Short-Term Saccadic Adaptation in Patients With Anisometropic Amblyopia

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Purpose. Amblyopia is a developmental disorder characterized by impairment of spatiotemporal visual processing that also affects oculomotor and manual motor function. We investigated the effects of amblyopia on short-term visuomotor adaptation using a saccadic adaptation paradigm.

Methods. A total of 8 patients with anisometropic amblyopia and 11 visually-normal controls participated. Saccadic adaptation was induced using a double-step paradigm that displaced a saccadic visual target (at ±19°) back toward central fixation by 4.2° during the ongoing saccade. Three test blocks, preadaptation, adaptation, and postadaptation, were performed sequentially while participants viewed binocularly and monocularly with the amblyopic and fellow eyes (nondominant and dominant eyes in controls) in three separate sessions. The spatial and temporal characteristics of saccadic adaptation were measured.

Results. Patients exhibited diminished saccadic gain adaptation. The percentage change in saccadic gain was lower in patients during amblyopic eye and binocular viewing compared to controls. Saccadic latencies were longer, and saccadic gains and latencies were more variable in patients during amblyopic eye viewing. The time constants of adaptation were comparable between controls and patients under all viewing conditions.

Conclusions. The short-term adaptation of saccadic gain was weaker and more variable in patients during amblyopic eye and binocular viewing. Our findings suggest that visual error information necessary for adaptation is imprecise in amblyopia, leading to reduced modulation of saccadic gain, and support the proposal that the error signal driving saccadic adaptation is visual.

Keywords: amblyopia, saccadic eye movements, adaptation

Saccades are rapid eye movements that bring the image of a target onto the fovea. Because visual resolution is maximized near the center of the fovea,[1] it is crucial that saccades remain accurate to enable high acuity vision. The accuracy of goal-directed saccades is defined by their gain (the ratio of saccadic amplitude to target amplitude), which typically is 0.90 to 0.95 for healthy individuals.[2,3] Because most saccades typically last less than 80 ms, the classic view was that visual feedback mechanisms did not have an important role in maintaining their accuracy.[4,5] However, saccades are not ballistic movements; there now is ample evidence that internal feedback processes monitor the efference copy of the ongoing saccadic motor commands to maintain movement accuracy.[6] More recent studies suggest that visual feedback can modify the in-flight saccadic trajectory.[7,8]

Saccadic accuracy is maintained by a sensorimotor adaptive mechanism known as saccadic adaptation,[9,10] which adjusts saccadic gain by modifying motor commands iteratively in the face of changing neural and mechanical oculomotor system properties due to aging and disease.[11–14] Accurate gain recalibration is achieved by using the spatial error information available at the end of primary saccades to modify the motor command issued for subsequent saccades, until the postsaccadic movement error is minimized or eliminated effectively. Much evidence suggests that the error signal driving saccadic adaptation is visual,[15–17] and is derived most likely from comparing the estimated postsaccadic retinal error to the actual postsaccadic retinal error.[18–22]

Amblyopia is a visual disorder that results from abnormal visual stimulation during early childhood without any structural eye abnormality, and it cannot be corrected optically.[23] Patients with amblyopia are known to have multiple sensory deficits,[24–28] including impaired spatial localization[25] and positional certainty.[26,29,30] We have shown that amblyopia also affects visuomotor functions. For example, patients with amblyopia have impaired planning and execution of visually-guided limb reaching movements,[31,32] altered temporal patterns of eye–hand coordination,[33] and diminished online control of 3D reaching movements.[34] These impairments also extend to oculomotor control, with patients exhibiting reduced saccadic spatial precision[35] and fixation instability.[36–38] However, to our knowledge no study has investigated the sensorimotor adaptation of saccadic gain in response to visual errors in patients with amblyopia.

In our study, we investigated the effects of anisometropic amblyopia on the short-term adaptation of visually-guided

Investigative Ophthalmology & Visual Science

TABLE 1. Clinical Characteristics of Patients With Anisometropic Amblyopia

			Snellen Visual Acuity (LogMAR)		Refractive Error		Deviation, Δ*		Sensory Fusion†		
I.D.	Age	Sex	Right Eye	Left Eye	Right Eye	Left Eye	Near, 0.33 m	Distance, 6 m	Worth 4 Dot	Bagolini	Stereoacuity, s of arc
1	25	F	20/20 (0.00)	20/50 (0.40)	−1.50 +1.50 × 80	−3.00 +2.50 × 80	E4	E1	Fused	N/A	120
2	18	F	20/20 (0.00)	20/60 (0.48)	−1.50 +0.50 × 80	+1.00 +1.25 × 95	LET2	LET2	Fused	N/A	200
3	30	M	20/15 (−0.10)	20/200 (1.00)	+4.00	+6.00 +1.75 × 90	LXT4	LXT8	Fused	N/A	Negative
4	44	F	20/200 (1.00)	20/15 (−0.10)	+4.50	Plano	RET2	RET2	Fused	N/A	3000
5	21	F	20/60 (0.48)	20/15 (−0.10)	−11.25	−3.00 +0.75 × 15	RET2, ET + E4‡	RET2, ET + E4‡	Suppress	Fused	Negative
6	25	F	20/15 (−0.10)	20/80 (0.60)	+2.25	+1.00	LET2	LET2	Fused	N/A	100
7	21	F	20/20 (0.00)	20/125 (0.80)	Plano	+2.00	LXT4	LXT2	Fused	N/A	3000
8	27	F	20/20 (0.00)	20/40 (0.30)	+0.25	+2.75	LET1, ET + X4‡	LET1	Fused	N/A	140

F, female; M, male; L, left eye; R, right eye; E, esophoria; ET, esotropia; XT, exotropia; N/A, not tested as the participant fused on the Worth 4 Dot test.

* Ocular deviation (in prism diopters Δ) was determined using the simultaneous prism and cover test, and the alternate prism cover test, for near (1/3 m) and far (6 m) viewing distances.

† Sensory fusion was determined using the Worth 4 Dot test and Bagolini striated lenses. All patients, with the exception of patient 5, had fusion on the Worth 4 dot test using a "peripheral target" (i.e., when tested at 1/3 m). Patient 5 demonstrated peripheral fusion on the Bagolini Test only. All 8 patients demonstrated central/foveal suppression on the Worth 4 Dot test using a "central target" (i.e., when tested at 6 m).

‡ The first measurement for these patients is that of the manifest deviation, and the second measurement indicates the total dissociated deviation.

saccades. It is known that the consistency or precision of postsaccadic visual error influences saccadic adaptation; that is, adaptation is strongest when the error is consistent and becomes weaker as the error becomes more variable.[21] We hypothesized that patients with anisometropic amblyopia will exhibit diminished saccadic gain adaptation as a result of decreased spatial precision of the visual error signal. We also hypothesized that patients will exhibit a higher variability in saccadic gain adaptation caused by increased spatial uncertainty in amblyopia. We found that patients with anisometropic amblyopia exhibit a diminished ability to modulate saccadic gain in response to target steps, and their gain also was more variable.

METHODS

Participants

A total of 8 patients with anisometropic amblyopia and 11 controls with normal or corrected-to-normal vision participated. Clinical characteristics are shown in Tables 1 and 2. Amblyopia was defined as visual acuity of 0.2 logMAR or worse in the amblyopic eye, 0.0 logMAR or better in the fellow eye, and an interocular visual acuity difference of $\geq$0.2 logMAR. Anisometropic amblyopia was defined as amblyopia in the presence of an interocular refractive error difference of $\geq$1 diopter (D) of spherical or cylindrical power. All anisometropic patients except patient 1 had a microtropia of $\leq$8 prism diopters (due to a foveal scotoma arising from the anisometropia) as detected using the simultaneous prism and cover test. Patient 1 had a phoria, but no visible manifest deviation on the cover test. Six patients (patients 1, 2, 4, and 6–8) met the criteria for monofixation syndrome.[39] The other two patients (patients 3 and 5) did not have stereopsis, but showed peripheral fusion with a central suppression scotoma. Five patients had moderate amblyopia (visual acuity of 0.3–0.7 logMAR in the amblyopic eye[40]) and three patients had severe amblyopia (visual acuity of 0.8–1.3 logMAR in the amblyopic eye[41]). Eye dominance for visually-normal observers was determined using the Dolman method.[42] The participant was instructed to view a distant object with both eyes, looking through a tube held at arms' length bimanually. The observer then alternately closed one eye to determine which eye was dominant. Exclusion criteria were any ocular cause for reduced visual acuity, prior intraocular surgery, or any neurologic disease. All participants provided written consent before participation. The study was approved by the Research Ethics Board at The Hospital For Sick Children and all experimental protocols conformed to the guidelines of the Declaration of Helsinki.

Apparatus

The visual target was a red laser dot ($\approx$0.2° diameter) rear-projected onto a translucent screen using a galvanometer (GSI Group, Bedford, MA). The experiments were conducted in a dimly-lit room with the participants seated 80 cm from the screen and their head stabilized on a chin rest. Eye movements were recorded using a video-based eye tracker (Chronos Vision GmbH, Berlin, Germany) at 200 Hz, with a spatial resolution of 0.1°.

Experimental Procedure

All participants were corrected to best-corrected visual acuity using contact lenses for the duration of the experiment. We did not record from any participants who were wearing spectacles. Participants were instructed to follow the visual

Table 2. Clinical Characteristics of Visually-Normal Participants

I.D.	Age	Sex	Snellen Visual Acuity (LogMAR)		Refractive Error		Stereoacuity, s of arc	Dominant Eye
			Right Eye	Left Eye	Right Eye	Left Eye		
1	42	F	20/20 (0.00)	20/20 (0.00)	−3.25	−3.25	40	Right
2	34	F	20/20 (0.00)	20/20 (0.00)	−1.50 +0.25 × 85	−1.50 +0.25 × 75	40	Right
3	24	M	20/15 (−0.10)	20/15 (−0.10)	Plano	Plano	30	Left
4	23	M	20/20 (0.00)	20/20 (0.00)	−4.50 +2.50 × 98	−5.00 +3.50 × 78	40	Right
5	29	M	20/15 (−0.10)	20/15 (−0.10)	−2.00	−1.25	40	Right
6	23	F	20/20 (0.00)	20/15 (−0.10)	−2.50	−2.50 +0.50 × 100	40	Right
7	20	M	20/20 (0.00)	20/15 (−0.10)	Plano	Plano	40	Right
8	21	F	20/20 (0.00)	20/15 (−0.10)	Plano	Plano	40	Right
9	23	F	20/20 (0.00)	20/15 (−0.10)	−1.50 +0.25 × 90	−1.00 +0.25 × 90	40	Right
10	24	M	20/20 (0.00)	20/20 (0.00)	Plano	Plano	40	Right
11	18	F	20/20 (0.00)	20/20 (0.00)	Plano	Plano	40	Right

target as quickly and as accurately as possible. A single experimental session (350 trials) comprised three test blocks: preadaptation, adaptation, and postadaptation blocks performed sequentially. Participants took a 1-minute break between blocks to minimize fatigue.

Pre- and Postadaptation Blocks. Target steps were presented randomly at ±19° horizontal positions for 800 ms, after an initial fixation period of 750 to 1250 ms. The preadaptation block consisted of 50 trials (30 in the adapting and 20 in the nonadapting direction), while the postadaptation block consisted of 100 trials (65 in the adapting and 35 in the nonadapting direction).

Adaptation Block. Saccadic adaptation was induced using a variant of the double-step target paradigm (Fig. 1).[43] Target presentation was similar to the preadaptation block, except that once the eyes started moving, the target (at ±19°) was shifted back toward central fixation by 4.2°. This intrasaccadic target step was triggered once the online eye velocity exceeded 50°/s, and was presented for saccades in one horizontal direction only (the adapting direction), randomized between participants. Vertical catch trials (±19°) also were included to minimize anticipatory eye movements and inattention.[44] The entire adaptation block consisted of 200 trials (120 in the adapting and 60 in the nonadapting direction, plus 20 vertical catch trials interleaved in a pseudorandom order).

Individual experimental sessions were performed under three viewing conditions in the following order: amblyopic eye (AE) viewing (controls, nondominant eye [NDE]), binocular viewing (BE), and fellow eye (FE) viewing (controls, dominant eye [DE]). Each viewing condition was tested on a separate day at least one week apart to prevent any long-term retention of the adapted saccadic gain from previous training.[45,46]

Data Analysis

Real-time eye position data were differentiated using a five-point quadratic Savitzky-Golay smoothing filter,[47] yielding an online eye velocity profile. Saccades were detected offline using a velocity threshold of 20°/s, and were omitted from analysis if they did not reach the threshold peak velocity of >100°/s, had a latency of <100 ms and/or >500 ms, or were contaminated by eye blinks or exhibited an atypical saccadic profile (e.g., glissades, staircase saccades).

There were five outcome measures: percentage change in saccadic gain, saccadic gain recovery percentage, saccadic gain variability, saccadic latency, and saccadic latency variability. For the first three measures, mean values for the preadaptation, adaptation, and postadaptation blocks were calculated using the last 25, 30, and 20 trials in the adapting direction of these blocks, respectively. Mean latency and latency variability (the last two measures) for the three experimental blocks were calculated using all the trials in the adapting direction. The percentage change in saccadic gain following adaptation was calculated using the following formulas:

$$\textit{Actual change in saccadic gain} = \frac{\textit{Mean preadapted gain} - \textit{Mean adapted gain}}{\textit{Mean preadapted gain}}$$

$$\textit{Ideal change in saccadic gain} = \frac{\textit{Size of the intrasaccadic target step } (4.2^\circ)}{\textit{Size of the initial target step } (19^\circ)} \approx 0.22$$

$$\textit{Percentage change in saccadic gain} = \frac{\textit{Actual change in saccadic gain}}{\textit{Ideal change in saccadic gain}} \times 100$$

Actual change in saccadic gain is more sensitive than computing the difference in saccadic gain before and after adaptation, as it accounts for normal saccadic undershooting during preadaptation.[2,3] The calculated percentage value of 0% indicates no adaptation, whereas 100% reflects complete adaptation. The saccadic gain recovery percentage was calculated using the following formula:

$$\textit{Saccadic gain recovery percentage} = \frac{\textit{Mean postadaptation gain}}{\textit{Mean preadaptation gain}} \times 100$$

To quantify the time course of adaptation, saccadic gain was modeled to decrease exponentially as a function of increasing number of trials. Individual data were fitted by a nonlinear regression equation $G(t) = G_0 + \Delta G e^{-t/\tau}$, where $G(t)$ is the saccadic gain at a given trial t, G_0 is the steady-state gain value (reached at the end of adaptation), ΔG is the change in gain from baseline to steady-state value, and τ is the time constant of adaptation (number of trials). Goodness of fit (R^2) values were computed for each fit.

Statistical analyses were performed using SAS 9.2. A two-way mixed ANOVA assessed the effects of amblyopia on the percentage change in saccadic gain and percentage of saccadic gain recovery using Group (controls and patients) as the between-subjects factor and Viewing Condition (AE/NDE, BE, and FE/DE) as the within-subjects repeated factor. All other

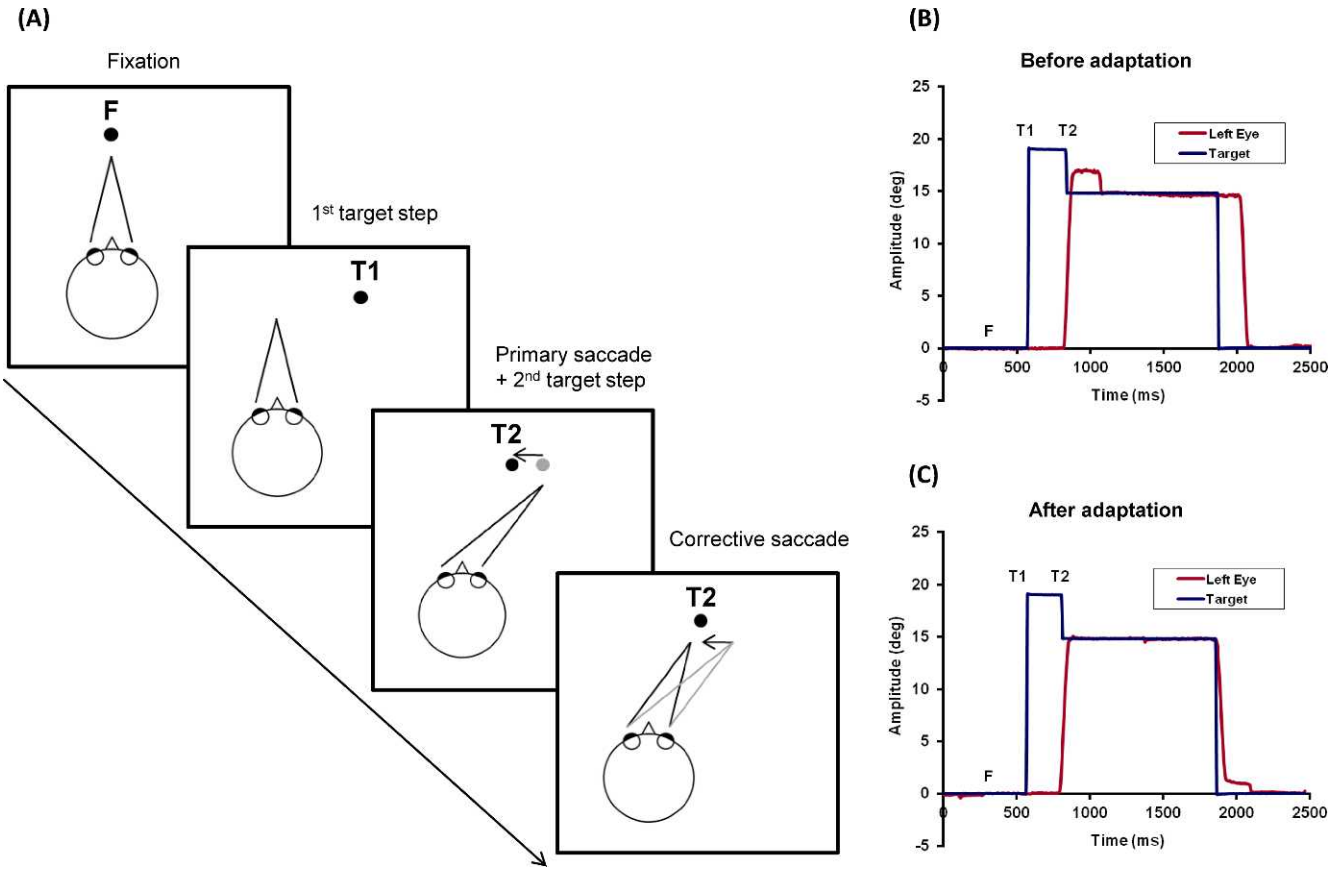

Figure 1. (**A**) The double-step target paradigm: participants fixated a central visual target (*F*). After a random interval of 750 to 1250 ms, the target stepped to 19° (*T1*, *rightwards* in this example). As soon as the primary saccade eye velocity exceeded 50°/s, the target stepped 4.2° back toward initial fixation (*T2*) before returning to central fixation. Participants were instructed to follow the target as quickly and as accurately as possible. The *right panel* shows the amplitude versus time graphs for target and eye position for single trials at the beginning (**B**) and near the end of the adaptation block (**C**). As adaptation neared completion, the primary saccade brought the eyes to the final target position.

measures were submitted to a three-way mixed ANOVA with Group as the between-subjects factor, and two within-subjects repeated factors: Viewing Condition and Experimental Block (preadaptation, adaptation, and postadaptation). All significant main effects and interactions were tested using post hoc Student's *t*-tests for pairwise multiple comparisons. To analyze the temporal characteristics of adaptation, an independent samples *t*-test was carried out for each viewing condition separately to assess the difference between the time constant and goodness of fit values from patients and controls. Conservative Greenhouse-Geisser corrected *P* values along with the partial η^2 ($\eta^2_{partial}$) values are reported for all ANOVA results.

Preliminary analysis found no difference between the percentage change in gain for saccades adapted in the rightward and leftward direction for either group ($F_{(2,29)} = 1.57$, $P = 0.23$). Therefore, adaptation data from either direction were pooled (within each group) for all subsequent analyses. Similarly, data from both eyes were comparable during binocular viewing ($F_{(1,16)} = 0.8$, $P = 0.45$). There also was no difference in percentage change in gain obtained from the amblyopic eye as compared to the fellow eye during binocular viewing ($t_{(7)} = -0.18$, $P = 0.86$). Therefore, only right eye data were reported (except for control patient 9 and patient 4, whose right eye data were noisy, so left eye data were reported instead).

Results

Saccadic Gain

Figure 2 depicts saccadic gain changes for a representative control participant (control 6) and patient (patient 4). In general, controls reduced their saccadic gain rapidly during adaptation until reaching a steady state, followed by recovery to baseline gain during postadaptation. Patients with amblyopia responded similarly, but their gain decreased to a lesser extent and depended on the specific viewing condition.

Percentage Change in Saccadic Gain. Figure 3 shows the percentage change in saccadic gain across all three viewing conditions. A main effect was found for Group ($F_{(1,17)} = 19.3$, $P = 0.0004$, $\eta^2_{partial} = 0.532$), where the saccadic gain reduction in patients (54.2 ± 15.7%) was less than in controls (71.9 ± 12.9%). A significant interaction between Group and Viewing Condition also was observed ($F_{(2,34)} = 6.0$, $P = 0.006$, $\eta^2_{partial} = 0.260$; Fig. 3). Post hoc analysis revealed that the percentage change in saccadic gain was significantly lower in patients during amblyopic eye (44.6 ± 10.8%) and binocular (53.2 ± 16.7%) viewing when compared to controls (nondominant eye, 71.3 ± 10.7%; binocular, 77.7 ± 11.5%). However, with fellow eye viewing, the saccadic gain change percentage in patients (64.6 ± 13.8%) was similar to controls during dominant eye viewing (66.7 ± 14.7%). The within-group analysis indicated that controls attained the highest percentage change in saccadic gain when viewing binocularly (i.e.,

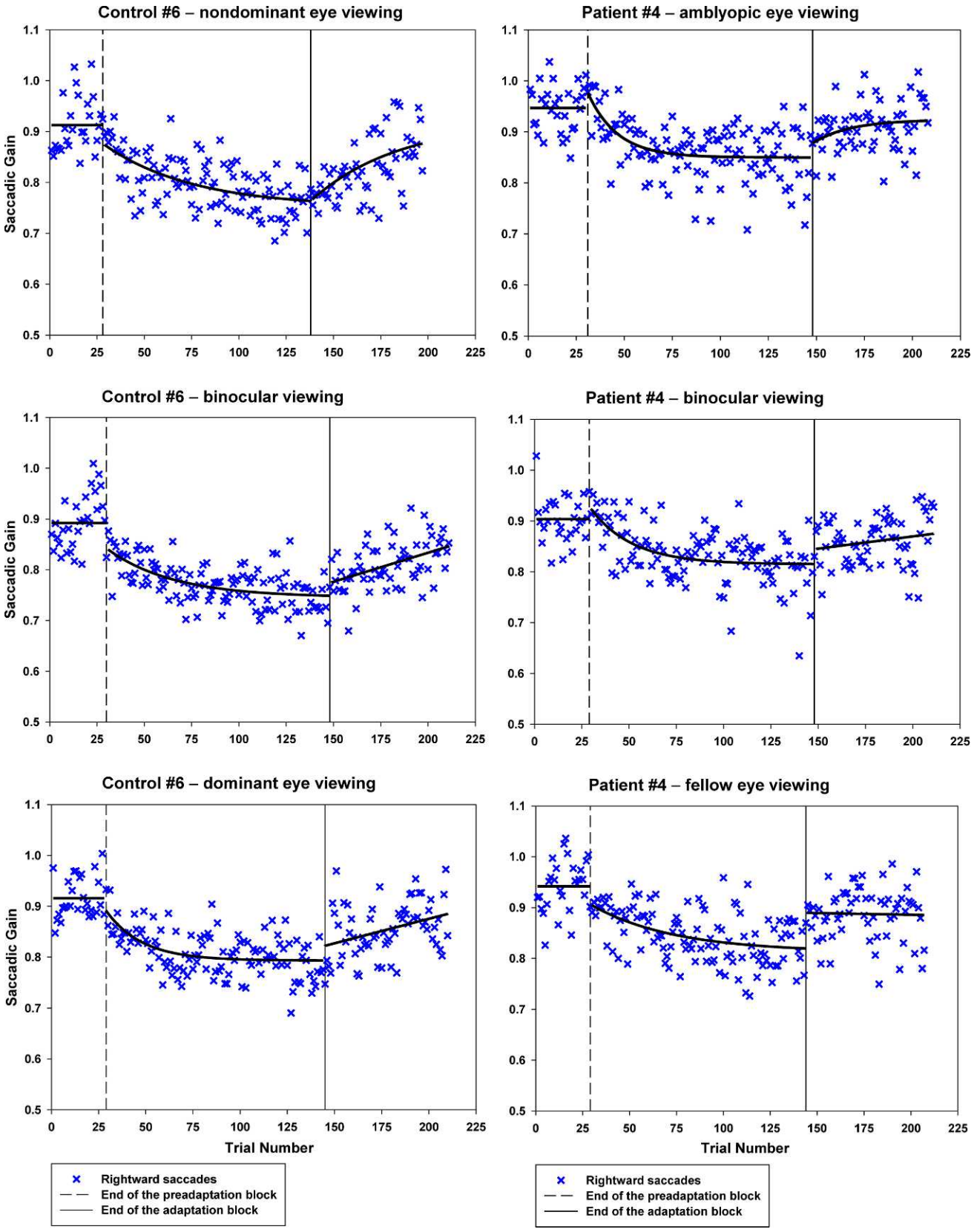

FIGURE 2. Changes in saccadic gain across all three experimental blocks, shown for control participant 6 (*left column*) and patient 4 (*right column*) during nondominant/amblyopic eye (*top row*), binocular (*middle row*), and dominant/fellow eye (*bottom row*) viewing conditions. The *dotted vertical lines* mark the end of the preadaptation blocks and *solid vertical lines* mark the end of the adaptation blocks. The control participant showed a consistently high change in saccadic gain during adaptation across all three viewing conditions, while the patient exhibited reduced and more variable change in saccadic gain during adaptation during amblyopic and binocular viewing. The preadaptation blocks were fit with a *horizontal line* indicating the average gain over that block; the adaptation blocks were fit with the decreasing exponential equation, $G(t) = G_0 + \Delta G e^{-t/\tau}$, and the postadaptation blocks were fit with the increasing exponential equation, $G(t) = G_0 + \Delta G(1 - e^{-t/\tau})$.

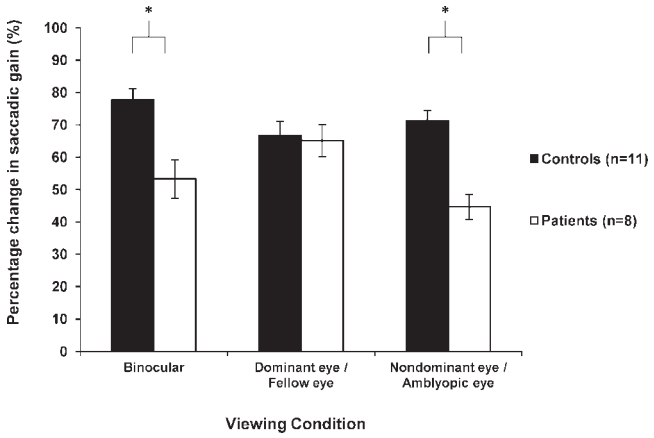

FIGURE 3. Mean percentage change in saccadic gain for controls and patients for the three viewing conditions. *Error bars* represent SEM. Patients showed a reduced percentage change in saccadic gain compared to controls during amblyopic eye and binocular condition. $^*P < 0.05$.

binocular advantage). In contrast, patients exhibited a significantly lower percentage change in saccadic gain during amblyopic eye compared to fellow eye viewing, but not binocular viewing. In agreement with adaptation values reported previously,[9,48–52] saccadic gain adaptation did not reach 100% even in normal participants; their gain decreased by approximately 75% of the ideal gain change at the end of adaptation.

To assess the effect of visual acuity deficits on saccadic adaptation, a Pearson's product-moment correlation was performed between the visual acuity of the amblyopic eye and the percentage change in saccadic gain during amblyopic eye viewing. A correlation coefficient (r) of –0.405 ($P = 0.32$) was found, indicating no significant relation between visual acuity and percentage change in saccadic gain.

Percentage of Saccadic Gain Recovery. The saccadic gain recovery percentage was comparable between controls (94.2 ± 3.3%) and patients (95.8 ± 3.4%) across all viewing conditions ($F_{(1,17)} = 3.0$, $P = 0.10$, $\eta^2_{partial} = 0.150$).

Saccadic Gain Variability. Variability was defined as the standard deviation of the mean saccadic gain. A main effect for Group was observed ($F_{(1,17)} = 10.6$, $P = 0.005$, $\eta^2_{partial} = 0.384$). Saccadic gains were more variable for patients (0.055 ± 0.01) compared to controls (0.044 ± 0.01). A significant main effect for Viewing Condition also was found ($F_{(2,34)} = 5.4$, $P = 0.009$, $\eta^2_{partial} = 0.243$). Saccadic gain variability was higher when all participants viewed with the amblyopic/nondominant eye (0.053 ± 0.02), compared to binocular (0.046 ± 0.01) and fellow/dominant eye (0.049 ± 0.01) viewing.

Saccadic Latency

A significant main effect for Experimental Block ($F_{(2,34)} = 3.2$, $P = 0.05$, $\eta^2_{partial} = 0.160$) was found, with the post hoc tests indicating that mean saccadic latencies were significantly longer for all participants during the adaptation block (205 ± 26 ms) compared to the preadaptation block (197 ± 25 ms). A significant interaction between Group and Viewing Condition also was observed ($F_{(1.41,23.92)} = 3.8$, $P = 0.049$, $\eta^2_{partial} = 0.184$, Fig. 4A). Patients exhibited increased mean saccadic latencies during amblyopic eye viewing (228 ± 34 ms) compared to controls during nondominant eye viewing (199 ± 25 ms). Within the patient group, mean saccadic latencies were significantly longer during amblyopic eye viewing compared to fellow eye (212 ± 24 ms) and binocular (187 ± 15 ms) viewing. In contrast, controls had significantly shorter latencies when viewing binocularly (185 ± 15 ms) compared to monocular viewing (dominant, 201 ± 21 ms; nondominant, 199 ± 25 ms).

Saccadic Latency Variability. There was a main effect for Experimental Block ($F_{(2,34)} = 8.8$, $P = 0.0008$, $\eta^2_{partial} = 0.342$), with the post hoc tests revealing that saccadic latencies were less variable during preadaptation (31 ± 9 ms) compared to adaptation (38 ± 12 ms) or postadaptation (36 ± 11 ms). A significant interaction also was observed between Group and Viewing Condition ($F_{(2,34)} = 3.7$, $P = 0.036$, $\eta^2_{partial} = 0.178$, Fig. 4B). Patients exhibited higher saccadic latency variability during amblyopic eye viewing (42 ± 14 ms) compared to controls during nondominant eye viewing (33 ± 9 ms).

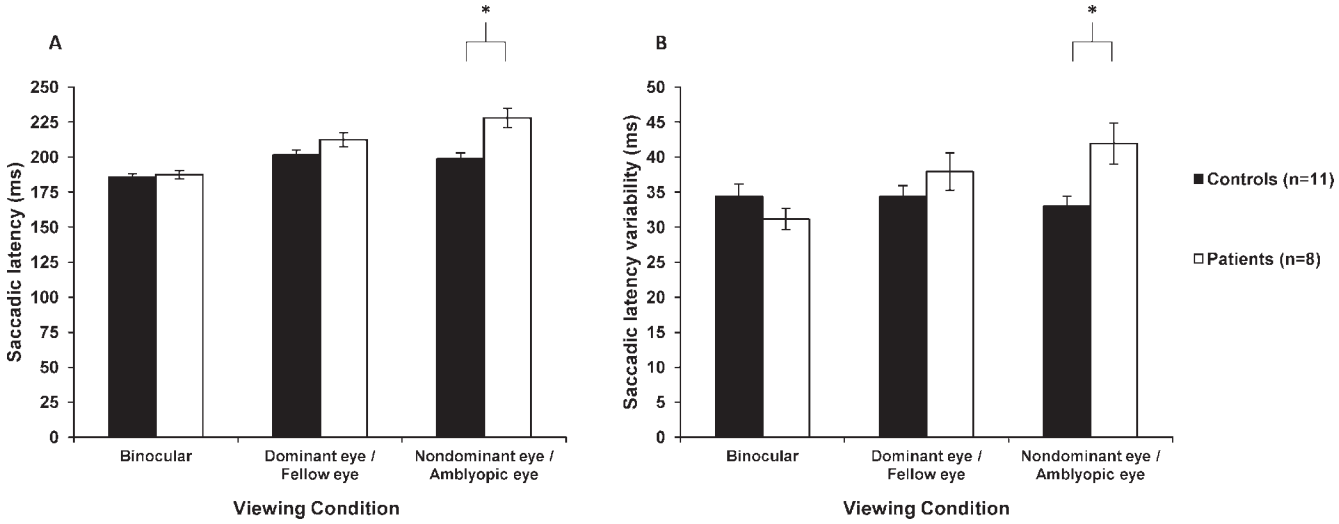

FIGURE 4. (**A**) Mean saccadic latency shown for controls and patients for all three viewing conditions, averaged over all experimental blocks. (**B**) Saccadic latency variability shown for controls and patients for all three viewing conditions, averaged across all experimental blocks. *Error bars* represent SEM. Patients exhibited longer and more variable saccadic latencies when viewing with the amblyopic eye compared to the nondominant eye of controls. $^*P < 0.05$.

TABLE 3. The Time Constants (τ) and Goodness of Fit (R^2) Values for All Participants in Control and Patient Groups, for NDE/AE, BE, and DE/FE Viewing Conditions

		NDE/AE		BE		DE/FE	
Group	I.D.	τ, *n* of Trials	R^2	τ, *n* of Trials	R^2	τ, *n* of Trials	R^2
Control	1	9	0.318	12	0.377	6	0.227
	2	8	0.299	31	0.475	14	0.360
	3	N/A	N/A	39	0.370	N/A	N/A
	4	36	0.503	38	0.296	16	0.163
	5	28	0.198	4	0.126	N/A	N/A
	6	17	0.298	29	0.381	20	0.226
	7	N/A	N/A	10	0.133	50	0.413
	8	21	0.437	37	0.486	25	0.278
	9	10	0.284	16	0.228	31	0.319
	10	4	0.169	25	0.327	35	0.333
	11	52	0.423	3	0.187	5	0.162
	Mean ± SD	20 ± 16	0.33 ± 0.11*	22 ± 14	0.31 ± 0.13	23 ± 15	0.28 ± 0.09
Patient	1	N/A	N/A	23	0.471	25	0.412
	2	28	0.210	38	0.239	12	0.174
	3	20	0.140	24	0.375	34	0.517
	4	17	0.259	25	0.266	39	0.236
	5	N/A	N/A	N/A	N/A	60	0.414
	6	12	0.170	N/A	N/A	15	0.127
	7	16	0.246	N/A	N/A	N/A	N/A
	8	N/A	N/A	24	0.248	N/A	N/A
	Mean ± SD	19 ± 6	0.21 ± 0.05*	27 ± 7	0.32 ± 0.10	31 ± 18	0.31 ± 0.16

All τ parameters were estimated from an exponential regression with a P value of <0.05. N/A, data that exhibited nonexponential (linear or other) time courses and, therefore, there were no τ and R^2 values.

* Indicates that pair of mean values differed significantly from each other ($P < 0.05$). Patients exhibited significantly lower mean R^2 values during amblyopic eye viewing compared to controls' nondominant eye viewing.

Time Course Analysis

Participants' data were fitted reliably using the exponential function, with the exception of a few individuals whose gain decreases were better described by a nonexponential fit in some viewing conditions. Table 3 summarizes the temporal course of saccadic gain changes during adaptation. During amblyopic eye viewing, five of eight patients' data were fit with a robust exponential adaptation curve (Fig. 5); however, their goodness of fit (R^2) values (0.21 ± 0.05) were lower than those of controls (0.33 ± 0.11, $t_{(12)} = 2.3$, $P = 0.04$). During binocular viewing, five patients showed exponential time courses, and during fellow eye viewing six patients had exponential time courses. In contrast to the amblyopic eye viewing, the R^2 values were comparable between controls and patients during binocular ($t_{(14)} = -0.19$, $P = 0.86$) and fellow eye ($t_{(13)} = -0.60$, $P = 0.56$, Fig. 6A) viewing. Patients decreased their saccadic gain, with mean time constants comparable to control time constants during all 3 viewing conditions: amblyopic eye (control = 20 ± 16, patients = 19 ± 6 trials; $t_{(12)} = 0.25$; $P = 0.81$), binocular (control = 22 ± 14, patients = 27 ± 7 trials; $t_{(14)} = -0.7$; $P = 0.50$), and fellow eye (control = 23 ± 15, patients = 31 ± 18 trials; $t_{(13)} = -1.0$; $P = 0.34$; Fig. 6B) viewing.

DISCUSSION

We investigated short-term saccadic gain adaptation in patients with anisometropic amblyopia. We found that, when viewing with the amblyopic eye and binocularly, patients with amblyopia exhibited a lower percentage change in saccadic gain compared to controls. The adapted saccadic gain also was more variable in patients across all viewing conditions. The mean time constant of adaptation in patients was comparable to controls in all conditions; however, patients exhibited weaker R^2 values for their exponential fits when viewing with the amblyopic eye. Patients had longer and more variable saccadic latencies during adaptation with amblyopic eye viewing.

Decreased Modulation of the Saccadic Gain During Adaptation

Patients with amblyopia exhibited a reduced percentage change in saccadic gain whenever the amblyopic eye was involved in viewing (i.e., during amblyopic eye and binocular viewing). Havermann and Lappe recently showed that the consistency of postsaccadic visual error influences saccadic adaptation, and adaptation is strongest when the error is consistent and becomes weaker as the error becomes more variable.[21] It is possible that the decrease in saccadic adaptation we observed may be due to imprecise postsaccadic visual error signals resulting from increased visual noise[29] and spatial uncertainty[25,26] in amblyopia. This is supported by findings in our previous[35] and current studies that the gain of primary saccades is significantly more variable in patients, leading to inconsistent postsaccadic visual error for adaptation.

The cerebellum is critical for motor learning, including short-term saccadic adaptation.[53,54] The cerebellum-mediated short-term saccadic adaptation has two components.[55] First, the initial motor command for subsequent saccades is modified offline or before saccade execution, accounting for the majority of the total adaptation response. Second, internal feedback of the initial motor command is sent to the cerebellum (via efference copy), allowing the saccadic system to make online modifications that correct for any errors in the saccadic trajectory during execution. This latter component of adaptive gain modulation occurs later in the saccadic

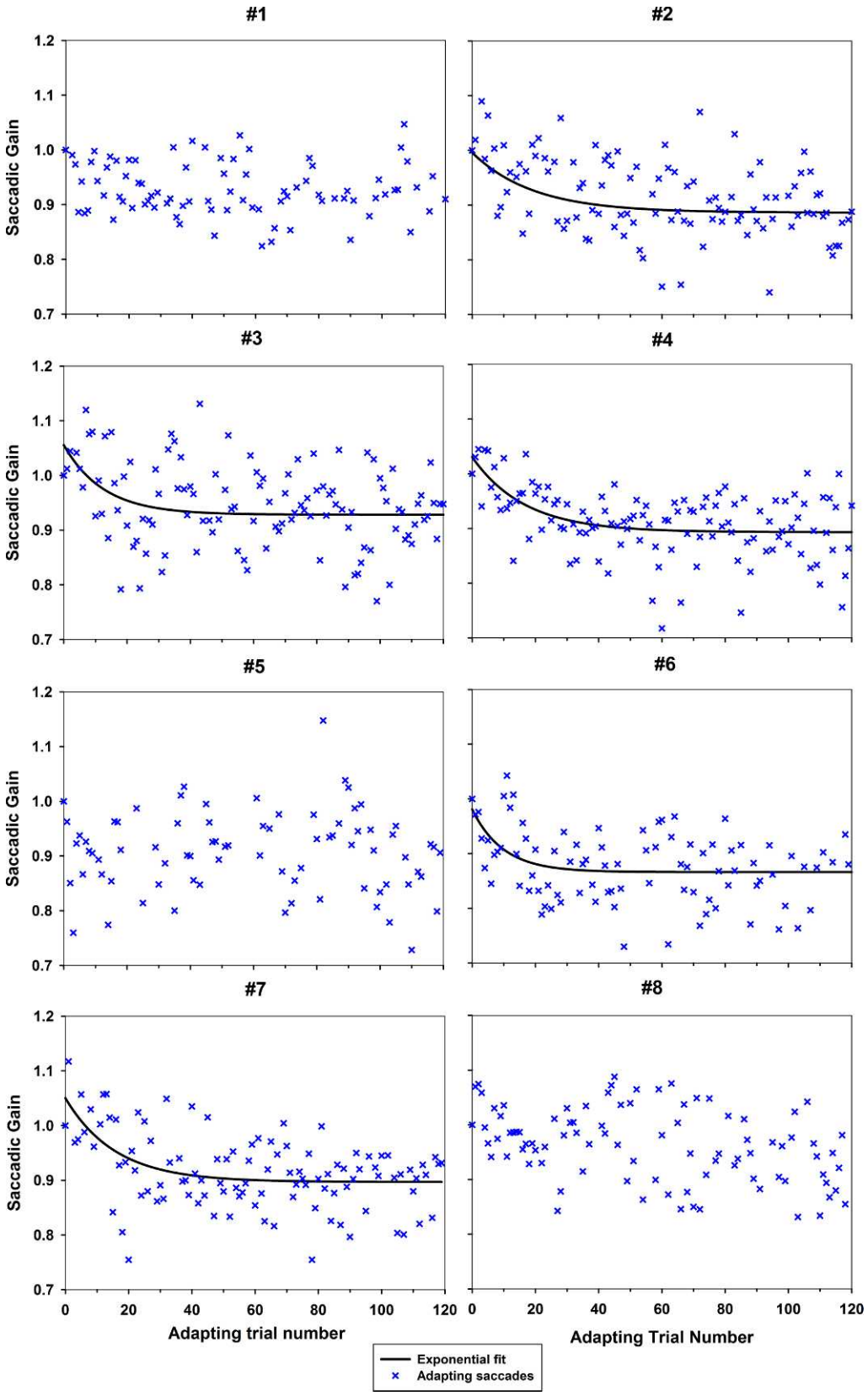

FIGURE 5. The time course of changes in saccadic gain for all patients during amblyopic eye viewing. The adaptation trials were fit by the decreasing exponential equation, $G(t) = G_0 + \Delta G e^{-t/\tau}$. It is noteworthy that patients 1, 5, and 8 did not exhibit an exponential change in the adapting saccadic gain.

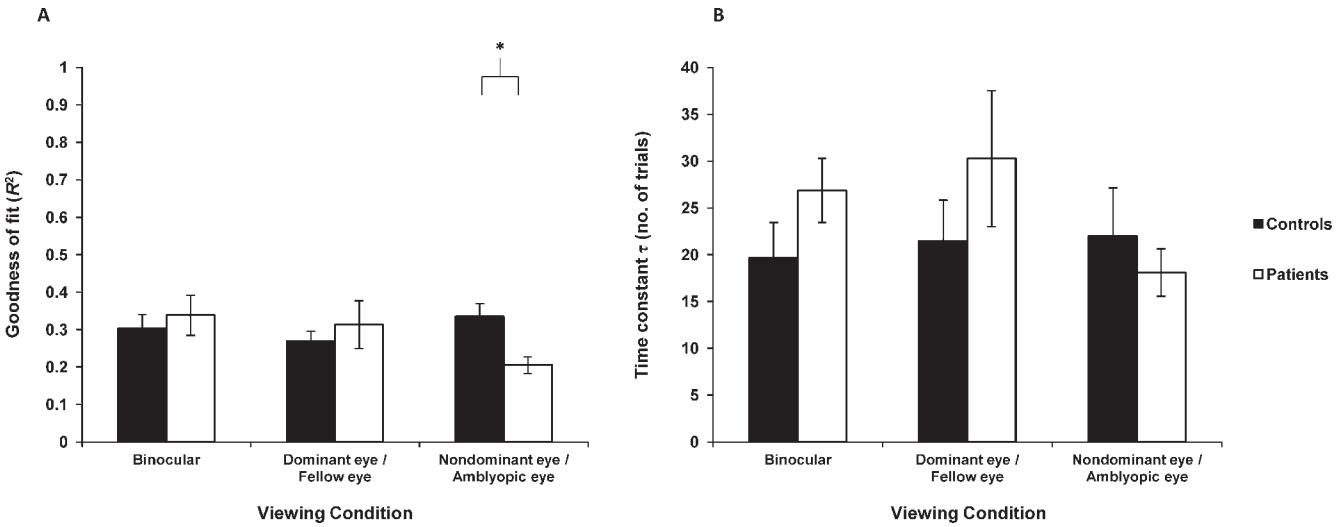

FIGURE 6. (**A**) Mean goodness of fit (R^2) values shown for binocular ($n_{controls} = 11$, $n_{patients} = 5$), dominant/fellow eye ($n_{controls} = 9$, $n_{patients} = 6$), and nondominant/amblyopic eye viewing conditions ($n_{controls} = 9$, $n_{patients} = 5$). (**B**) Mean time constants (τ) shown for controls and patients for all three viewing conditions. *Error bars* represent SEM. Patients exhibited weaker R^2 values when viewing with the amblyopic eye, but comparable time constants of adaptation under all viewing conditions. $^*P < 0.05$.

trajectory, accounting for the rest of the adaptation response. The reduced saccadic gain adaptation in patients with amblyopia can be explained in this dual-component framework. First, the initial saccadic motor commands may not benefit fully from accurate offline modifications because of the loss of spatial precision in amblyopia.[25,26,29,30,55] Second, the internal feedback processes that use the efference copy of the initial motor command may not function optimally due to imprecise postsaccadic errors as a result of amblyopia.[55] Hence, a decrease in offline and online gain modulation may explain the decreased adaptation we observed in patients with amblyopia.

Time Course of Saccadic Adaptation

Generally, the temporal course of saccadic adaptation in visually-normal individuals is characterized by an exponential function—the adapting gain undergoes rapid initial change, followed by a more gradual change that asymptotes at a new steady-state gain.[51] For gain-decrease adaptation, the steady-state gain usually is reached within 100 saccades.[49–52,56] Is the reduced adaptation of saccadic gain in patients due to an impairment in the short-term ability to adapt, or is it due to a temporal course difference, such that they require more trials to adapt?

We found that the majority of patient data (Table 3) could be fit with an exponential time function. In addition, their time constants were comparable to controls, suggesting that saccadic gain decreased in patients at a rate similar to visually-normal people. Inspection of the raw data also revealed no further decrease in saccadic gain near the end of the adaptation period for either patients or controls, indicating that a steady state was reached within 120 adaptation trials. However, due to greater response variability, patients exhibited weaker R^2 values for exponential fits with the amblyopic eye viewing. It is noteworthy that three patients had nonexponential time courses during amblyopic eye viewing (Fig. 5). A similar nonexponential adaptation time course also was observed by Havermann and Lappe when postsaccadic visual error became extremely variable in healthy people (compare Fig. 2 in their study[21]). While this may suggest that highly imprecise visual error signals in patients may lead to a time course that differs from the stereotypical decreasing exponential waveform, these three patients had only moderate visual acuity loss (0.3–0.5 logMAR). We currently are recruiting a larger number of patients with varied visual acuity loss to investigate further the temporal characteristics of adaptation in amblyopia.

Longer and More Variable Saccadic Latencies During Adaptation

We found that patients with amblyopia had longer and more variable saccadic latencies compared to controls during adaptation with amblyopic eye viewing. This is consistent with a generalized increase in saccadic latency in patients with amblyopia reported previously by us[33,35,57] and others.[38,58] Moreover, the saccadic latencies were longer for all participants during the adaptation block compared to the preadaptation block. There is a possibility that fatigue could increase the latency of saccades in the adaptation and postadaptation blocks. However, given that the mean saccadic latency in the adaptation block (205 ± 26 ms) was higher than those in the preadaptation (197 ± 25 ms) and postadaptation (201 ± 27 ms) blocks, it is likely that the prolonged latency we observed is due to the adaptation paradigm (as reported in the literature[59]). Also, because the order of preadaptation, adaptation, and postadaptation blocks always was the same for all participants, fatigue is not expected to affect differentially the saccadic latencies of controls and patients.

Effect of Visual Acuity Deficit on Adaptation

Is it possible that the reduced saccadic gain adaptation merely reflects the visual acuity deficit alone, rather than a reduced ability that is specific to amblyopia? Two lines of evidence suggest that the diminished adaptation in patients is unique to amblyopia. First, by inducing monocular blur in visually-normal people,[57] we have shown that the spatial uncertainty of saccades evident in amblyopia is not simply due to visual acuity loss alone. Second, no significant correlation was observed here between the visual acuity deficit and the percentage change in saccadic gain during amblyopic eye viewing. Patients with moderate amblyopic eye acuity deficits (better than 0.8

logMAR) exhibited comparable adaptation impairment to those with severe visual acuity deficits (0.8 logMAR and worse).

Implications of Reduced Saccadic Adaptation in Patients With Amblyopia

Sensorimotor adaptive mechanisms are essential for compensating for changes in saccadic performance that occur in normal aging[14] and disease.[11–13,60] We used a short-term saccadic adaptation paradigm, where a gain decrease is elicited within minutes to hours and typically shows considerable recovery overnight.[52] This is distinct from long-term saccadic adaptation that develops over several days and shows no significant recovery.[11–13,45,46,61] Our results suggest that patients have reduced ability of making short-term modifications to their saccadic gains, for example, as required in response to experimental errors and transient extraocular muscle fatigue. However, over a longer term their mean saccadic gain appears normal because long-term saccadic adaptation is intact. This is supported by the fact that we and others[35,58,62,63] have not found any persistent saccadic dysmetria in patients, suggesting that the mechanisms that mediate long-lasting changes in saccade metrics are intact in amblyopia.

Insights on the Mechanisms of Short-Term Saccadic Adaptation

Short-term saccadic adaptation has been studied extensively over the past decade. Despite considerable research, the neurophysiological mechanism of saccadic adaptation has not yet been identified definitively to our knowledge.[9] One mechanism that is under active investigation is the nature of the error signal(s) that drive saccadic adaptation. Most studies suggest that the control signal for adaptation is a visual error derived from the comparison of the actual postsaccadic retinal position to the predicted postsaccadic retinal position.[18–22] Amblyopia serves as an excellent visual deprivation model to study the properties of the adapting error signal, and the impairments in saccadic adaptation in patients with amblyopia provide additional support that a reliable visual error signal is important for adaptation.

In conclusion, to our knowledge our study is the first to investigate short-term sensorimotor adaptation of saccadic eye movements in patients with anisometropic amblyopia. Our results showed that patients exhibit an impaired ability to implement short-term changes in saccadic gain required for maintenance of optimal movement accuracy whenever the amblyopic eye is involved in viewing. We propose that this impaired adaptation results from a reduced capability of the saccadic motor commands to be modified accurately because of imprecise postsaccadic error signals as a result of amblyopia-related visual losses.

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