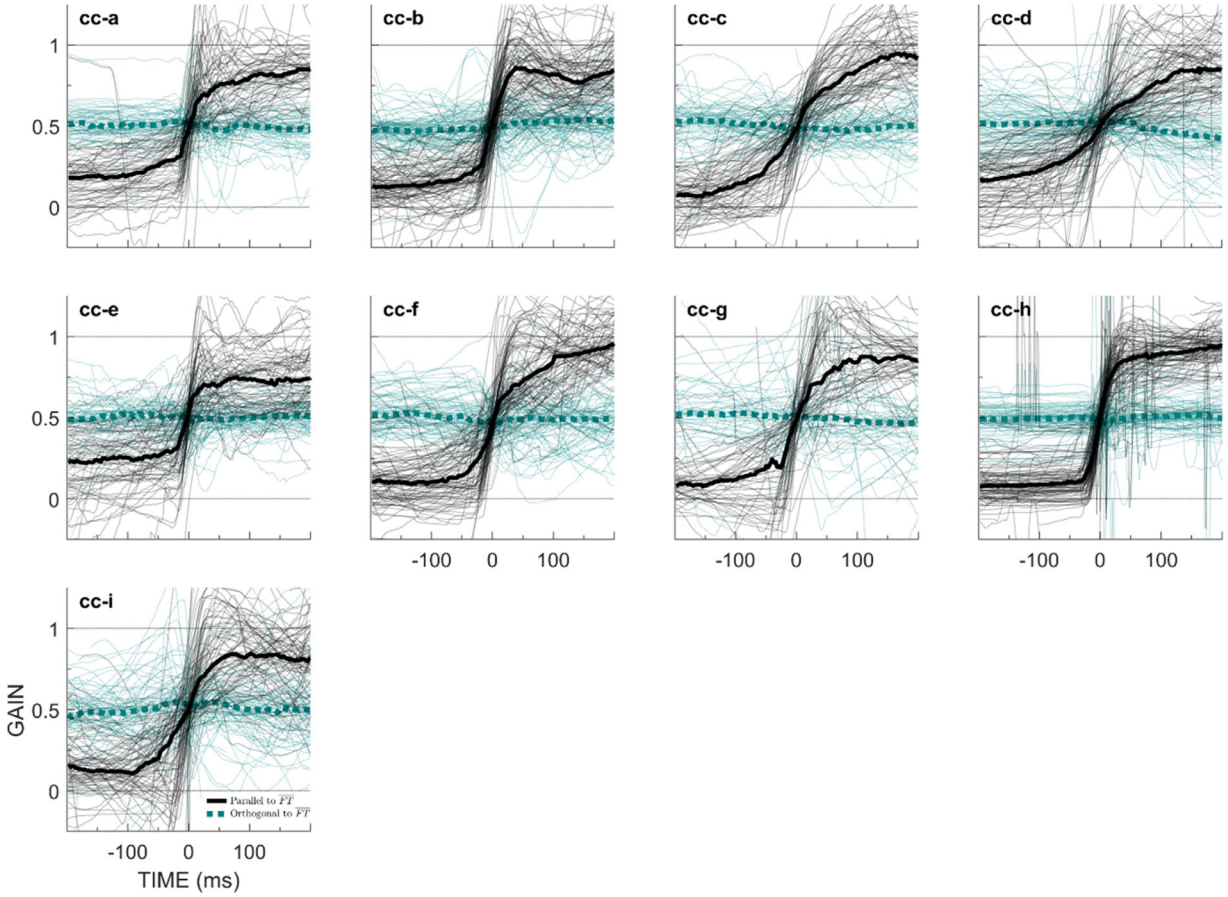


Figure A.5. Eye movement traces for each individual in the congenital cataract reversal group. Eye movement traces started 200 ms before and ended 200 ms after a detected midpoint and indicate gaze position after transformation into two components: displacement parallel (*gray solid lines*) and orthogonal (*cyan dotted lines*) to the axis between the fixation target and saccade target. Traces were centered on the eye movement midpoint of each trial and were normalized to the distance between fixation target and saccade target. Horizontal dotted lines represent the normalized fixation target (0) and saccade target position (1). Individual plots show position traces for all trials with a detectable midpoint (thin lines) and the corresponding median trace of a participant (median position at each time point; thick lines). See also Figure 2.

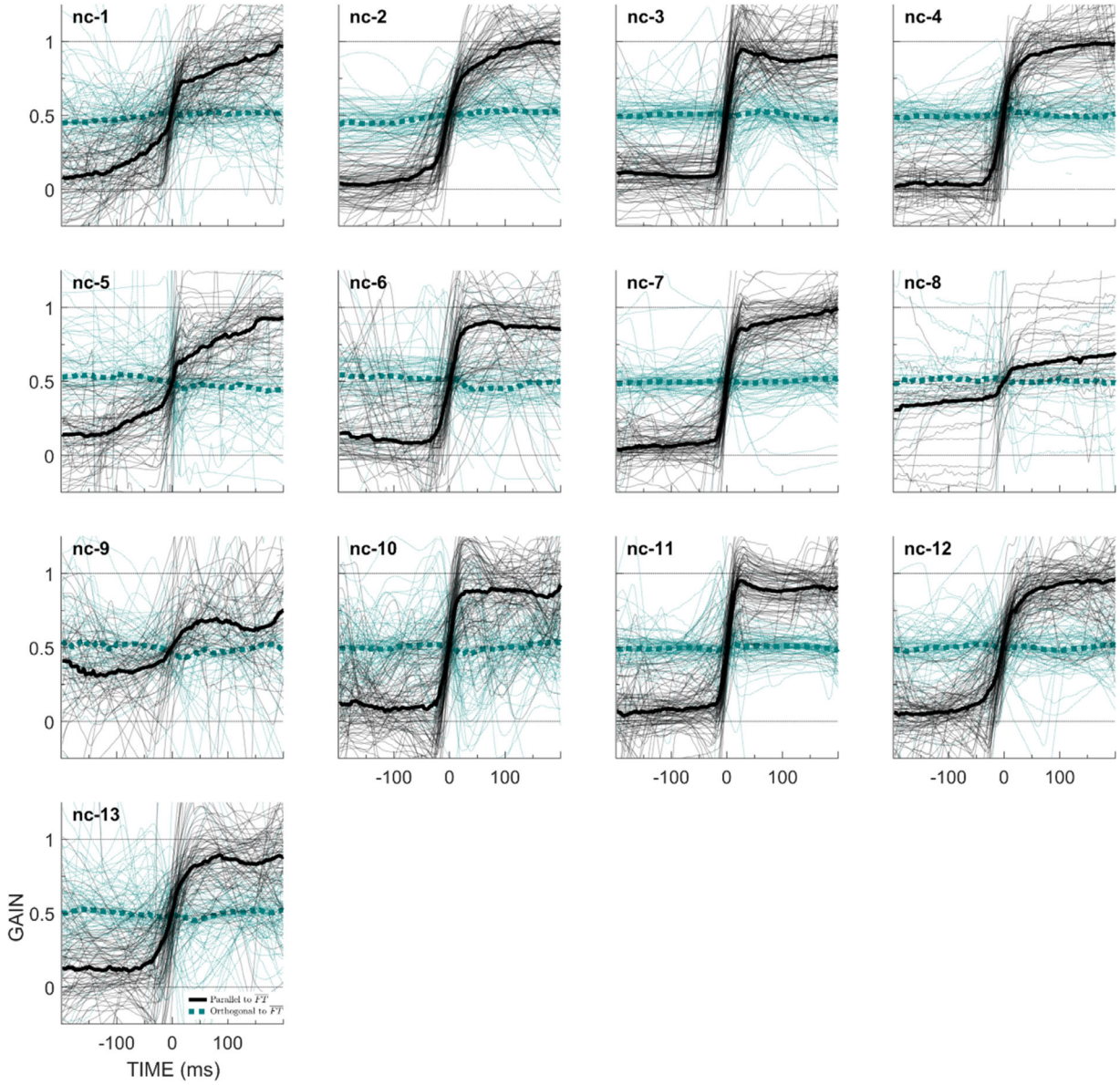


Figure A.6. Eye movement traces for each individual in the nystagmus group. See also Figure A.5 and Figure 2.

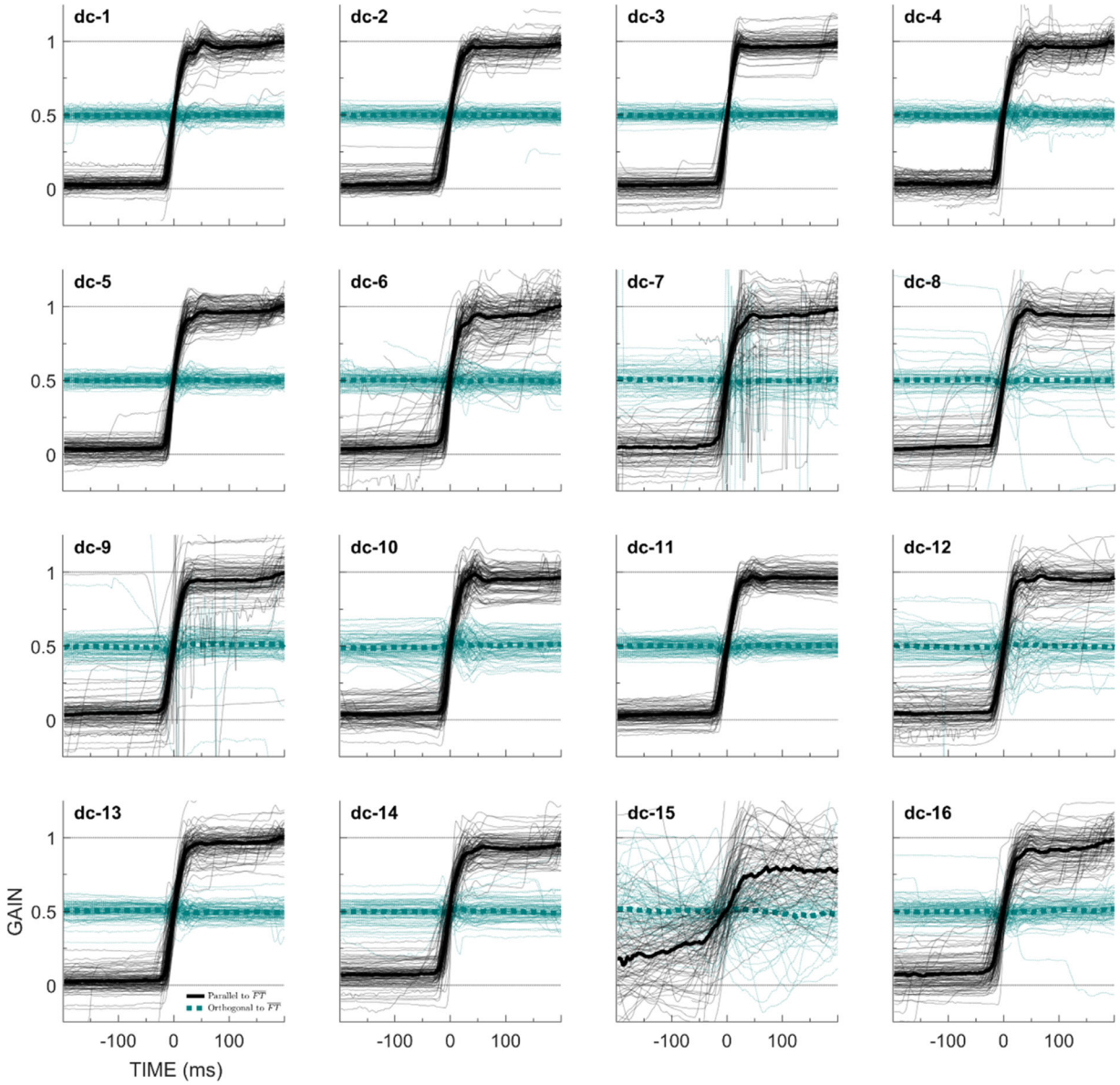


Figure A.7. Eye movement traces for each individual in the developmental cataract reversal group. See also Figure A.5 and Figure 2.

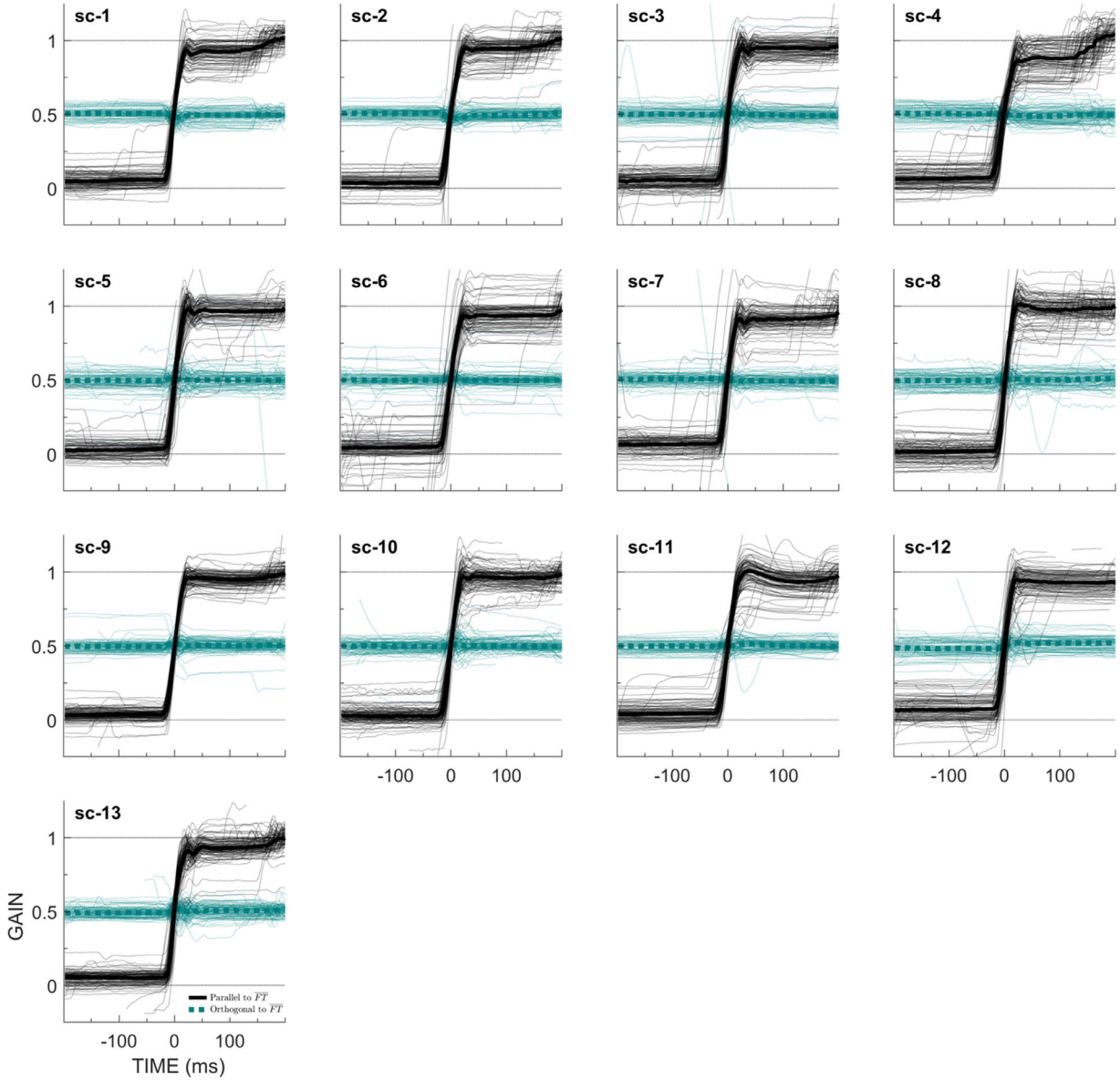


Figure A.8. Eye movement traces for each individual in the normally sighted group. See also Figure A.5 and Figure 2.

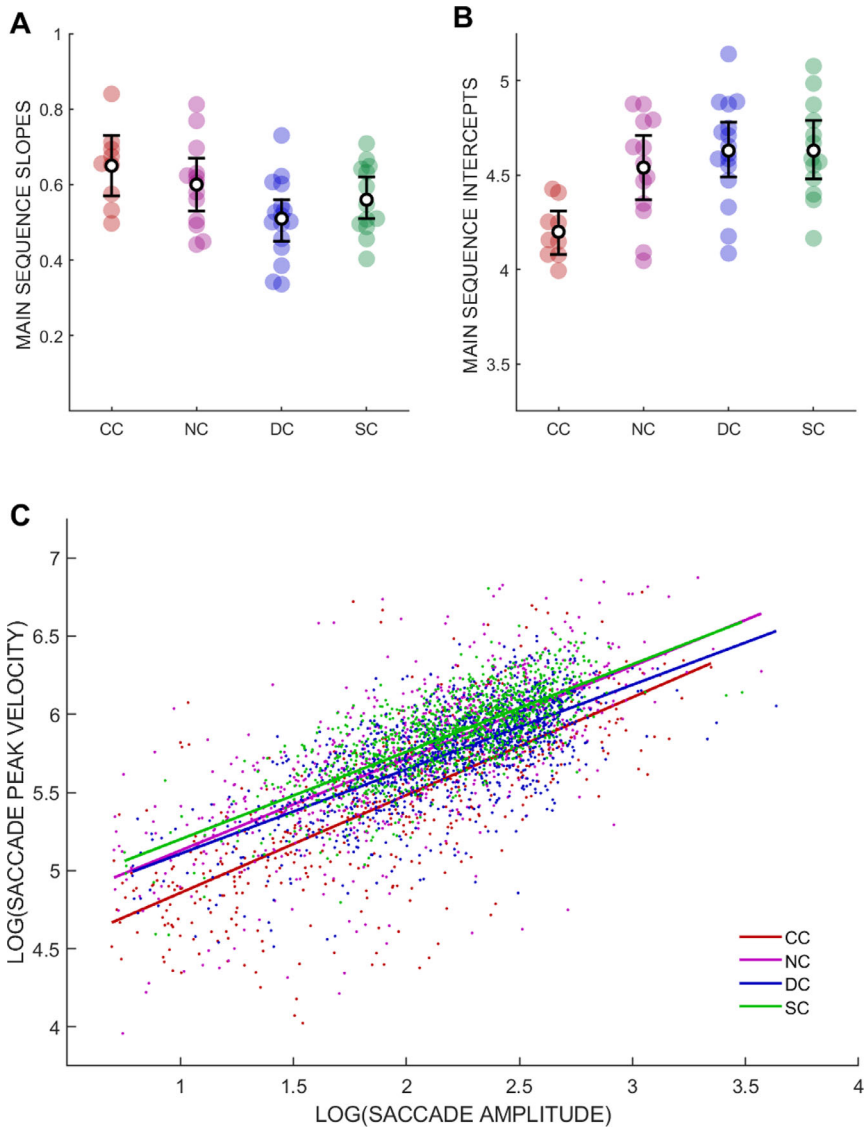


Figure A.9. Results of the saccade main sequence analysis. (A) Slopes. (B) Intercepts. *Colored, filled circles* represent individual subject values; *black, open circles* represent estimated posterior distribution means per group; and *bars* represent 95% highest density intervals. (C) Visual display of linear regression fits on all saccades per group.

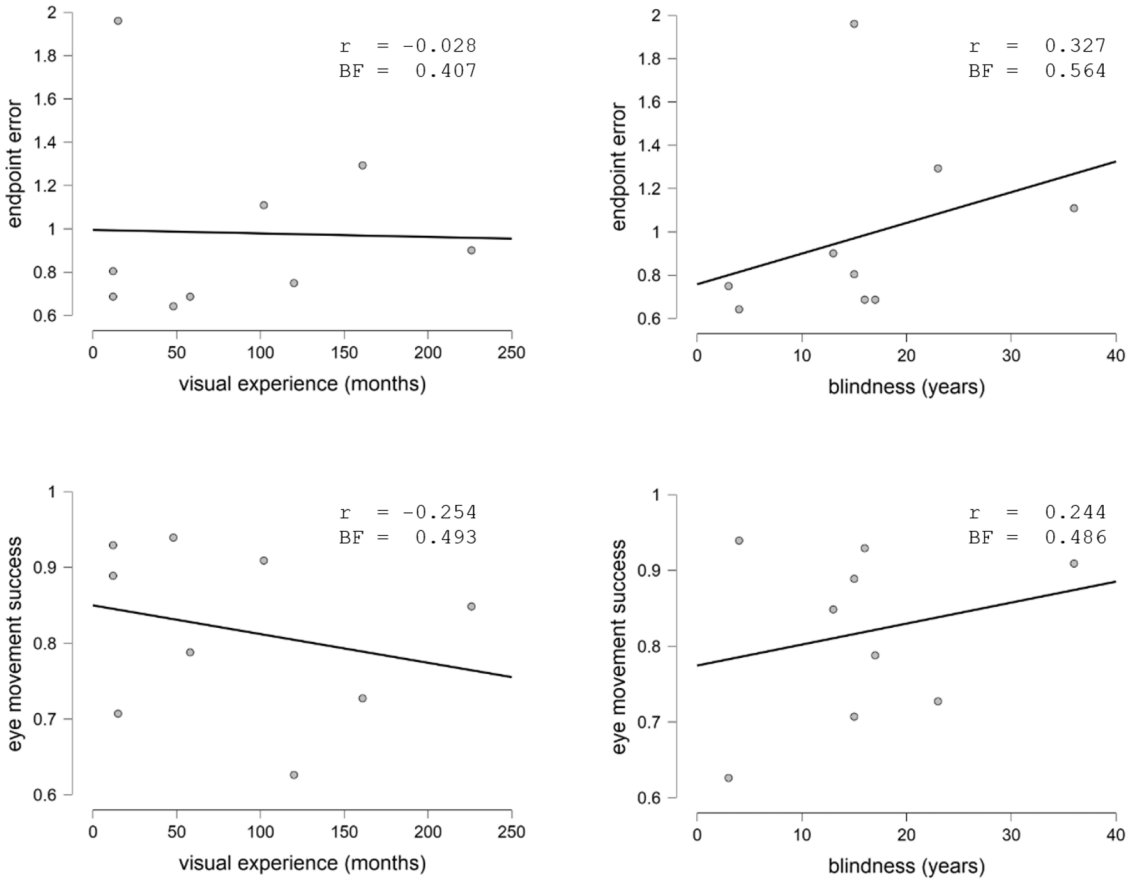


Figure A.10. Correlations among duration of visual experience, duration of blindness, endpoint error, and eye movement success.