Adaptation to Laterally Displacing Prisms in Anisometropic Amblyopia

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PURPOSE. Using visual feedback to modify sensorimotor output in response to changes in the external environment is essential for daily function. Prism adaptation is a well-established experimental paradigm to quantify sensorimotor adaptation; that is, how the sensorimotor system adapts to an optically-altered visuospatial environment. Amblyopia is a neurodevelopmental disorder characterized by spatiotemporal deficits in vision that impacts manual and oculomotor function. This study explored the effects of anisometropic amblyopia on prism adaptation.

METHODS. Eight participants with anisometropic amblyopia and 11 visually-normal adults, all right-handed, were tested. Participants pointed to visual targets and were presented with feedback of hand position near the terminus of limb movement in three blocks: baseline, adaptation, and deadaptation. Adaptation was induced by viewing with binocular 11.4° (20 prism diopter [PD]) left-shifting prisms. All tasks were performed during binocular viewing.

RESULTS. Participants with anisometropic amblyopia required significantly more trials (i.e., increased time constant) to adapt to prismatic optical displacement than visually-normal controls. During the rapid error correction phase of adaptation, people with anisometropic amblyopia also exhibited greater variance in motor output than visually-normal controls.

CONCLUSIONS. Amblyopia impacts on the ability to adapt the sensorimotor system to an optically-displaced visual environment. The increased time constant and greater variance in motor output during the rapid error correction phase of adaptation may indicate deficits in processing of visual information as a result of degraded spatiotemporal vision in amblyopia.

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optically using wedge prisms, the sensorimotor system adjusts to compensate for the new visuospatial environment. For example, when a person points to a visual target while viewing through wedge prisms that displace the visual world optically in the leftward direction, an initial pointing error to the left of the target occurs. Subsequently, as the person points repeatedly to the target over several trials in the presence of visual feedback, this pointing error decreases to the baseline level. When the prisms are removed, pointing error in the opposite direction occurs (i.e., to the right of the target position) before performance returns to baseline after repeated pointing in the presence of visual feedback. This is termed the negative aftereffect. Prism adaptation consists of two phases: The first phase is a rapid error correction phase, in which visually normal participants correct their motor errors iteratively over successive trials. This phase is thought to represent a high-level spatial remapping by the cognitive system to reduce performance error quickly. For instance, performance error can be reduced rapidly by using error information obtained from a previous pointing trial to guide the next trial (i.e., resetting the movement plan using feedback at the end of the trial), or by the strategic use of online visual feedback. The second phase is a plateau phase in which visually normal participants reach the same precision and accuracy as during baseline pointing. This phase is thought to be based on offline feedback mechanisms. In this study, we investigated the effects of anisometropic amblyopia on adaption to displacement of the visual world using wedge prisms, a well-established experimental paradigm for the study of sensorimotor adaptation.

**METHODS**

**Participants**

A total of 11 visually-normal controls (6 males, age = 29 ± 8 years) with normal or corrected-to-normal vision, and eight participants with anisometropic amblyopia (2 males, age = 32 ± 11 years, see Table), all right-handed, participated in this study. All participants were tested with their habitual optical correction. Amblyopia was defined as visual acuity of 20/25 or worse in the amblyopic eye (range, 20/25–20/100), 20/20 or better in the fellow eye, and an interocular difference of two or more chart lines. Anisometropic amblyopia was defined as amblyopia in the presence of an interocular refractive error difference of ≥ 1 diopter (D) in spherical or cylindrical power. All participants underwent a full assessment by a certified orthoptist, who assessed visual acuity (using the Early Treatment of Diabetic Retinopathy Study [ETDRS] chart), stereo acuity (using the Randot test), fusion (using Worth-4-Dot), and eye deviations (by the prism and cover tests). Exclusion criteria included any eye deviations on the cover test of ≥8 prism diop ters (PD) indicating a strabismic or mixed-mechanism amblyopia, ocular pathology resulting in reduced visual acuity, previous ocular surgery, or neurologic disease. Written consent was obtained to enroll in this study. This investigation was approved by the Research Ethics Board at The Hospital for Sick Children and conformed to the Declaration of Helsinki.

**Apparatus**

A large drafting table inclined at 45° was placed 46 cm in front of participants at eye level. Visual targets generated by a custom C++ program were displayed on a cathode ray tube monitor (Mitsubishi CRT Diamond Pro 2070SB-BK, viewing area of 20 × 15 inches; Cambridge Research Systems, Rochester, Kent, UK) at 120 Hz and reflected off a semi-silvered mirror. These small square white targets subtended a visual angle of 0.25° at a viewing distance of 46 cm, and were presented randomly along a single horizontal axis at either 0°, ±5°, or ±9° on a virtual plane. The targets were perceived as being coplanar with the table surface. The horizontal and vertical axes constituted an orthogonal basis for the virtual plane. The horizontal and vertical axes lay in the plane of the table, which was inclined 45° relative to the transverse plane of the participant. The vertical axis lay in the sagittal plane and the horizontal axis was parallel to the participant’s coronal plane (Fig. 1).

Reaching movements were recorded using an infrared motion capture system (Optotrak Certus, spatial accuracy 0.1 mm, resolution 0.01 mm, sampling frequency 200 Hz; Northern Digital, Waterloo, Canada). All pointing movements were made using the dominant right hand of the participant. The infrared marker used by the motion capture system to record finger position throughout the movement trajectory was secured to the right index finger. Visual feedback of finger position was presented to the participant in real-time as a 1.2° circle rendered on the CRT and reflected onto the semi-silvered mirror; thus, appearing on the same plane as the visual targets. This feedback was only presented near the terminus of movement, defined here as when the finger position reached 75% of the elevation-axis distance to the target from a consistent start position (indicated by a coin affixed to the surface of the drafting table that served as a tactile cue) in all three experimental blocks. Terminal feedback was chosen to reduce oblique and/or secondary movements especially during prism adaptation trials.

**Experimental Protocol**

The experimental procedure comprised 3 blocks: baseline (50 trials, Fig. 2A), adaptation (200 trials, Fig. 2B), and dead-
adaptation (70 trials, Fig. 2C). During all three experimental blocks, participants viewed binocularly while wearing goggle frames fitted with hinge-mounted 20 PD (~11.4°) left-shifting wedge prisms on top of permanently-affixed plano lenses in front of both eyes. The viewing angle for each eye through these lenses was approximately 90°, and, thus, encompassed the entire stimulus range, in both the prism and nonprism conditions. During the adaptation block, the prisms were swung down in front of the eyes. During the baseline and deadaptation blocks, only the plano lenses were in front of the eyes.

**Figure 1.** The experimental apparatus used for the prism adaptation protocol. Hand movements were tracked by an Optotak Certus. Visual targets were rendered on a CRT monitor and reflected off a semi-silvered mirror such that they appear coincident with the plane of the inclined drafting table. Hand position feedback appeared in real time as a small white circle when the right index finger position reached 75% of the elevation axis distance to the target.

**Figure 2.** (A) Baseline pointing task. (B) Prism adaptation task during the (i) rapid error correction phase and (ii) plateau phase. (C) Prism deadaptation task during the (i) early phase and (ii) plateau phase. Dotted arrows depict the expected trajectory of the hand. Gray square represents the veridical position of the target of interest.
eyes. This ensured that the goggles themselves had no impact on the effect of prism adaptation.

A force-sensitive resistor (FSR, 15 mm diameter; Tekscan, Boston, MA, USA) was used to initiate and end each trial, and was triggered by tapping it with the left index finger. It was placed outside the stimulus display area at the bottom left corner of the inclined table. The FSR signal was sent to the computer controlling the experimental protocol by the analog-to-digital converter of the ViSaGe stimulus generator system (Cambridge Research Systems) via a custom interface board. The end of the trial was indicated when the participant pressed the FSR for the second time.

Participants were instructed to point as accurately as possible to the visual target while pacing their limb movements with a metronome set at 1.33 Hz. This frequency was chosen to reduce the incidence of oblique/secondary movements, especially during the prism adaptation task. To ensure that all participants were able to keep to the beat of the metronome, practice trials were given to each participant before the baseline trials were initiated (ranging from 20–30 depending on individual performance).

**Data Analysis**

The main outcome measures were: (1) constant and variable error during baseline pointing; (2) magnitude of adaptation, rate of adaptation, and variance of the residuals of pointing during the rapid error correction and plateau phases of adaptation; and (3) magnitude and rate of deadaptation. All outcome measures used the azimuth (horizontal) axis pointing position for analysis, as this was the plane of the prism perturbation.

During baseline pointing, the mean accuracy, or constant error, was defined as the mean difference between terminal finger position and veridical target position. This was calculated within subject by computing the mean constant error across all 50 baseline block trials. The precision, or variable error, was defined as the mean standard deviation (SD) of the constant error across the baseline block. The SD was calculated within subject using all 50 baseline block trials.

The time course (rate) and magnitude of adaptation were estimated by fitting an exponential rise to maximum function to all 200 trials during the adaptation block, where the pointing error spatial magnitude in the azimuthal plane decreased as a consequence of an increasing number of trials. Each participant’s individual pointing data were fitted using the function:

\[ f(n) = f_0 + a(1 - e^{-bn}) \]

Where \( f(n) \) represents the predicted pointing accuracy on a given trial \( n \), \( f_0 \) denotes the predicted pointing accuracy at \( n = 0 \), \( a \) represents the change in pointing accuracy from \( n = 0 \) \( f(0) \) to \( n \rightarrow \infty \) \( f(\infty) \), and \( b \) denotes the rise/decay constant of adaptation. The value of \( \frac{a}{b} \) is considered to be the time constant of adaptation (the number of trials to reach \( 63.2\% \) of total adaptation) and was used for subsequent analysis. Similarly, the time course (rate) and magnitude of deadaptation were estimated by fitting an exponential decay function to all 70 trials during that block using the same equation. Magnitudes of adaptation and deadaptation were assessed for each participant individually by computing the difference between predicted pointing response on trial 1 \( f(1) \) and the asymptotic value of the exponential fit. This characterizes the magnitude of change in constant error from the beginning to the end of the adaptation and deadaptation blocks, respectively. Any trials that fell on or outside the 99% confidence intervals (± 3 SD) of the exponential fit were considered outliers and were eliminated from analysis.

Variable error during adaptation between the two groups was compared by calculating the squared mean of residuals for the rapid error correction and plateau phases of adaptation. The squared mean of residuals characterizes the variance of data points around the estimated exponential function. The squared mean of residuals was calculated by averaging the squared residual distances from the exponential function for the number of trials equal to the time constant (rapid error correction phase) of each individual participant (except one participant with amblyopia who did not exhibit a time constant significantly different from zero), as well as the last five trials of the adaptation block (plateau phase) using the following equations:

\[ D = f(n)_{\text{observed}} - f(n)_{\text{predicted}} \]

\[ f(n)_{\text{predicted}} = f_0 + a(1 - e^{-bn}) \]

where \( D \) is vertical distance of the point in question to the exponential function, \( f(n)_{\text{observed}} \) is the constant error in the azimuthal plane for a given trial, and \( f(n)_{\text{predicted}} \) is the constant error of the pointing movement in the azimuthal plane as predicted by the exponential model.

Statistical analysis was conducted using the R 3.1.1 software package, where the ez package was used for the ANOVAs performed. All comparisons used the azimuth-axis position for analysis, as this was the plane of prism perturbation. For baseline constant error and variable error, magnitudes of adaptation and deadaptation, and the time course of adaptation (and deadadaptation), a 3-way ANOVA was performed with Group as the between-subject factor (2 levels; visually-normal controls and participants with anisometropic amblyopia) and two within-subject repeated factors of Block (3 levels; Baseline, Adaptation, and Deadaptation) and Target Position (5 levels; \( -9^\circ, -3^\circ, 0^\circ, 3^\circ, \) and \( 9^\circ \)) for constant and variable error. In these analyses, a Greenhouse-Geisser correction was used when the assumption of sphericity was violated. Additionally, in the adaptation and deadaptation blocks only the last 10 trials for each target position were taken into consideration, such that the initial constant error induced by the wedge prisms did not confound the results. These data then were collapsed across all target positions, and each of the 5 outcome measures were compared between the control and amblyopia groups using independent sample Student’s \( t \)-tests followed by a false discovery rate (FDR) correction to compensate for multiple planned comparisons. All significant main effects and interactions were assessed using post hoc Student’s \( t \)-test followed by an FDR correction to correct for multiple comparisons. All outcome measures are reported as mean ± SD, and all \( P \) values are reported as adjusted \( P \) values after correction for multiple comparisons. All negative values indicate a leftward bias.

The variance of residuals during adaptation was analyzed using a 2-way mixed ANOVA with Group as the between-subject factor (2 levels; visually-normal controls and participants with anisometropic amblyopia) and Phase of Adaptation as the repeated within-subject factor (2 levels; rapid error correction and plateau phases).

**Results**

**Baseline Pointing**

There was no significant interaction between Group and Block for either constant error (\( F_{1,234} = 2.7, P = 0.08 \)) or variable error (\( F_{1,234} = 0.1, P = 0.9 \)). This indicates that during baseline
pointing, there was no significant difference between controls and participants with amblyopia for constant error (controls $= -0.36 \pm 0.68$, amblyopia $= 0.08 \pm 0.68$; $t_{[93]} = 0.21$, adjusted $P = 0.13$) or variable error (controls $= 0.87 \pm 0.38$, amblyopia $= 0.85 \pm 0.38$; $t_{[93]} = 0.5$, adjusted $P = 0.9$).

**Prism Adaptation**

**Magnitude of Adaptation.** There was no significant difference in mean magnitude of spatial adaptation when comparing visually-normal controls ($9.1^\circ \pm 2.3^\circ$) and participants with anisometric amblyopia ($8.2^\circ \pm 4.5^\circ$; $t_{[17]} = 0.62$, adjusted $P = 0.82$).

As a secondary analysis, we assessed how close the constant error at the end of adaptation and deadaptation came to constant error at the end of the baseline block. To do this, adaptation and deadaptation were assessed for each participant individually by computing the mean of the last 10 baseline trials, and subtracting it from the mean of the last 10 trials of the adaptation block or of the deadaptation block. By the last 10 trials of the adaptation and deadaptation blocks, all participants in both groups had reached the plateau phase of the adaptation and deadaptation. There was no difference in the ability to attain baseline constant error values at the end of adaptation between visually-normal controls ($-0.15^\circ \pm 0.84^\circ$) and participants with amblyopia ($-0.47^\circ \pm 0.69^\circ$; $t_{[17]} = 0.89$, adjusted $P = 0.38$).

**Time Course of Adaptation.** In general, prism adaptation in both groups demonstrated a well-characterized temporal pattern, with an initial rapid error correction phase followed by a gradual error correction phase that eventually plateaued at a steady state (Fig. 3A). However, the time course differed between groups—participants with amblyopia had a mean time constant of $17 \pm 6$ trials that was significantly longer than the $4 \pm 3$ trials time constant for controls ($t_{[6.5]} = 3.6$, adjusted $P = 0.03$; Fig. 3B).

To address whether the greater time constant is associated with a reduction in binocularity (stereopsis) that accompanies amblyopia versus amblyopia per se, we performed Pearson’s correlation analyses in participants with amblyopia. We found no significant correlation between stereoacuity (range, 40-3000 arc sec) and time constant of adaptation ($r = -0.17$, $P = 0.72$), nor between visual acuity (range, 20/25-20/100) of the amblyopic eye and time constant of adaptation ($r = 0.61$, $P = 0.15$).

**Variance of Residuals During Prism Adaptation.** Participants with amblyopia exhibited more variance of residuals (less precision) during early adaptation (the rapid
error correction phase) than controls (Fig. 4A). There was a Group by Phase of Adaptation interaction ($F_{1,16} = 14.2, P = 0.002$), with a significantly higher mean variance of residuals in participants with amblyopia ($2.99 \pm 1.21$) compared to controls (adjusted $P = 0.004$). Additionally, among participants with amblyopia, there was a significantly greater mean variance of residuals during rapid error correction phase compared to plateau phase of adaptation (adjusted $P = 0.02$).

**Time Course of Deadaptation.** Only 9 of 19 participants (4 visually-normal controls, 5 participants with amblyopia) exhibited an exponential decay that was modeled well by the exponential decay fit. This reduced sample size made it difficult to conduct a meaningful statistical analysis on an individual basis. When using group means, however, these data were well modeled by an exponential decay fit (Fig. 5). Based on the fits of the grouped mean responses, there was no difference in the time course of deadaptation between controls ($-0.47 \pm 0.6^\circ$) and participants with amblyopia ($-0.25 \pm 0.6^\circ$; $t_{17} = -0.82, P = 0.43$).

**Movement Duration.** To verify that there were no between group differences in performance on the pointing task, we used a repeated measures ANOVA to compare movement duration across baseline, adaptation, and deadaptation. There was no significant main effect of Group ($F_{1,13} = 3.5, P = 0.09$) and Block.
A significant main effect of Block ($F_{1,28, 16.6} = 0.50, P = 0.60$), nor was there a significant interaction between Group and Block ($F_{1,28, 16.6} = 0.44, P = 0.64$). This indicates that the movement time was consistent across the two groups and the three blocks—all participants were able to keep to the beat of the metronome consistently under all experimental conditions.

**Effects of Target Position on Accuracy and Precision During Baseline Pointing, Adaptation, and Deadaptation**

For pointing accuracy, a 3-way ANOVA demonstrated a significant main effect of Target Position ($F_{1,5, 25.2} = 13.7, P < 0.001$) with a small difference in pointing accuracy among target positions (ranging from $-0.76^{\circ}$ to $0.25^{\circ}$; Supplementary Table S1). A significant main effect of Block ($F_{12, 54} = 29.7, P < 0.001$) also was found with a small difference in pointing accuracy among blocks (ranging from $0.43^{\circ}$ to $0.87^{\circ}$; Supplementary Table S2).

For pointing precision, a significant main effect of Block was found ($F_{12,54} = 6.5, P = 0.004$) attributable to a small difference in pointing precision among blocks (ranging from $0.80^{\circ}$ to $1.0^{\circ}$; Supplementary Table S3).

**DISCUSSION**

We investigated the effects of anisometropic amblyopia on adaption to lateral displacement of the visual world using wedge prisms, a well-established experimental paradigm for the study of sensory-motor adaptation. When prisms are used to induce a large sensory prediction error that is novel to visually-normal controls, they introduce an offset between the altered visual input and the resultant efferent motor output for a given pointing action. During the rapid error correction phase of adaptation, visual information available during a movement is used to modify trajectories within a single trial and on subsequent trials to allow for compensation in visuomotor function for an optically displaced environment, leading to improved pointing accuracy and, hence, prism adaptation. In this study, we showed that participants with amblyopia exhibited the same magnitude of adaptation as visually-normal controls, but they demonstrated a longer time constant (i.e., required more trials) and increased variance of residuals during the early rapid error correction phase of adaptation.

The ability to integrate sensory and motor information properly follows a developmental trajectory. During normal development, repeated exposure to coincident visual-motor stimuli (e.g., when making a visually-guided action to a target) results in the creation of strong relations between motor commands and the visual outcome of motor actions, which allows optimal movement accuracy and precision to an intended target. This developmental course of visuomotor integration is particularly relevant in the context of anisometropic amblyopia, a neurodevelopmental disorder of spatiotemporal vision. Amblyopia is associated with decreased reliability of the visual signal. We have demonstrated previously that during binocular viewing, participants with anisometropic amblyopia demonstrate greater variability in saccadic latencies and amplitudes and decreased saccadic adaptation, compared to visually-normal controls. We hypothesized that these deficits occur secondary to more variable visual information, rather than deficits in the motor system itself. During early childhood, people with amblyopia likely develop atypical visuomotor correlations based upon abnormal visual afferent information as a result of increased signal variability, spatial undersampling, and spatial distortions. We have documented some of these atypical visuomotor interactions previously in people with amblyopia, including altered kinematic strategies during visually-guided reaching (e.g., decreased peak acceleration/velocity and a prolonged acceleration phase). In this study, we hypothesized that people with anisometropic amblyopia may require more trials to integrate the spatial information as a result of a lower-fidelity visual error signal available to aid in realigning the sensory and motor coordinate frames after exposure to a laterally displaced visual environment. This idea of a decreased adaptation/learning rate secondary to increased sensory noise conforms well with theories of Bayesian inferences in motor learning — for a consistent perturbation (in this case, the constant optical displacement), the more sensory noise that is present in the error command, the longer the learning will take.

Visual input provides an important signal to the cerebellum, which not only has a major role in visually-guided coordination of ongoing movements but also in prism adaptation as evident from lesion studies in humans and nonhuman primates, and from functional imaging studies in humans. Patients with cerebellar dysfunction exhibit reduced or absent adaptation to a shifted optical world, even after many repeated trials with visual feedback. Therefore, it is reasonable to postulate that as a result of decreased
fidelity of the visual signal reaching the cerebellum in anisometric amblyopia, prism adaptation will be impacted. This is supported by our finding that more trials were required (i.e., greater time constant) for participants with amblyopia to achieve a comparable magnitude of adaptation to visually-normal controls.

**Increased Variance in Residuals During the Rapid Error Correction Phase of Adaptation**

Deficits along the dorsal visual pathway have been identified in people with amblyopia. The dorsal visual pathway, one of the two extrastriate visual streams, runs along the parietal lobe and is involved in processing of visual information for action. The parietal lobe also has been implicated in the transformation of the eye-centered extrinsic information from the visual cortex into hand-centered reference frames used by the motor cortex. This is accomplished by creating a synergistic sensory signal composed of information from the visual, somatosensory and vestibular systems that is sent to the frontal cortex and used in motor action. The parietal lobe, specifically the posterior parietal cortex (PPC), anterior intraparietal sulcus (aIPS), angular gyrus, parietal occipital sulcus (POS), and superior parietal lobule (SPL) have been shown to be involved during the rapid error correction phase of prism adaptation, transforming novel sensory input into motor commands.

**Differences Between Prism Adaptation and Saccadic Adaptation**

We found that the spatial characteristics of prism adaptation as measured by the magnitude of adaptation in participants with anisometric amblyopia were comparable to controls. This is in contrast to our findings in saccadic adaptation, in which we used gain-down adaptation and found that participants with anisometric amblyopia had decreased spatial magnitude of saccadic adaptation (i.e., reduced saccadic adaptation gain). Although prism adaptation and saccadic adaptation involve modulating the motor system output in response to sensory perturbations, there are differences in their mechanisms that may have led to this discrepancy. Unlike prism adaptation, saccadic gain-down adaptation is not a global process. Deubel, as well as Hopp and Fuchs have shown that gain-down saccadic adaptation is vector-specific, and only transfers to target positions similar in magnitude and direction. In contrast, prism adaptation is a nontask workspace-specific process and transfers globally to other pointing actions along nonstimulated vectors. This local versus global transfer of adaptation distinction indicates that gain-down saccadic adaptation and prism adaptation paradigms induce sensorimotor adaptation by different mechanisms, which may explain the differential results we observed.

Additionally, it has been shown that gain-down and gain-up saccadic adaptation produce their effects through different adaptive mechanisms. Gain-down adaptation is believed to occur as a result of adapting the internal model of each saccade (i.e., altering saccade dynamics), whereas gain-up adaptation uses spatial remapping of the representation of the environment. Because prism adaptation involves high-level realignment of discordant sensory reference frames; that is, spatial remapping, it may be more akin to the gain-up saccadic adaptation paradigm. It is possible that the differences in results we observed in our gain-down saccadic adaptation study and the present prism adaptation study is related to different mechanisms contributing to the adaptation process.

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