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Context cue-dependent saccadic adaptation in rhesus macaques cannot be elicited using color

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[1]*Department of Biology, Elizabethtown College, Elizabethtown, Pennsylvania;* [2]*Department of Otolaryngology, University of Pittsburgh, Pittsburgh, Pennsylvania;* [3]*Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania;* [4]*Department of Ophthalmology, University of Pittsburgh, Pittsburgh, Pennsylvania;* [5]*Department of Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania; and* [6]*The Center for Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, Pennsylvania*

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Cecala AL, Smalianchuk I, Khanna SB, Smith MA, Gandhi NJ. Context cue-dependent saccadic adaptation in rhesus macaques cannot be elicited using color. *J Neurophysiol* 114: 570–584, 2015. First published May 20, 2015; doi:10.1152/jn.00666.2014.—When the head does not move, rapid movements of the eyes called saccades are used to redirect the line of sight. Saccades are defined by a series of metrical and kinematic (evolution of a movement as a function of time) relationships. For example, the amplitude of a saccade made from one visual target to another is roughly 90% of the distance between the initial fixation point (T_0) and the peripheral target (T_1). However, this stereotypical relationship between saccade amplitude and initial retinal error (T_1-T_0) may be altered, either increased or decreased, by surreptitiously displacing a visual target during an ongoing saccade. This form of motor learning (called saccadic adaptation) has been described in both humans and monkeys. Recent experiments in humans and monkeys have suggested that internal (proprioceptive) and external (target shape, color, and/or motion) cues may be used to produce context-dependent adaptation. We tested the hypothesis that an external contextual cue (target color) could be used to evoke differential gain (actual saccade/initial retinal error) states in rhesus monkeys. We did not observe differential gain states correlated with target color regardless of whether targets were displaced along the same vector as the primary saccade or perpendicular to it. Furthermore, this observation held true regardless of whether adaptation trials using various colors and intrasaccade target displacements were randomly intermixed or presented in short or long blocks of trials. These results are consistent with hypotheses that state that color cannot be used as a contextual cue and are interpreted in light of previous studies of saccadic adaptation in both humans and monkeys.

adaptation; contextual; monkey; motor learning; saccade

SACCADES have been frequently studied in an attempt to uncover the neural mechanisms underlying the maintenance of movement accuracy and precision. Furthermore, saccades have been frequently used to study the ability of primates to pair arbitrary sensory stimuli (e.g., a visual object's color, shape, orientation, and/or motion properties) with a specific motoric response (for reviews see Gold and Shadlen 2007; Herman et al. 2013; Hopp and Fuchs 2004; Iwamoto and Kaku 2010; Liversedge et al. 2011; Pélisson et al. 2010; Shadlen and Kiani 2013). Saccades are rapid, conjugate eye movements that may be used to reorient the line of sight such that the high-resolution region of the retina (the fovea) can be aligned with objects of interest (Leigh and Zee 1999). Primate saccades are defined by a series of stereotypical metrical relationships between amplitude, peak velocity, and duration (Bahill et al. 1975; Baloh et al. 1975; van Gisbergen et al. 1984) and primary saccade gain (movement amplitude/initial retinal error) is approximately 0.90–0.95 (Becker 1972; Becker and Fuchs 1969; Henson 1978, 1979; Hyde 1959; Kowler and Blaser 1995; Prablanc et al. 1978). Modifications to these relationships may result from neuromuscular disease (Leigh and Zee 1999) or, in the case of saccade gain, by experimental manipulations.

Under laboratory conditions, motor learning in the saccadic system ("saccadic adaptation") has mostly been studied by surreptitiously introducing a visual error at the end of a saccade that was aimed at a target located at a particular vector (magnitude and direction) relative to where the subject was fixating (Albano 1996; Deubel 1987, 1991; Deubel et al. 1986; McLaughlin 1967; Miller et al. 1981; Noto et al. 1999; Robinson et al. 2003; Scudder et al. 1998; Semmelow et al. 1987; Straube et al. 1997). Under these circumstances: *1*) changes in primary saccade amplitude follow a roughly exponential time course with "rate constants" around 30–60 saccades in humans (Albano 1996; Deubel et al. 1986; Deubel 1987) and 100–800 saccades in monkeys (Straube et al. 1997); *2*) the change in primary saccade gain is appropriate to reduce the visual error induced at the end of the movement, but is rarely large enough to consistently place the fovea on the location of the target after it was displaced during the saccade; *3*) the magnitude of backward adaptation is larger than forward adaptation in response to the same post-saccadic visual error (Straube et al. 1997); *4*) adaptation effects transfer to saccades with vectors similar to those initially adapted ("adaptation fields"; Noto et al. 1999); and *5*) a corrective movement is not necessary for learning to progress (Wallman and Fuchs 1998), which indicates that a visual error signal is sufficient enough to drive this form of motor learning.

There has recently been a great deal of interest in "context-dependent" saccadic adaptation (for reviews, see Herman et al. 2013; Pélisson et al. 2010). In this type of experiment a cue, either internal (e.g., proprioceptive feedback of eye position) or external (e.g., visual target properties), is used during and after the learning process to elicit different gain states. For example, Alahyane and Pélisson (2004) have shown that human horizontal saccade amplitude can be simultaneously reduced and

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increased to the same initial target displacement (T_1-T_0) depending upon the vertical orbital eye position (either 12.5° up or 25° down) at which a subject initiates the primary saccade. On the other hand, differential changes in saccade gain based on eye position have proven difficult to elicit in rhesus monkeys under similar conditions (figures 2 and 8 in Tian and Zee 2010).

The use of external visual cues to drive different gain states during saccadic adaptation has led to a mixture of results in human subjects. Deubel (1995), in a few human subjects, was unable to elicit distinct gain states during horizontal adaptation using colored, static targets (red crosses and green circles) that were displaced by a few degrees of visual angle along the same axis as the primary saccade. Subsequent investigations of human saccadic adaptation were also unable to elicit context-dependent adaptation using either static shapes (diamonds vs. squares; Bahcall and Kowler 2000) or moving visual targets with different shapes and colors (Azadi and Harwood 2014). However, other explorations of saccadic adaptation have shown that visual cues such as flickering vs. nonflickering targets (Herman et al. 2009), yellow squares vs. green circles (Madelain et al. 2010), and other properties of moving targets (speed and direction) (Azadi and Harwood 2014) can be used to elicit different gain states.

Given the different behaviors of human subjects in context cue adaptation experiments using different visual stimuli, and the potential for monkeys to have different behavior to the same stimuli that elicited context-dependent adaptation behavior in humans, we designed the current study to test the hypothesis that color can be used as a contextual cue in a saccade adaptation task. Although our results concur with those observations made by Deubel (1995) and Azadi and Harwood (2014), our experiments provide a more extensive data set to support the assertion that the saccadic adaptive control system does not differentiate between color targets of the same shape. These data are interpreted in the light of previous context-dependent adaptation studies.

MATERIALS AND METHODS

All procedures were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals. Three male rhesus monkeys (BB, BU, and WE) weighing 7.0–13.0 kg served as subjects. Each monkey had a small head-restraint device secured to the skull during an aseptic surgery. In an additional aseptic surgery, monkeys BB and BU had a scleral coil implanted for monitoring gaze position (Judge et al. 1980). After full recovery, each animal was trained to sit in a primate chair with their head restrained and a sipper tube was placed near the mouth for reward delivery. Subjects were subsequently trained to make gaze shifts to visual targets but were not used for adaptation studies prior to their participation in the current series of experiments.

For monkeys BB and BU, visual stimuli, behavioral control, and data acquisition were controlled by a custom-built program that uses LabVIEW architecture on a real-time operating system supported by National Instruments (Austin, TX) (Bryant and Gandhi 2005). These animals sat inside a frame containing two alternating magnetic fields that induced voltages in the eye coil and thus permitted measurement of horizontal and vertical eye positions (Robinson 1963). Visual targets were displayed on a 55-in., 120-Hz resolution LED monitor. For monkey WE, eye movements were monitored using an eye tracker (Eye Link 1000, SR Research Ltd, Mississauga, Ontario, Canada) and visual targets were presented on a 21-in., 100-Hz resolution CRT monitor.

General Chronology of Experimental Sessions, Trial Types, and Reward Criterion

Every adaptation session had at least three phases that occurred in the following chronological order: *1*) a "preadaptation phase" in which only probe trials were presented; *2*) an "adaptation phase" in which only adaptation trials were presented; and *3*) a "postadaptation phase" in which only probe trials were presented. Both probe and adaptation trials (Fig. 1, *A* and *B*) began with the illumination of an initial fixation target (T_0). Subjects were required to look at and maintain fixation of T_0 for a variable duration (500-1,000 ms, 50- or 100-ms increments). Trials were aborted if the line of sight deviated beyond a computer-defined window (3° radius) surrounding T_0. However, if fixation was maintained, a peripheral target (T_1) was illuminated. T_0 and T_1 overlapped between 0 to 750 ms in 250-ms increments. If the subject continued to maintain fixation of T_0 for the duration of this overlap period, then T_0 was extinguished, cuing the animal to make a saccade to T_1. To this point both probe and adaptation trial types were identical. During "probe" trials (Fig. 1*A*), T_1 remained illuminated until the position of the line of sight exited the computer window centered on the location of the no longer visible T_0. T_1 was turned off after the line of sight crossed this position criterion during probe trials; therefore, no visual feedback was available on these trials. "Adaptation" trials (Fig. 1*B*) were similar to probe trials except that after T_1 was extinguished, a target (T_2) was immediately illuminated in a new spatial location. The new location could be further away from (forward adaptation) or closer to (backward adaptation) T_0 along the horizontal meridian during trials attempting to elicit adaptation of the horizontal component of the primary saccade vector (Fig. 1*C*). In experiments attempting to elicit changes in the vertical component of the primary saccade vector, targets could be displaced above (upward adaptation) or below (downward adaptation) the horizontal meridian (Fig. 1*D*). The latter experiments are hereafter referred to as "orthogonal adaptation" experiments. Last, note that the horizontal direction (left or right) of the primary saccade during adaptation trials was pseudorandomly alternated between sessions.

During the preadaptation phase, the locations of T_1 always included the T_1 used during adaptation trials and typically the T_2 locations and a target location that would evoke a primary saccade in the direction opposite that produced during adaptation trials (for specific examples of targets, see *Hypotheses, Predictions, and Experimental Session Subtypes* below). Subjects were rewarded for entering a window surrounding T_1 that had a radius of 6° and remaining in the window for a minimum of 250 ms. During the adaptation phase, the reward window associated with T_1 was elliptical, centered on a location between T_1 and T_2, and enlarged such that it encompassed and extended beyond these targets by ~5°. The reward window associated with the T_1 used during adaptation trials remained enlarged during the postadaptation probe phase and subjects needed to maintain fixation within this window for a minimum of 250 ms to be rewarded. The reward criterion for other T_1 locations during the postadaptation phase was the same as that used during the preadaptation phase.

In each of our color cue experiments, the targets (T_0, T_1, T_2) were red, green, or yellow dots subtending ~1° of visual angle. Target color remained constant within a given trial and trials using a particular color were randomly intermixed throughout all phases of the experiment. Therefore, during adaptation trials, the fixation point color could indicate forward (green) or backward (red) adaptation. Target locations during probe and adaptation trials remained fixed within a data collection session.

The exact number of probe trials during the pre- and postadaptation epochs varied depending upon the number of colors used in a given

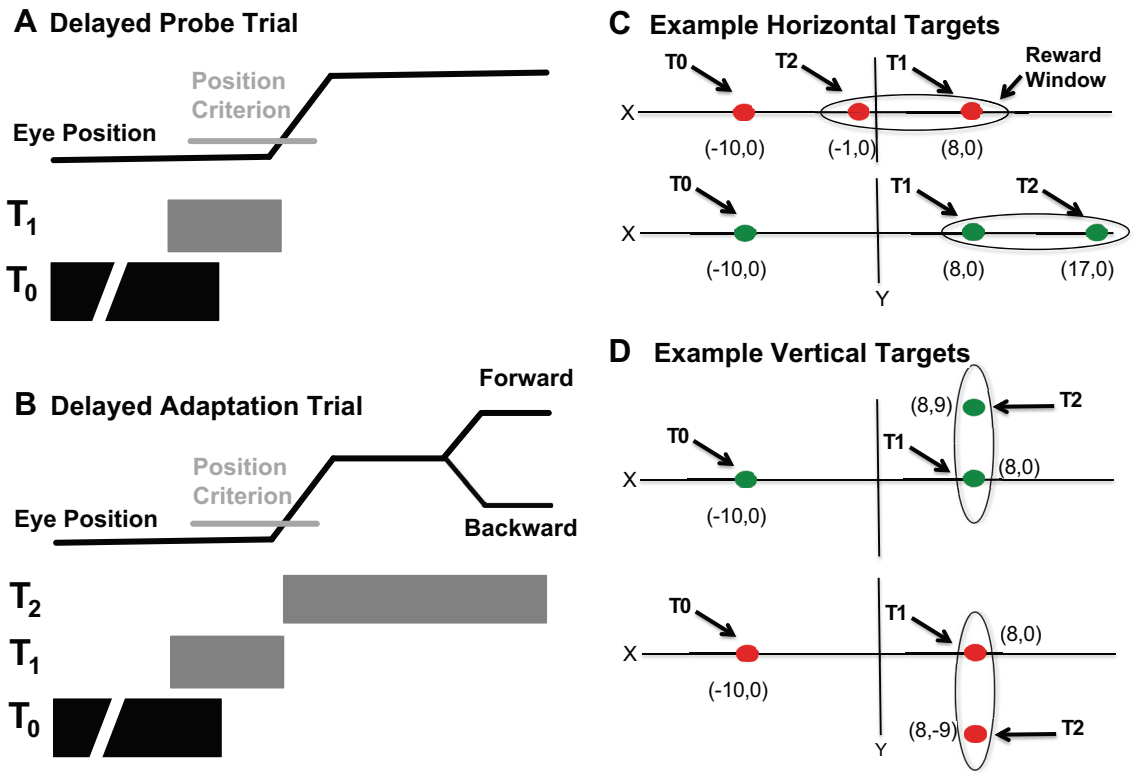

Fig. 1. Delayed probe and backward adaptation trial types and target locations. Probe (*A*) and adaptation (*B*) trials begin in the same fashion. Subjects are initially required to fixate a target (T_0) for a variable duration within a computer-defined window. A peripheral target (T_1) is then presented and the subject must maintain fixation of T_0 for a variable "delay period" during which T_0 and T_1 overlap. If the subject maintains fixation to the end of the delay period, then T_0 is extinguished, cuing the subject to produce a saccade to T_1. When the subject produces a saccade towards T_1 they will leave the computer-defined window and trigger the offset of T_1. In probe trials, this target is never illuminated again. In backward adaptation trials, another target (T_2) is presented at a location between T_0 and T_1. During a forward adaptation experiment T_2 would be presented at a more eccentric location. Although not shown here, note that the color of the target remains constant within a trial. However, the target color may be red, green, or yellow between trials. Panels *C* and *D* illustrate the location of targets during horizontal and vertical adaptation experiments, as well as the location of the reward windows during adaptation trials. Colors correspond to those used during adaptation trials in the adaptation phase (See MATERIALS AND METHODS for further details).

experiment (one vs. three), the type of experiment and thereby the number of potential T_1 and T_2 locations used during adaptation trials, and the willingness of the subject to sustain effort for long periods during the postadaptation phase. Furthermore, we attempted to keep the length of the adaptation phase relatively constant across experimental sessions such that the subject experienced 450 or more adaptation trials per condition (900+ adaptation trials total per session). Hence, the duration of the adaptation phase was relatively constant across sessions within a subject.

Data Acquisition and Analysis

For both animals, each trial was digitized and stored on the computer's hard disk for off-line analysis in MATLAB (R2013b; Natick, MA). Horizontal and vertical eye positions were stored with a resolution of 1 ms. Component velocities were obtained by differentiating the eye position signals. The onset and offset of saccades were identified using a velocity criterion of 40°/s. Saccade amplitude was defined as the change in eye position from the beginning to end of the eye movement based on this velocity criterion. All of the data reported here are the result of measuring the first ("primary") saccade made towards T_1 that was associated with the adaptation trials for a particular session. This has traditionally been used to assess the subject's motoric state at various time points during adaptation experiments (for review see Hopp and Fuchs 2004). The primary saccade needed to occur within 500 ms after the offset of T_0 and have a horizontal amplitude greater than 5° to be considered for further analysis.

Saccade gain was defined by the following formula:

$$\text{saccade gain} = \frac{\text{saccade amplitude}}{T_1 - \text{initial eye position}}$$

By definition a saccade with a gain that is <1.0 is hypometric whereas a saccade with a gain > 1.0 is hypermetric. During color context cue experiments, trials were then parsed based on whether the target color within a trial was red, green, or yellow. For each color, the average gain or amplitude of saccades made during all preadaptation phase probe trials using the T_1 that was used during adaptation trials ("preprobe trials") was compared with average of an equal number of probe trials presented after a particular adaptation segment ("postprobe" trials). Across all color cue experiments, the mean ($\pm$ SD) number of pre- and postadaptation trials used for comparison was 22.9 $\pm$ 6.0 (range = 12:42) and was not different across colors (green = 22.9 $\pm$ 6.1; yellow = 23.2 $\pm$ 6.2; red = 22.1 $\pm$ 5.6; $P = 0.8106$ Kruskal-Wallis test). The difference between pre- and postadaptation means for a given color within an experimental session was compared using a Wilcoxon rank sum test. A Kruskal-Wallis test was used to assess the effect of color on gain across multiple sessions. All tests were done in the *MATLAB Statistical Toolbox*; significance was determined using a Bonferroni corrected P value ($P < 0.0167$) in the case where three means were compared.

Hypotheses, Predictions, and Experimental Session Subtypes

During saccadic adaptation, a sensory signal can be considered a contextual cue if at least two different gain states are elicited based on

that cue (Alahyane and Pelisson 2004; Herman et al. 2009; Tian and Zee 2010). Experiments detailed in the current report were designed to test the hypothesis that a target's color could act as a contextual cue. This hypothesis predicts that saccade gain changes between the pre- and postadaptation phases within experimental sessions will be dependent upon the retinal error associated with adaptation trials that use different colored targets. During the adaptation phase of our horizontal adaptation experiments, red targets were associated with retinal errors that typically elicit gain decreases and green targets were associated with retinal errors that typically elicit gain increases. The aforementioned hypothesis would be supported by results showing that gain of postadaptation probe trials relative to preadaptation probe trials are consistently smaller for saccades to red targets and larger for saccades to green targets. Furthermore, probe trials using colors not associated with persistent retinal errors during the adaptation phase (e.g., yellow) should elicit similar gain states between the pre- and postadaptation phases. The null hypothesis in our study states that any change in gain between the pre- and postadaptation phases of a given experiment will not be dependent upon target color. We tested these predictions using the following types of experiments and describe the specific outcomes based the aforementioned general hypotheses in each case:

1) Horizontal intermixed color experiments. During horizontal intermixed color experiments, the fixation target (T_0) was fixed at (−10°,0°) in some sessions and at (10°,0°) in other sessions. As illustrated in Fig. 1*C*, if a subject began horizontal adaptation trials by fixating a T_0 located at (−10°,0°), then T_1 during these trials was always located at (8°,0°). T_2 could be located at (−1°,0°) or (17°,0°) during horizontal backward (red targets) and forward (green targets) adaptation trials, respectively. The difference between T_1 and T_2 was always 9° during horizontal adaptation experiments. The mirror images (as reflected through the ordinate) of these targets were used during adaptation trials that began at (10°,0°). For simplicity, we will describe the remaining experiments and portray data in our figures as if all trials began with the T_0 located at (−10°,0°). During horizontal intermixed color experiments, if color can be used as a contextual cue, then saccade gain during postadaptation probe trials should be significantly smaller for trials using red targets and larger for trials using green targets relative to matched color probe trials in the preadaptation phase. However, if gain does not change between the pre- and postadaptation phases or a significant gain change occurs in same direction regardless of target color, then color does not act as a contextual cue.

2) Backward-null color intermixed. Backward-null adaptation sessions used the same T_0 and T_1 as horizontal color intermixed experiments and the T_2 during red trials (backward) was also located at (−1°,0°). However, during green "adaptation" trials, the target remained lit at the T_1 for the duration of the trial. As with the horizontal intermixed color experiments, trials using a particular color were randomly intermixed throughout all phases of the experiment. During these experiments, if color can be used as a contextual cue, then saccade gain during postadaptation probe trials should be significantly smaller for trials using red targets and remain constant for trials using green targets relative to matched color probe trials in the preadaptation phase. However, if gain does not change between the pre- and postadaptation phases or a significant gain change occurs in same direction regardless of target color, then color does not act as a contextual cue.

3) Orthogonal color intermixed. Orthogonal adaptation sessions used the same T_0 and T_1 as horizontal experiments. However, during these sessions T_2 was located either 9° above (green targets) or below (red targets) T_1 during upward and downward adaptation trials, respectively (Fig. 1*D*). As with the horizontal intermixed experiments, trials using a particular color were randomly intermixed throughout all phases of the experiment. During these experiments, if color can be used as a contextual cue, then the vertical component of saccades during postadaptation probe trials should be deviated significantly downward for trials using red targets and upward for trials using green targets relative to matched color probe trials in the preadaptation phase. However, if the vertical component does not change between the pre- and postadaptation phases or a significant change in the vertical component occurs in the same direction regardless of target color, then color does not act as a contextual cue.

4) Backward-upward color intermixed experiments. Backward-upward color intermixed sessions used the same T_0 and T_1 as horizontal experiments. However, during these sessions T_2 was located either 9° above [(8°,9°), green targets] or closer to the initial fixation point [(−1°,0°), red targets]. As with the horizontal intermixed experiments, trials using a particular color were randomly intermixed throughout all phases of the experiment. During these experiments, if color can be used as a contextual cue, then the vertical component of saccades during postadaptation probe trials should be significantly deviated upward for trials using green targets and the horizontal component should be significantly smaller relative to matched color probe trials in the preadaptation phase. However, if there is not a change in these components between the pre- and postadaptation phases or a significant change in the vertical and horizontal components occur in same direction regardless of target color, then color does not act as a contextual cue.

5) Horizontal short and long block color experiments. Previous context cue adaptation experiments (e.g., Herman et al. 2009; Tian and Zee 2010) have suggested that presenting short, alternating blocks of trials with each cue can aid the progression of context-dependent adaptation. The target locations (T_0, T_1, T_2), pre- and postadaptation phases during our block color experiments were identical to those used during the horizontal intermixed color experiments described above. However, during the adaptation phase of short block experiments, red (backward) and green (forward) adaptation trials were presented in alternating blocks of approximately thirty trials. In long block (or sequential) experiments, a "red adaptation only" phase consisting of ~600 trials was followed by a "green adaptation only" phase of approximately the same length. Note also that a brief (~30 trials) "red only probe" phase occurred between these two adaptation epochs in the sequential experiments. The predictions of our hypotheses for these block experiments were identical to those of the horizontal intermixed color experiments.

6) White target experiments. Horizontal and backward-null intermixed experiments using white targets subtending ~1° of visual angle were used to assess our subjects' motoric output without the potential for color as a contextual cue. The target locations, trial types, and epoch sequence were the same as the horizontal intermixed and backward-null color experiments mentioned above. Note that if a differential gain state can be elicited using color and these changes are color dependent, then we should observe no differential gain states in the white target experiments. Furthermore, if color cannot be used as a contextual cue in the color experiments, then we should observe the same change in gain as we observed in the color cue experiments.

7) Initial eye position short block experiments. Initial eye position (IEP) context cue experiments were patterned off of those previous reported by Tian and Zee (2010). The same targets used during white target experiments were used during our IEP experiments, which means the only contextual cue available to the subject was the eye position at saccade onset. Similar to the aforementioned color and white target experiments, the primary saccade direction could be leftward or rightward in any given experiment; however, all data are portrayed as if saccades were rightward. Furthermore, backward or forward adaptation could occur in a given session from either of the vertical eye positions (±10°); however, all data are portrayed and hypotheses are discussed as if backward adaptation trials always occurred when saccades were initiated from the downward eye position and all forward adaptation trials occurred when saccades were initiated from the upward eye position. Last, the horizontal distance between the T_0, T_1, and T_2 locations during IEP experiments was the

same as that used during the aforementioned horizontal color cue and white target control experiments (T_1-T_0 = 18°; T_2-T_1 = ±9°).

During the preadaptation phase of IEP experiments, subjects performed only probe trials whose T_0 locations, and therefore IEP, varied randomly. The adaptation phase consisted of alternating blocks of ~30 adaptation trials. All trials within a block were initiated from a single T_0 position, which meant that vertical eye position was kept roughly constant within a given block. The postadaptation phase consisted of two blocks of ~30 probe trials in which IEP was held constant. In line with previous reports (Alahyane and Pélisson 2004; Tian and Zee 2010), if IEP can be used as a contextual cue under these circumstances, then postadaptation probe trials relative to preadaptation probe trials should have a smaller horizontal gain when initiated from the downward IEP and larger horizontal gain when saccades initiated from the upward IEP. If IEP is not a robust contextual cue, then horizontal should not change or change in the same direction from both eye positions.

RESULTS

Horizontal Intermixed Color Experiments

Figure 2*A* portrays data from a horizontal intermixed color experiment (BBHI3). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was similar regardless of color (green = 0.92 ± 0.03; red = 0.90 ± 0.05; yellow = 0.91 ± 0.03). Qualitatively, saccade gain during red (backward) and green (forward) adaptation trials did not change during the adaptation phase and saccade gain during probe trials executed in the postadaptation phase was similar to the preadaptation phase (postprobe green = 0.90 ± 0.04; red = 0.88 ± 0.05; yellow = 0.89 ± 0.04). In fact, saccade gain did not change significantly for any of the colors between the pre- and postadaptation phases ($P > 0.016$, Bonferroni corrected Wilcoxon rank sum test).

Figure 2*B* portrays data from another horizontal intermixed color experiment (WEHI4). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was similar regardless of color (green = 0.93 ± 0.03; red = 0.94 ± 0.04; yellow = 0.93 ± 0.03). In contrast to the previous example (Fig. 2*A*), saccade gain during red (backward) and green (forward) adaptation trials increased during the adaptation phase resulting in postadaptation probe trials that were larger than those in the preadaptation phase (postprobe green = 0.99 ± 0.03; red = 1.01 ± 0.04; yellow = 1.01 ± 0.05; $P < 0.0001$, Bonferroni corrected Wilcoxon rank sum test).

The histogram in Fig. 2*C* provides the mean (± SD) change in gain between pre- and postadaptation probe trials for each color across all 12 experimental sessions (Monkey BB: $n = 5$, WE: $n = 5$, BU: $n = 2$). In 5/12 experiments (42%) saccade gain did not change between pre- and postadaptation epochs for any of the colors. In 5 of the remaining experiments, gain values for at least two colors changed significantly; however, note that gain changes were always in the same direction in these experiments. Last, the histogram plot in Fig. 2*D* summarizes the change in saccade gain between pre- and postadaptation probe trials for each color across all 12 horizontal intermixed color experiments. In brief, the change in saccade gain was not different between

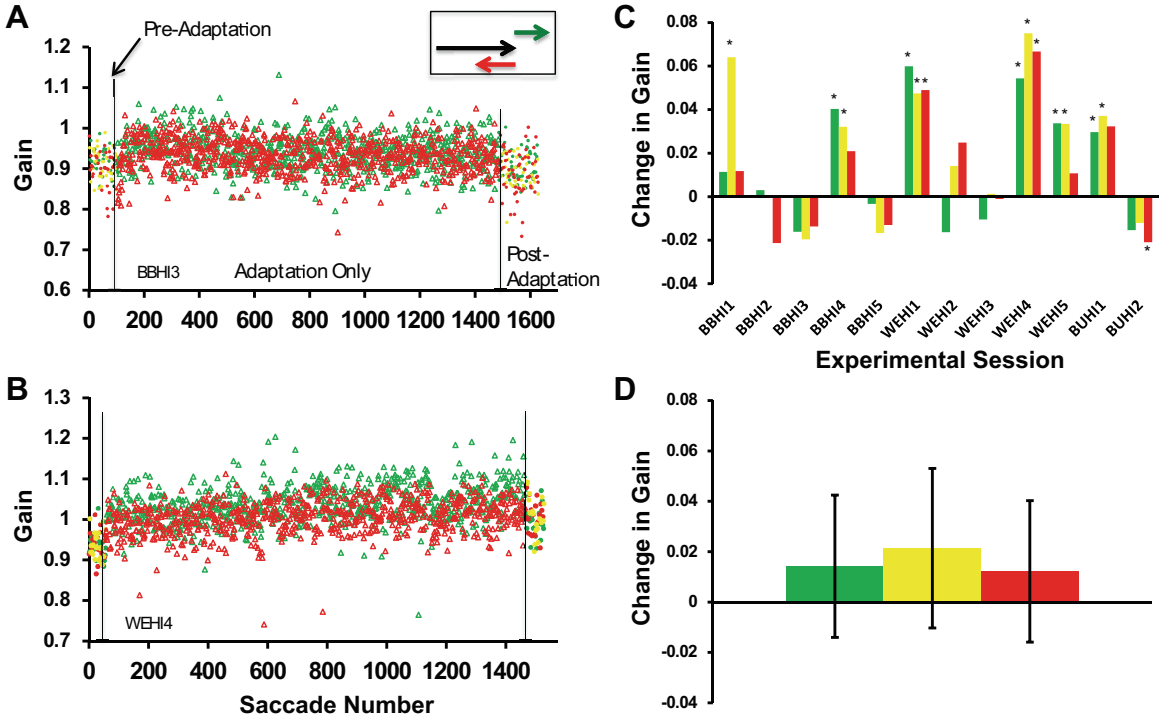

Fig. 2. Horizontal intermixed color experiments. Horizontal, primary saccade gain during the preadaptation, adaptation, and postprobe segments of experiments BBHI3 (*A*) and WEHI4 (*B*). Each symbol (circle or triangle) represents data from a single trial. Circles represent probe trials; triangles represent adaptation trials; symbol colors represent the color of the targets within a given trial. *Inset* portrays the direction of the primary saccade (black arrow) and the direction of the intrasaccade target displacement during red (red arrow) and green (green arrow) adaptation trials. *C*: each bar represents the change in gain between pre- and postadaptation probe trials of a particular color (green, yellow, or red) for each of the 12 horizontal intermixed experimental sessions. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). *D*: the average change in gain (± SD) for each color across all 12 experimental sessions. The change in gain was not different between colors ($P = 0.7527$, Kruskal-Wallis test).

colors ($P = 0.7527$, Kruskal-Wallis test) nor were any of the changes in gain different from zero (green P value = 0.2334; yellow $P = 0.0522$; red $P = 0.2744$; Wilcoxon signed rank test).

Horizontal Intermixed White Target Experiments

Figure 3*A* portrays data from a horizontal intermixed white target experiment (BBWTHI1). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was 0.96 ± 0.04. Qualitatively, saccade gain during backward (black triangles) and forward (gray triangles) adaptation trials did not change during the adaptation phase and saccade gain during probe trials executed in the postadaptation phase was similar to the preadaptation phase (postprobe gain = 0.95 ± 0.05; $P = 0.3711$, Bonferroni corrected Wilcoxon rank sum test).

In contrast, Fig. 3*B* portrays data from another horizontal intermixed white target experiment (BBWTHI3) in which saccade gain changes between the pre- and postadaptation phases. During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was 0.92 ± 0.06. Qualitatively, saccade gain during backward (black triangles) and forward (gray triangles) adaptation trials increased slightly during the adaptation phase resulting in a postprobe saccade gain that was larger than the preadaptation phase (postprobe gain = 0.97 ± 0.06; $P = 0.0029$, Bonferroni corrected Wilcoxon rank sum test).

The histogram in Fig. 3*C* provides the mean (± SD) change in gain between pre- and postadaptation probe trials across all 11 experimental sessions (Monkey BB: $n = 3$, WE: $n = 5$, BU: $n = 3$). In 5/11 experiments (45%) saccade gain changed between pre- and postadaptation epochs and this change tended to be an increase (4/5 experiments). However, as with the horizontal intermixed color experiments described above, the change in gain across all 11 experiments (Fig. 3*D*) was not different from zero ($P = 0.1748$, Wilcoxon signed rank test).

Backward-Null Intermixed Color Experiments

Figure 4*A* portrays data from a horizontal backward-null intermixed color experiment (BBNS2). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was similar regardless of color (green = 0.96 ± 0.04; red = 0.94 ± 0.05; yellow = 0.94 ± 0.05). Qualitatively, saccade gain during red (backward) and green (forward) adaptation trials decreased during the adaptation phase resulting in postadaptation gains for every color that were significantly smaller than the preadaptation phase (postprobe green = 0.88 ± 0.04; red = 0.87 ± 0.05; yellow = 0.88 ± 0.03; $P < 0.000001$, Bonferroni corrected Wilcoxon rank sum test).

Figure 4*B* portrays data from another horizontal backward-null intermixed color experiment (BBSN4). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was similar regardless of color (green = 0.90 ± 0.03; red = 0.89 ± 0.04; yellow = 0.90 ± 0.04). In contrast to the previous example (Fig. 4*A*), saccade gain during red (backward) and green (forward) adaptation trials remained relatively constant during the adaptation phase. In postadaptation phase, saccades made during probe trials were either not different from (postprobe green = 0.92 ± 0.05;

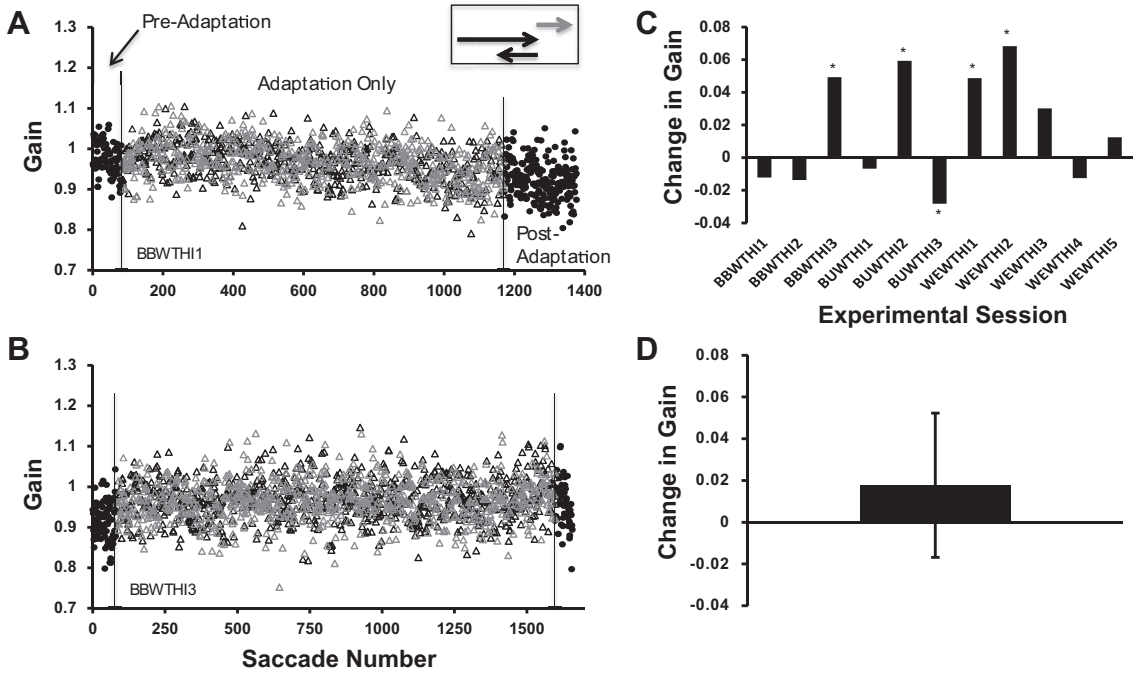

Fig. 3. Horizontal intermixed white target experiments. Horizontal, primary saccade gain during the preadaptation, adaptation, and postprobe segments of experiments BBWTHI1 (*A*) and BBWTHI3 (*B*). Each symbol (circle or triangle) represents data from a single trial. Circles represent probe trials; triangles represent adaptation trials; during the adaptation phase, black triangles represent backward adaptation trials, whereas gray symbols represent forward adaptation trials. *Inset* portrays the direction of the primary saccade (black arrow pointed to the right) and the direction of the intrasaccade target displacement during backward (black arrow pointed to the left) and forward (gray arrow) adaptation trials. *C*: the change in gain between pre- and postadaptation probe trials is plotted for each of the 11 white target horizontal intermixed experimental sessions. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). *D*: the average change in gain (± SD) across all 11 experimental sessions. The change in gain was not different from zero ($P = 0.1748$, Wilcoxon signed rank test).

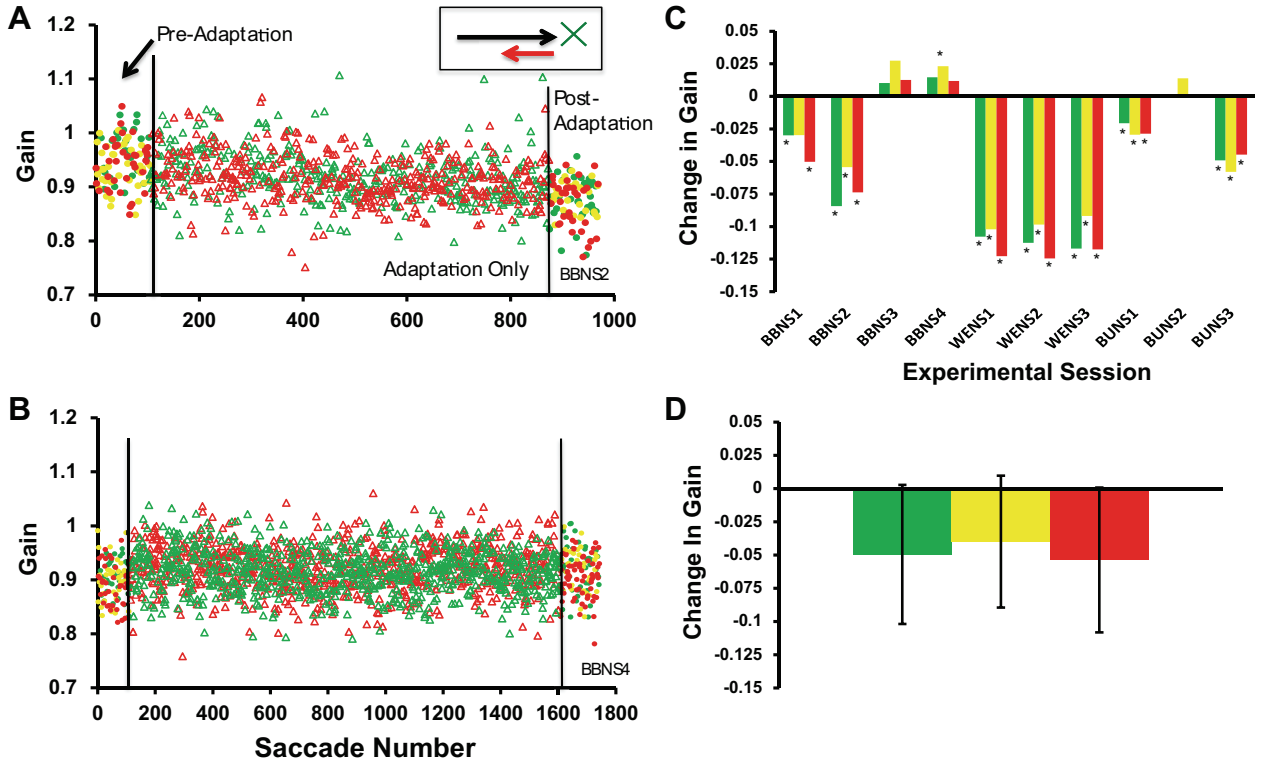

Fig. 4. Backward-null color experiments. Horizontal, primary saccade gain during the preadaptation, adaptation, and postprobe segments of experiment BBNS2 (*A*) and BBNS4 (*B*). Symbols, colors, and *inset* are the same as described for Fig. 2. *C*: each bar represents the change in gain between pre- and postadaptation probe trials of a particular color (green, yellow, or red) for each of the 10 backward-null experimental sessions. Note: a very small positive change in gain did occur for the green and red trials in experiment BUNS2. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). *D*: the average change in gain (± SD) for each color across all 10 experimental sessions. The change in gain was not different between colors ($P = 0.7217$, Kruskal-Wallis test).

red = 0.90 ± 0.04; $P > 0.016$, Bonferroni corrected Wilcoxon rank sum test) or slightly larger than those in the preadaptation phase (yellow = 0.92 ± 0.04, $P = 0.0099$).

The histogram in Fig. 4*C* provides the mean (± SD) change in gain between pre- and postadaptation probe trials for each color across all 10 experimental sessions (Monkey BB: $n = 5$, WE: $n = 5$, BU: $n = 2$). In 6/10 (60%) experiments, saccade gain significantly decreased between pre- and postadaptation epochs for all three colors. The histogram plot in Fig. 4*D* summarizes the change in saccade gain between pre- and postadaptation probe trials for each color across all 10 horizontal backward-null color experiments. In summary, the change in saccade gain was not different between colors ($P = 0.7217$, Kruskal-Wallis test) and the change in gain was different from zero for each color ($P < 0.05$, Wilcoxon signed rank test).

Backward-Null White Target Intermixed Experiments

Figure 5*A* portrays data from a horizontal-null white target intermixed experiment (BBWTN1). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was 0.94 ± 0.04. Qualitatively, saccade gain during backward (black triangles) and forward (gray triangles) adaptation trials did not change during the adaptation phase and saccade gain during probe trials executed in the postadaptation phase was similar to the preadaptation phase (postprobe gain = 0.94 ± 0.07; $P = 0.7958$, Bonferroni corrected Wilcoxon rank sum test).

In contrast, Fig. 5*B* portrays data from another horizontal intermixed white target experiment (BUWTN2) in which saccade gain changes between the pre- and postadaptation phases. During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was 0.99 ± 0.02. Qualitatively, saccade gain during backward (black triangles) and forward (gray triangles) adaptation trials increased slightly during the adaptation phase resulting in a postprobe saccade gain that was larger than the preadaptation phase (postprobe gain = 0.95 ± 0.03; $P < 0.0001$, Bonferroni corrected Wilcoxon rank sum test).

The histogram in Fig. 5*C* provides the mean (± SD) change in gain between pre- and postadaptation probe trials across all 8 experimental sessions (Monkey BB: $n = 2$, WE: $n = 3$, BU: $n = 3$). In 6/8 experiments (75%) saccade gain changed between pre- and postadaptation epochs and this change tended to be a decrease (5/8 experiments). Although there was a trend towards a decrease in saccade gain across all 8 experiments, this change was not different from zero (Fig. 5*D*; $P = 0.1094$, Wilcoxon signed rank test).

Orthogonal Intermixed Color Experiments

Figure 6, A (BBUDC4) and *B* (WEUDC4), portrays data from two orthogonal intermixed color experiments in which vertical saccade amplitude significantly increased between the pre- and postadaptation epochs for all three colors. The histogram in Fig. 6*C* provides the mean (± SD) change in gain between pre- and postadaptation probe trials for each color across all 9 experimental sessions (Monkey BB: $n = 4$, WE:

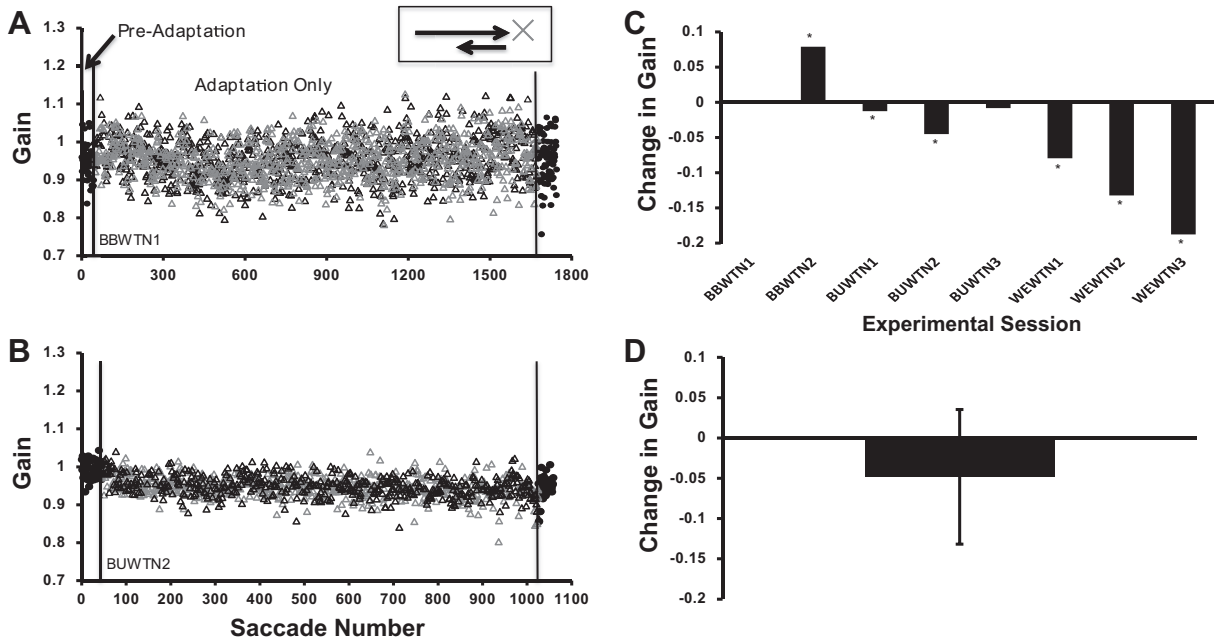

Fig. 5. White target backward-null experiments. Horizontal, primary saccade gain during the preadaptation, adaptation, and postprobe segments of experiments BBWTN1 (*A*) and BUWTN2 (*B*). Each symbol (circle or triangle) represents data from a single trial. Circles represent probe trials; triangles represent adaptation trials; during the adaptation phase, black triangles represent backward adaptation trials, whereas gray symbols represent null trials. *Inset* portrays the direction of the primary saccade (black arrow pointed to the right) and the direction of the intrasaccade target displacement during backward adaptation (black arrow pointed to the left) and null (gray X) trials. *C*: the change in gain between pre- and postadaptation probe trials is plotted for each of the 8 white target horizontal backward-null experimental sessions. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). Note, the change in BBWTN1 between pre- and postadaptation probe trials was zero. *D*: the average change in gain (± SD) across all 8 experimental sessions. The change in gain was not different from zero ($P = 0.1094$, Wilcoxon signed rank test).

$n = 5$). In 5/9 (56%) experiments saccade gain increased significantly between pre- and postadaptation epochs for all three colors. Last, the histogram plot in Fig. 6*D* summarizes the change in saccade gain between pre- and postadaptation probe trials for each color across all 9 orthogonal intermixed color experiments. In brief, the change in saccade gain was not different between colors ($P = 0.9569$, Kruskal-Wallis test) nor were any of the changes in gain different from zero (green P value = 0.0742; yellow $P = 0.0769$; red $P = 0.0547$; Wilcoxon signed rank test).

Horizontal (Short) Block Color Experiments

Figure 7*A* portrays data from a horizontal block color experiment (BBHB2). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was similar regardless of color (green = 0.95 ± 0.05; red = 0.95 ± 0.05; yellow = 0.94 ± 0.04). Qualitatively, saccade gain during red (backward) and green (forward) adaptation trials did not change during the adaptation phase in which adaptation trials were presented in alternating blocks of ~30 trials. Furthermore, saccade gain during probe trials executed in the postadaptation phase was not different from those in the preadaptation phase (postprobe green = 0.94 ± 0.04; red = 0.95 ± 0.04; yellow = 0.92 ± 0.05; $P > 0.016$, Bonferroni corrected Wilcoxon rank sum test).

Figure 7*B* portrays data from another horizontal block color experiment (BUHB2). During the preadaptation phase of this experiment the mean (± SD) gain of primary saccades made to T_1 was similar regardless of color (green = 0.95 ± 0.02; red = 0.94 ± 0.03; yellow = 0.94 ± 0.03). In contrast to the previous example (Fig. 7*A*), saccade gain during red (backward) and green (forward) adaptation trials increased during the adaptation phase resulting in postadaptation probe trials that were larger than those in the preadaptation phase (postprobe green = 0.99 ± 0.03; red = 0.99 ± 0.03; yellow = 0.99 ± 0.04; $P < 0.00001$, Bonferroni corrected Wilcoxon rank sum test).

The histogram in Fig. 7*C* provides the mean (± SD) change in gain between pre- and postadaptation probe trials for each color across all 9 experimental sessions (Monkey BB: $n = 2$, WE: $n = 4$, BU: $n = 3$). In 3/12 experiments (25%) saccade gain changed between pre- and postadaptation epochs for all three colors and, as with previous examples, the change in gain was always in the same direction. Last, the histogram plot in Fig. 7*D* summarizes the change in saccade gain between pre- and postadaptation probe trials for each color across all 9 horizontal block color experiments. In brief, the change in saccade gain was not different between colors ($P = 0.7662$, Kruskal-Wallis test) nor were any of the changes in gain different from zero (green P value = 0.3008; yellow $P = 0.3008$; red $P = 0.5703$; Wilcoxon signed rank test).

Horizontal Sequential (Long Block) Color Experiments

Figure 8*A* portrays data from an exemplar horizontal sequential experiment (BBHS3). The gains of saccades made to T_1 were similar regardless of color in the preadaptation phase of this experiment (green = 0.94 ± 0.06; red = 0.94 ± 0.05; yellow 0.92 ± 0.04). During the first adaptation block (red trials, backward adaptation), the gain of the primary saccades gradually declined such that the gain of the red probe trials that immediately followed this adaptation block was significantly smaller than the red probe trials from the preadaptation phase (postprobe mean ± SD = 0.80 ± 0.05; $P < 0.0001$, Bonfer-

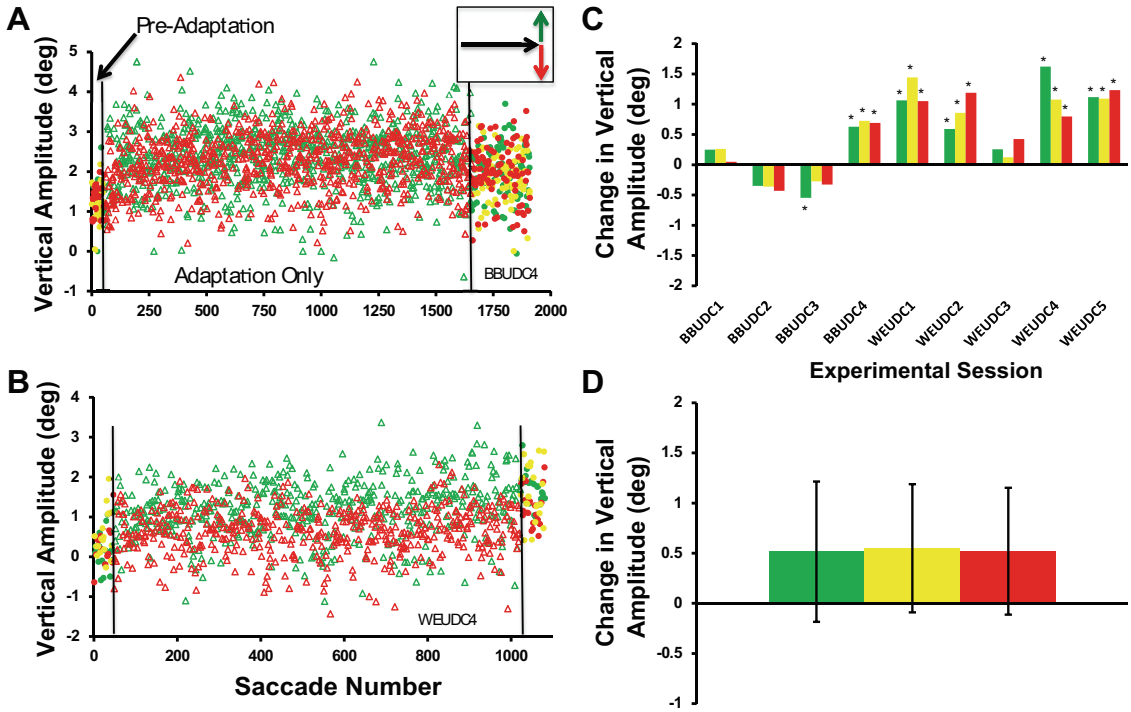

Fig. 6. Orthogonal intermixed experiments. Vertical, primary saccade amplitude during the preadaptation, adaptation, and postprobe segments of experiment BBUDC4 (*A*) and WEUDC4 (*B*). Symbols, colors, and *inset* are the same as described for Figs. 2 and 4. *C*: each bar represents the change in vertical amplitude between pre- and postadaptation probe trials of a particular color (green, yellow, or red) for each of the 9 backward-null experimental sessions. *Significant change in amplitude ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). *D*: the average change in amplitude (± SD) for each color across all 9 experimental sessions. The change in amplitude was not different between colors ($P = 0.9569$, Kruskal-Wallis test).

roni corrected Wilcoxon rank sum test). During the ensuing green (forward) adaptation block, the gain of saccades produced gradually increased such that the gain of the last 15 green adaptation trials at of this segment was qualitatively similar to that of the preadaptation green probe trials (mean ± SD 1.00 ± 0.03). In fact, the gain of the preadaptation probe trials for green, red, and yellow targets were not different from the postadaptation probe trials of that same color (postprobe

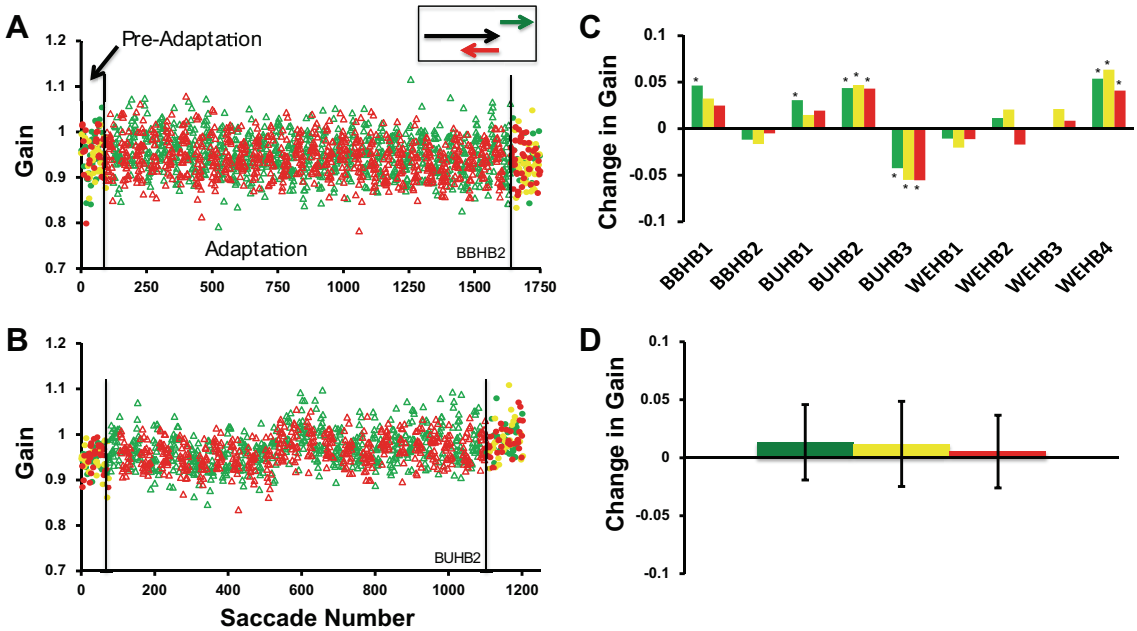

Fig. 7. Horizontal color block experiments. Horizontal, primary saccade gain during the preadaptation, adaptation, and postprobe segments of experiment BBHB2 (*A*) and BUHB2 (*B*). Symbols, colors, and *inset* are the same as described for Figs. 2, 4, and 6. *C*: each bar represents the change in gain between pre- and postadaptation probe trials of a particular color (green, yellow, or red) for each of the 9 horizontal color block experimental sessions. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). Note the change in gain between pre- and postadaptation green probe trials in experiment WEHB3 was nearly zero. *D*: the average change in gain (± SD) for each color across all 9 experimental sessions. The change in gain was not different between colors ($P = 0.7662$, Kruskal-Wallis test).

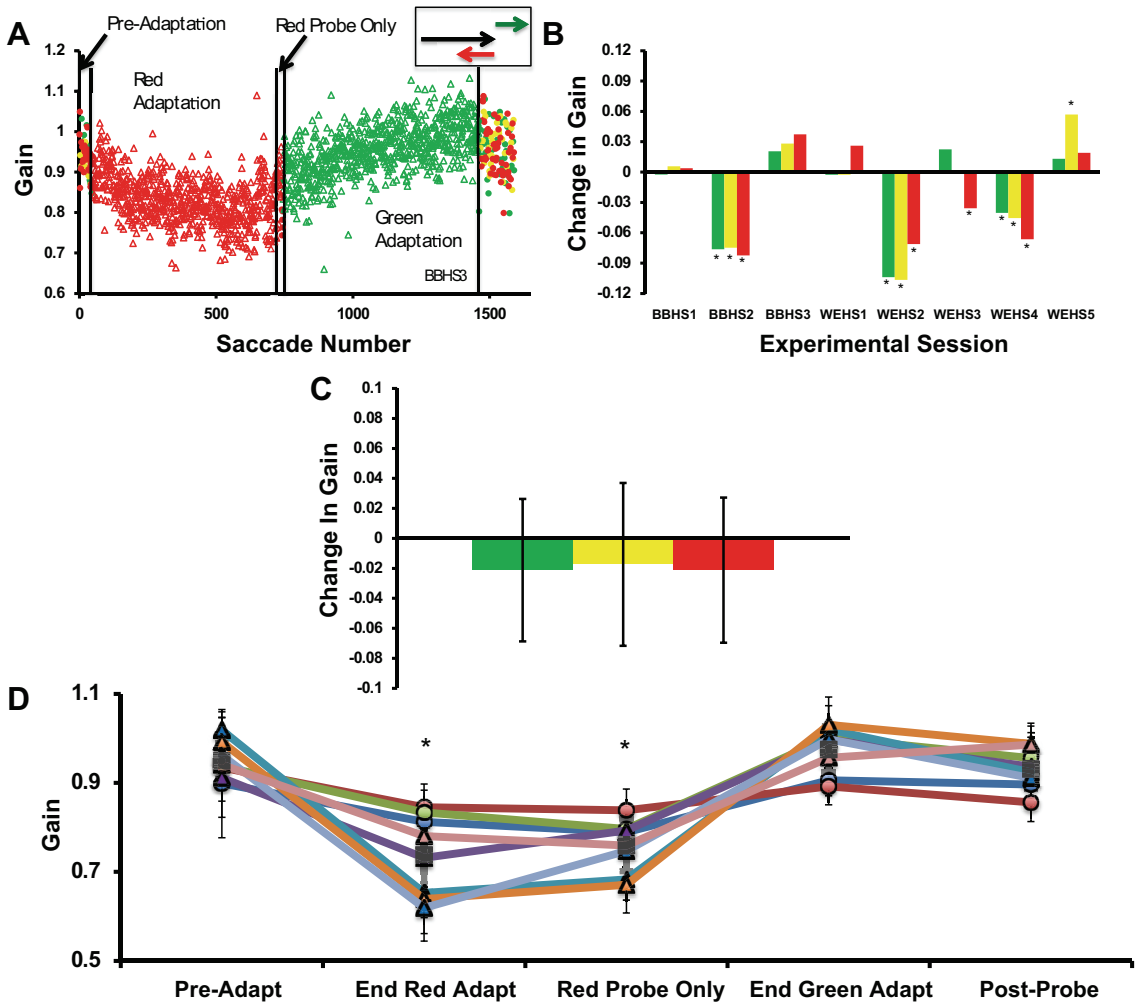

Fig. 8. Horizontal sequential experiments. *A*: horizontal, primary saccade gain during the preadaptation, red and green adaptation, red probe only, and postprobe segments of experiment BBHS3. Symbols, colors, and *inset* are the same as described for Figs. 2, 4, 6, and 7. *B*: each bar represents the change in gain between pre- and postadaptation probe trials of a particular color (green, yellow, or red) for each of the 8 horizontal color sequential experimental sessions. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). Note the change in gain between pre- and postadaptation yellow probe trials in experiment WEHS3 was nearly zero. *C*: the average change in gain (± SD) for each color across all 8 experimental sessions. The change in gain was not different between colors ($P = 0.9614$, Kruskal-Wallis test). *D*: saccade gain as a function of session epoch (Pre-Adapt, End Red Adapt, Red Probe Only, End Green Adapt, and Post-Probe) during all Horizontal Sequential Experiments. Circles and triangles represent data from monkeys BB and WE, respectively. Pre-, Red Only, and Post-Probe mean were taken from all trials in that epoch regardless of color. Gains from the adaptation phases were calculated using either the last 15 (End Red Adapt and End Green Adapt epochs) or the first 15 (Begin Green Adapt epoch) adaptation trials. Gray squares represent the grand mean (± SD) across all sessions for that epoch. *Significant change in the grand mean between an epoch and the preadaptation phase ($P < 0.01$, Kruskal-Wallis test).

green = 0.95 ± 0.06, red = 0.95 ± 06, yellow = 0.96 ± 0.05; two-tailed *t*-test, $P > 0.05$, Bonferroni corrected Wilcoxon rank sum test).

The histogram in Fig. 8*B* provides the mean (± SD) change in gain between pre- and postadaptation probe trials for each color across all 8 experimental sessions (Monkey BB: $n = 3$, WE: $n = 5$). In the majority of cases (5/8), two or more of the colors did not change significantly between the pre- and postadaptation phases. In the remaining three cases (BBHS2, WEHS2, WEHS4), postadaptation probe trials were significantly smaller than preadaptation probe trials for all three colors; this is most likely the result of incomplete recovery from the gain reduction that occurred during the red adaptation segment. Regardless, it should be noted that the change in gain in these three cases is in the same direction. Last, the histogram plot in Fig. 8*D* summarizes the change in saccade gain between pre- and postadaptation probe trials for each color across all 8 horizontal sequential experiments. In brief, the change in saccade gain was not different between colors ($P = 0.9614$, Kruskal-Wallis test) nor were any of the changes in gain different than zero (green P value = 0.4609; yellow $P = 0.5469$; red $P = 0.3828$; Wilcoxon signed rank test).

Unlike the outcome of horizontal intermixed and blocked sessions, changes in saccade gain were observed during the red-only and green-only adaptation phases in sequential blocks which illustrates that each of our subjects were able to modify saccade gain in response to large intra-saccade target displacements within the time frame of our experiments. Figure 8*D* illustrates this point by plotting the gain across the different epochs. Each session was divided into six epochs. Mean (± SD) gain during "Pre-Adapt Probe", "Red Probe Only", and "Post-Adapt Probe" epochs was assessed by averaging all probe trials within these segments regardless of color. Mean gain during the adaptation epochs was assessed by averaging 15 adaptation trials

at the end of a particular adaptation segment. In this figure, each session is represented by a different color and each monkey by a different symbol (BB = circles; WE = triangles). Last, the mean (± SD) across all sessions for a particular epoch is represented by a gray square and dotted line. Generally, the changes in gain observed across phases in the exemplar session (Fig. 8*A*) were present across all experimental sessions (Fig. 8*D*). On average, saccade gain: *1*) decreased significantly between Pre-Adapt Probe and End Red Adapt ($P = 0.0016$, Kruskal-Wallis test) epochs; *2*) was maintained at this new, lower gain state throughout the Red Probe Only phase ($P = 0.0021$, Kruskal-Wallis test) and; *3*) returned to baseline levels by the last 15 trials of the green adaptation phase (End Green Adapt; $P = 0.1348$, Kruskal-Wallis test).

Backward-Up Intermixed Color Experiments

The results from each of the aforementioned experiments suggest that the adaptive control system does not use color as a contextual cue. If this is true, then error signals provided on adaptation trials using one color should transfer to both adaptation and probe trials that use other colors. We tested this prediction by concurrently intermixing backward (red) and upward (green) adaptation trials during the adaptation phase of our concurrent experiments. Figure 9*B* shows the horizontal amplitude vs. trial plots for one of these experiments in subject BB (BBBUC1). As with the previously described experiments, the horizontal amplitude of saccades during the preadaptation phase was similar between probe trials using different colors. During the adaptation phase, the horizontal amplitude of saccades decreased during adaptation trials using both red and green targets even though target displacement in the horizontal direction only occurred during red adaptation trials. This reduction in horizontal amplitude was also observed in the postprobe phase such that probe trials using red, green, and yellow targets were significantly smaller than that of comparable trials in the preadaptation phase. Finally, the percent transfer (green or yellow change in gain/red change in gain) from red to green probe trials was 92% whereas the transfer between red and yellow probe trials was 103% for this experiment.

Significant changes in horizontal saccade amplitude were seen for all three colors in all four experiments (Fig. 9*C*). The percent transfer from red to green probe trials was 85% whereas the transfer between red to yellow probe trials was 80% across all experiments.

Figure 9*B* shows the vertical amplitude vs. trial plots for the same experiment as Fig. 9*A*. The vertical amplitude was similar between probe trials using different colors in the preadaptation phase. During the adaptation phase, the vertical amplitude of saccades increased (was deviated upwards) during adaptation trials using both red and green targets even though target displacement in the vertical direction only occurred during green adaptation trials. This increase in vertical amplitude was also observed in the postprobe phase such that probe trials using red, green, and yellow targets were significantly larger than that of comparable trials in the preadaptation phase. Finally, the percent transfer (red or yellow change in gain/

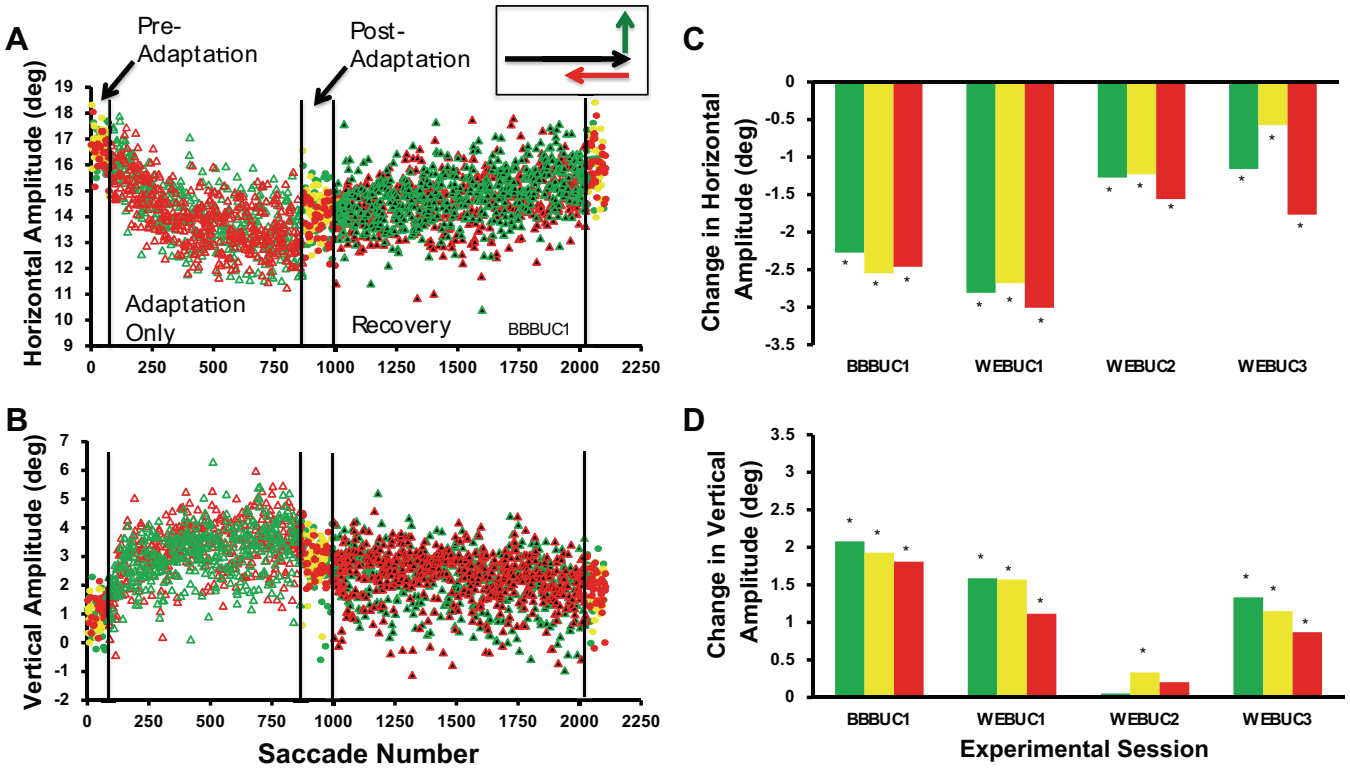

Fig. 9. Backward-up intermixed experiments. Horizontal (*A*) and vertical (*B*) primary saccade amplitude during the preadaptation, adaptation, and postprobe segments of experiment BBBUC1. A circle or triangle represents data from a single trial. Solid colored circles represent probe trials; open colored triangles represent adaptation trials; black triangles with colored borders represent recovery trials. Symbol/outline colors (red, green, or yellow) represent the color of the targets within a given trial. *Inset* portrays the direction of the primary saccade (black arrow), the direction of the intrasaccade target displacement during red (red arrow) and green (green arrow) adaptation trials. *C* and *D*: each bar represents the change in vertical (*C*) or horizontal (*D*) gain between pre- and postadaptation probe trials for the 4 backward-up experiments. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test).

green change in gain) from green to red probe trials was 87% whereas the transfer between green and yellow probe trials was 94% for this experiment.

Significant changes in vertical amplitude were seen in all three colors in 3 of 4 experiments (Fig. 9*D*). The percent transfer from green to red probe trials was 79% whereas the transfer between green to yellow probe trials was 80% across all experiments.

Initial Eye Position (Short) Block Experiments

Previously, Tian and Zee (2010) were able to show that initial eye position (IEP) could be used to elicit differential gain states as along as backward and forward trials were presented in alternating blocks during the adaptation phase. We attempted to repeat this experiment to compare the magnitude of gain modifications using an external (target color) with an internal (proprioceptive) cue. Figure 10 portrays data from two exemplar IEP experiments in monkey WE (*A*: WEIEPB3; *B*: WEIEPB4). In Fig. 10*A*, the mean (± SD) gain of primary saccades made to T_1 and initiated from the up IEP (gray circles) during the preadaptation phase was smaller than those initiated from the down IEP (black circles; $P < 0.00001$, Wilcoxon rank sum test). Qualitatively, gain for those saccades initiated from the up IEP (forward adaptation trials, gray triangles) increased slightly whereas saccades initiated from the down IEP (backward adaptation, black triangles) decreased slightly. Postadaptation probe trials were run in blocks of ~30 trials (Tian and Zee 2010). Saccade gain during down IEP postadaptation probe trials were smaller than those in the preadaptation phase ($P < 0.0001$, Wilcoxon rank sum test). Saccade gain during up IEP postadaptation probe trials were larger than those in the preadaptation phase ($P < 0.0001$, Wilcoxon rank sum test). This pattern occurred in 3/9 of our experiments (Fig. 10*C*).

In the remaining six experiments saccade gain either changed in the same direction regardless of IEP (e.g., Fig. 10*B*; Fig. 10*C*, 2/9 experiments) or saccade gain changed significantly for saccades initiated from only one of the two IEPs (Fig. 10*C*, 4/9 experiments). The histogram in Fig. 10*D* provides the mean (± SD) change in gain between pre- and postadaptation probe trials across all nine experimental sessions (Monkey BB: $n = 3$, WE: $n = 5$, BU: $n = 1$). The change in gain was not different from zero for backward adaptation ($P = 0.3008$, Wilcoxon signed rank test), but was different from zero for forward adaptation contexts ($P = 0.0195$, Wilcoxon signed rank test). This type of variability within and between subjects was also reported by Tian and Zee (2010) (see DISCUSSION).

DISCUSSION

Major Observations

The experiments reported here were designed to test the hypothesis that distinct saccade gain states could be elicited using static, colored targets as the contextual cue. In our

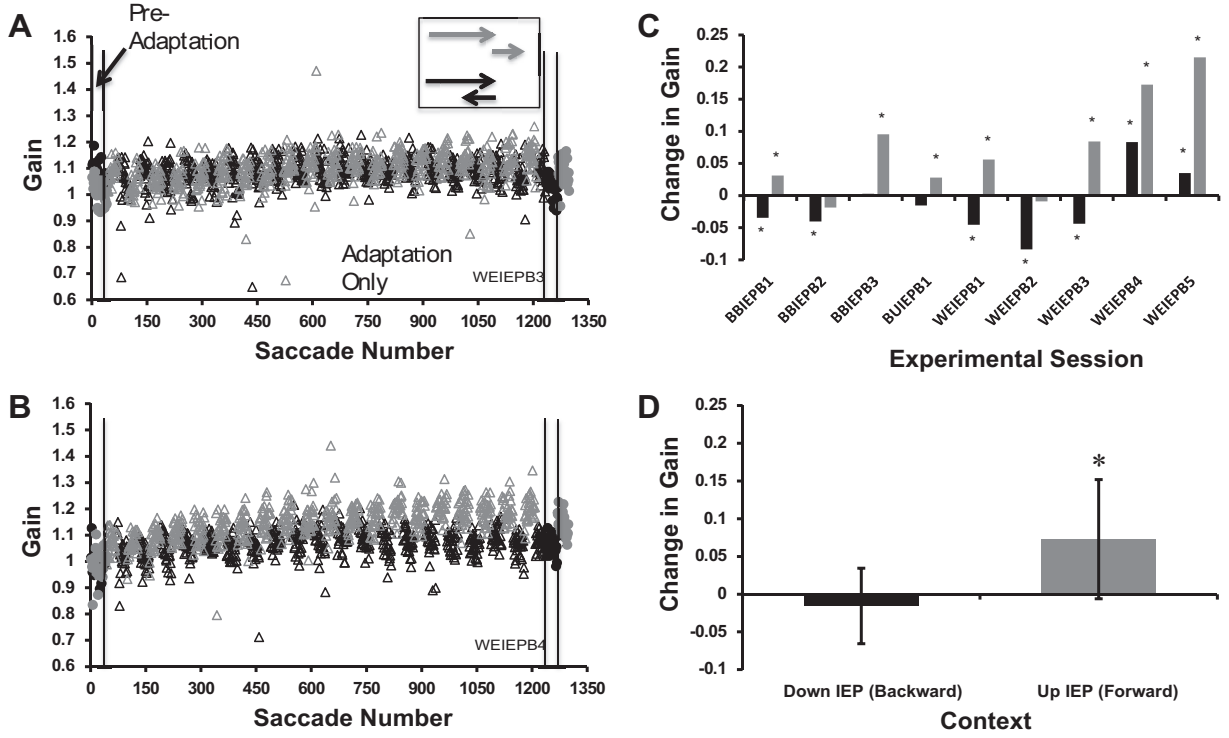

Fig. 10. Initial eye position (IEP) context cue experiments. Horizontal, primary saccade gain during the preadaptation, adaptation, and two postprobe segments of experiments WEIEPB3 (*A*) and WEIEPB4 (*B*). Circles represent probe trials; triangles represent adaptation trials; during the adaptation phase, black triangles represent backward adaptation trials, whereas gray triangles represent forward adaptation trials. *Inset* portrays the direction of the primary saccade (longer black or gray arrow pointed to the right) as well as the direction of the intra-saccade target displacement when the eyes were deviated 10° downward (black, backward adaptation) or upward (gray, forward adaptation). *C*: the change in gain between pre- and postadaptation probe trials is plotted for each of the 9 IEP experimental sessions. *Significant change in gain ($P < 0.016$, Bonferroni corrected Wilcoxon rank sum test). *D*: the average change in gain (± SD) across all 9 experimental sessions. The change in gain was not different from zero for backward adaptation ($P = 0.3008$, Wilcoxon signed rank test), but was different from zero for forward adaptation contexts (*$P = 0.0195$, Wilcoxon signed rank test).

experiments the intra-saccade target displacement during adaptation trials was large (9° or ~50% of primary saccade amplitude) and was either along the same axis as (Figs. 2, 4, 7, 8), or orthogonal (Fig. 6) to, our subjects' primary saccades. Under these conditions, subjects were unable to elicit distinct adaptation states based on color regardless of whether the color cues were presented in randomly intermixed trials (Figs. 2 and 6), in short (Fig. 7) or long blocks (Fig. 8), or when only one (red) of the three possible color cues had an intra-saccade target displacement (Fig. 4). Furthermore, we observed near complete transfer between trials meant to reduce horizontal amplitude (using red targets) and those trials that were meant to increase the vertical component of the primary movement (using green targets; Fig. 9). Last, the behavior of our subjects during control trials using white targets (Figs. 3 and 5) was qualitatively similar to that observed during color cue experiments. These observations are consistent with those hypotheses that state that color cannot be used as a visual cue for adaptation and are in line with prior observations made in humans (Azadi and Harwood 2014; Benjamin et al. In press; Deubel 1995).

A rather simple and parsimonious explanation can readily account for our findings: adaptation is driven by the average error (visual or motor) across numerous trials. During horizontal randomly intermixed trials (Figs. 2 and 3), the average error is zero and, hence, no change in saccade gain was observed. This was true for color context trials and white target trials. During "backward-null" trials, the target either stepped closer to the original fixation point or remained illuminated at the original location. The average error across trials for this condition is therefore larger than the error during the horizontal intermixed experiments and in a direction that would normally elicit backward adaptation. Accordingly, the saccade gain decreased (Figs. 4 and 5) relative to the slight (but not significant) increase in the former condition (Figs. 2 and 3). For the sequential adaptation experiment (Fig. 8), the target steps in the same direction on every trial. Thus the average error is greatest in this condition, as is the change in saccade gain. Finally, Fig. 9 provides a test of the simple hypothesis. When the target location is displaced either horizontally or vertically in randomly intermixed trials, the average error across trials contains a combination of both components. As predicted, saccades adapted in both dimensions.

Context-Dependent Adaptation: Comparison to Previous Observations

Attempts to elicit context-dependent saccadic adaptation have primarily been made using human subjects (for reviews see Herman et al. 2013; Pélisson et al. 2010; but note Tian and Zee 2010). To the best of our knowledge, the experiments discussed in the current report were the first attempt to elicit context-dependent saccade adaptation in the rhesus monkey using a visual cue of any type. Furthermore, our report improves and extends the human experiments performed by both Deubel (1995) and Azadi and Harwood (2014) in several ways: *1*) Deubel made his observations in two human subjects with very few trials and only two experiments. Our data set therefore represents a much more powerful assessment of Deubel's preliminary observations using colored, static targets; *2*) we used large intra-saccade target displacements (50% of target eccentricity) which have been successful at eliciting large gain changes in head-restrained monkey subjects (figure 11 from Cecala and Freedman 2009). This should have increased the likelihood of observing even a small, color-dependent change in saccade gain; *3*) both Deubel (1995) and Azadi and Harwood (2014) attempted to simultaneously increase and decrease saccade gain within the same axis of the primary saccade, which is much like the "horizontal intermixed" experiments in the current report (Fig. 2). Our "horizontal short block" (Fig. 7), "horizontal sequential" (Fig. 8), "backward-null" (Fig. 4), "orthogonal intermixed" (Fig. 6), and "backward-up intermixed" (Fig. 9) experiments represent novel tests of the stated hypotheses (see MATERIALS AND METHODS) and therefore help to clarify our understanding of the adaptive mechanism underlying primate adaptation. What remains unclear is why the saccadic adaptive control system would take into account some internal and external cues (initial eye position: Alahyane and Pélisson 2004; target flicker: Herman et al. 2009; target shape, color: Madelain et al. 2010; moving target direction and/or speed: Azadi and Harwood 2014), but not others (target shape, color: Deubel 1995; Bahcall and Kowler 2000; Azadi and Harwood 2014).

Previous work in both humans (Alahyane and Pélisson 2004) and monkeys (Tian and Zee 2010) has shown that differential modifications to saccade gain can occur if different post-saccade visual errors are provided to saccades that were initiated from markedly different orbital eye positions. We were able to replicate this, albeit noisy, phenomenon using methods similar to that of Tian and Zee (2010) as a control for our color cue experiments (Fig. 10). Additional studies of eye position effects in monkeys and humans have shown that gain modifications at one eye position only partially transfer to saccades generated from other orbital eye positions and that the amount of transfer declines in a roughly Gaussian fashion (Haverman et al. 2011; Wulff et al. 2012; Zimmermann and Lappe 2011). Wulff and colleagues (2012) have hypothesized that the differential gain states observed in the aforementioned experiments could result from eye position modulation of the adaptive control mechanism's afferents during saccade production. The adaptive control mechanism would thereby recognize each of these inputs as a unique motor command to be assigned a unique gain state.

The medioposterior cerebellum (MPC), composed of the caudal fastigial nucleus and the oculomotor vermis, has been implicated in the adaptive control of saccadic eye movements (for reviews see Iwamoto and Kaku 2010; Prsa and Thier 2011; Robinson and Fuchs 2001). Saccade-related information from the deeper layers of the superior colliculus (dSC) is believed to be relayed to the MPC via the nucleus reticularis tegmenti pontis (NRTP). Single unit recordings from the dSC suggest that the motor command produced in this structure: *1*) specifies the amplitude and direction of a saccade (see Gandhi and Katnani 2011 for review); *2*) is modulated by orbital eye position (Campos et al. 2006; Krauzlis et al. 2000; Paré and Munoz 2001; van Opstal et al. 1995); and *3*) specifies a movement to the location of the first peripheral target (T_1), not the subject's actual movement, during the McLaughlin task (Frens and Van Opstal 1997; Quessy et al. 2010; but see Takeichi et al. 2007). Therefore, an eye position modulated motor command meant to generate a saccade towards T_1 during the McLaughlin task could be sent from the dSC to the

cerebellar adaptive control mechanism and paired with a particular saccade gain state (Wulff et al. 2012). This hypothesized mechanism could account for eye position effects on gain adaptation observed in primate subjects.

Why then might some external (in this case visual) cues be able to drive context dependent learning and not others? In our experiments, the use of chromatic cues (red, green, or yellow visual targets) was unable to drive contextual adaptation. Chromatic modulation of sensory activity has been observed in the dSC (White et al. 2009; White and Munoz 2011) and is most likely the result of inputs to these layers from V4 (Fries 1984; Lock et al. 2003) and/or the frontal eye fields (FEF; Schall et al. 1995). However, the chromatic visual responses of neurons in the SC show "strong sensitivity, but only moderate selectivity, for color" (White et al. 2009) and the motor responses of visuomotor cells may not be significantly different under the conditions used in our, and previous, context cue experiments using color (Azadi and Harwood 2014; Deubel 1995; White et al. 2009; White and Munoz 2011). Based on these physiological observations, and the assumption that an efference copy of the color invariant SC motor command is provided to the cerebellar adaptive control mechanism, we would not expect target color would be able to drive context-dependent adaptation because there is not a gain field for color in the dSC like there is for eye position.

Using human subjects, Herman and colleagues (2009) were able to elicit context-dependent adaptation using flickering (a square wave at a rate of 5 Hz) vs. nonflickering visual targets. To our knowledge no one has contrasted the effects of this exact stimulus on the motor activity produced by single units in the deeper layers of the SC. However, neuronal adaptation in the visual response has been observed in the superficial and deep layers of the SC to sequentially presented stimuli at time intervals similar to that used by Herman and colleagues (e.g., 1.25–59 Hz, Mayo and Sommer 2008; 0.8–20 Hz Fecteau and Munoz 2005). Therefore, it is possible that flickering and nonflickering stimuli are represented differently within the SC and that the motor commands associated with these stimuli can be differentiated by the cerebellar adaptive control mechanism. This hypothesis can account for the context-dependent learning observed in human adaptation experiments using flickering cues and can be addressed empirically with neuronal recordings in the deep layers of the SC of monkeys.

Azadi and Harwood (2014) were able to use the speed and direction (clockwise or counterclockwise) of circularly moving targets as a contextual cue in humans. Keller et al. (1996) compared the movement fields of deep layer SC neurons of monkeys when they produced saccades to stationary targets vs. when they made interceptive saccades to targets moving at either 45 or 60°/s away from the fixation point. While their dataset was not exhaustive, these authors observed a systematic shift in the center of the movement field in the direction of target motion and a reduction in the firing rate for the optimal vector. If the SC population activity is different during motions at different speeds and directions, then the cerebellar adaptive control system could use this information to recognize two distinct "contexts" and pair these contexts with specific gains. Again, this hypothesis can be addressed empirically with single unit neuronal recordings.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: A.L.C. and N.J.G. conception and design of research; A.L.C., I.S., and S.B.K. performed experiments; A.L.C. analyzed data; A.L.C., M.A.S., and N.J.G. interpreted results of experiments; A.L.C. prepared figures; A.L.C. drafted manuscript; A.L.C., I.S., S.B.K., M.A.S., and N.J.G. edited and revised manuscript; A.L.C., I.S., S.B.K., M.A.S., and N.J.G. approved final version of manuscript.

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