Signals driving the adaptation of saccades that require spatial updating

Robijanto Soetedjo[1, 2]

Department of Physiology and Biophysics[1], Washington National Primate Research Center[2], University of Washington, Seattle, Washington, Washington 98195, USA.

Abbreviated title: retinotopic target and saccade adaptation

Correspondence:
Robijanto Soetedjo,
1705 NE Pacific Street, HSB Room G424,
Box 357290, University of Washington,
Seattle, WA 98195-7290.
E-mail: robi@uw.edu
Phone: 1-206-616-1431. Fax: 1-206-685-0305.

Keywords: Saccade, Adaptation, Transfer, Movement Spatial Updating

Abstract

Saccades adapt to persistent natural or artificially imposed dysmetrias. The characteristics and circuitry of saccade adaptation have been revealed using a visually guided task (VGT) where the vectors of the target step and the intended saccade command are the same. However, in real life, another saccade occasionally intervenes before the saccade to the target occurs. This necessitates an updating of the intended saccade to account for the intervening saccadic displacement, which dissociates the visual target signal and the intended saccade command. We determined whether the adaptation process is similar for VGT and updated saccades by studying the transfer of adaptation between them. The ultimate visual target was dissociated from the intended saccade command with double-step saccade tasks (DSTs) in which two targets are flashed sequentially at different locations while the monkey maintains fixation. The resulting saccades toward the first and second targets occur in the dark. The transfer of visually guided saccade adaptation to the second saccades of a DST and vice versa depended on the eccentricity of the second visual target, and not the second saccade command. If a target with the same eccentricity as the adapted target appears briefly during the intersaccadic interval of a DST, more adaptation transfers. Because a brief appearance of the visual target either before the first saccade or during the intersaccadic interval influences how much adaptation transfer the second saccade will express, the processing of adaptation and DST updating may overlap.

New & Noteworthy:

Adaptation and the spatial updating of saccades are thought to be independent processes. When we dissociate the visual target and the intended saccade command, the transfer of visually guided saccade adaptation to the saccades of the DST and vice versa is driven by a visual not motor error. The visual target has an effect until the second saccade of a DST occurs. Therefore, the processing of adaptation and the spatial updating of saccades may overlap.

Introduction

The ability of saccades to recover following nerve palsy (Kommerell et al. 1976) or injury to the extraocular muscles (Optican and Robinson 1980) suggests that the saccadic system has access to adaptation mechanisms that gradually repair persistent motor errors. To elicit saccade adaptation in the laboratory, the oculomotor system is deceived into thinking it is in error by jumping the visual target during a saccade to a target so the eye either overshoots or undershoots (McLaughlin 1967). After a delay, a backward or forward corrective saccade, respectively, eliminates the visual error created by the intrasaccadic target step (ISS). After many such deceptions [~100 for human (Albano 1996; Deubel et al. 1986; Frens and van Opstal 1994) and ~1000 for monkey (Straube et al. 1997)], the first saccade gradually becomes smaller or larger to reduce the visual error.

Most studies suggest that adaptation modifies the motor command of saccades (Hopp and Fuchs 2004). Indeed, saccade adaptation has been used in both behavioral and neurophysiological studies as a tool to dissociate the visual and motor aspects of saccade programming (Frens and Van Opstal 1997; Quaia et al. 2010; Quessy et al. 2010; Steenrod et al. 2013; Takeichi et al. 2007). However, recent evidence suggests that saccade adaptation also affects the perception of the location of targets (Awater et al. 2005; Bahcall and Kowler 1999; Moidell and Bedell 1988; Zimmermann and Lappe 2009). These studies suggest that adaptation may occur at the sensory level, at least partially. The visually guided saccade task (VGT), which has been used to characterize saccade adaptation, cannot distinguish these two possibilities. In the VGT, a fixated spot jumps to a new location, and after a reaction time, the subject makes a saccade to foveate the target spot at its new location. Therefore, the retinotopic vector of the visual target step and the vector of the desired saccade motor command (DSMC) for the saccade are the same. In this situation, it is unclear whether adaptation operates on a signal related to the retinotopic target vector or the DSMC. To understand the mechanisms underlying saccade adaptation, we must disambiguate these two signals.

It is possible to dissociate a visual target signal from the saccadic motor command used to reach the target by employing a double step saccade task (DST, Fig. 1B-E). In a DST, two target spot locations (T1 and T2) are flashed sequentially before the subject makes a saccade to T1 (Hallett and Lightstone 1976a; b). When the presentations of T1 and T2 are timed appropriately (Becker and Jurgens 1979), the subject makes two sequential saccades to T1 and T2 in the dark. Before any saccade has occurred, the command for the second saccade would be the distance to T2 (T2-F). After the first saccade, however, the motor command for the second saccade must be updated by subtracting the first saccade vector from T2 in order to take into account the eye position before the second saccade (Quaia et al. 2010; Tanaka 2003). Now the vectors of the initial visual target T2 and the desired motor command for the second saccade have been dissociated.

In this study, we employed various DSTs to dissociate the retinotopic target location from the desired motor command for the saccade, and manipulated these two signals independently to determine their relative influences on the adaptation of saccades. We adapted VGT saccades and determined the transfer of adaptation to the second saccades of a DST where the visual target signal and saccade command signals were different. Also, we adapted the second saccades of a DST and assessed the transfer to VGT saccades.

Our results suggest that the retinotopic target vector influences the transfer of saccade adaptation and that saccade motor command signals do not. Moreover, when a DST fully dissociates the retinotopic target and the saccade motor command signals, adaptation does not transfer between VGT saccades and the second saccades of a DST. These observations allow us to speculate where and how the brain might use these signals to process saccade adaptation and to produce the second saccades of a DST.

Figure 1 near here

Methods

All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals and exceeded the minimum requirements recommended by the Institute of Laboratory Animal Resources and the Association for Assessment and Accreditation of Laboratory Animal Care International. All the procedures were evaluated and approved by the local Animal Care and Use Committee of the University of Washington.

General procedures

The techniques that we use to monitor eye movements, and to train monkeys (*Macaca mulatta*) to follow small jumping targets with their eyes have been described in detail previously (Soetedjo et al. 2002). Briefly, the eye position of a head fixed monkey was measured using a scleral search coil technique that was approximately linear within ± 20° horizontally and vertically and had a sensitivity of 15 min arc (Fuchs and Robinson 1966). The target for a saccade was a red laser spot (~0.25° diameter) projected onto a tangent screen facing the monkey via an orthogonal set of computer controlled mirror galvanometers. A homemade Spike2 program controlled a Power 1401 data acquisition system (Cambridge Electronics Design, Cambridge, UK). This system controlled the laser power and the galvanometers as well as the reward to produce the tracking tasks. It also digitized the vertical and horizontal eye and target positions as well as the laser on-off state at a 1kHz sampling rate.

Two monkeys (L and M) were trained to track jumping target spots with their eyes (Fuchs 1967). They were required to saccade to a new target location within 400ms of a target jump and then to keep their gaze within a ±2.5° window surrounding the target location for at least 500ms. The next trial started 700-1400ms later. The monkeys were rewarded with a dollop of apple sauce every 1200-1400ms as long as they maintained the accuracy and timing requirements. If they did not, the reward was delayed for 2000-2500ms, and the reward schedule was resumed when they started working correctly again. The timing requirements between trials were the same for the other tasks described below.

Once the monkeys were trained to track a jumping target spot reliably for at least 2 hours, we switched to a visually guided saccade task with the target flashed for 40ms (VGT saccades, Fig. 1A) when we gathered data before and after adaptation. We flashed the VGT target to match the condition of the flashing target presentation of the DST tasks.

We also started training the monkeys on the DST tasks (Fig. 1B-E). Because saccade adaptation in monkeys appears to occur on the horizontal or vertical component of the eye movement independently, all tasks involved only horizontal saccades (Kojima et al. 2005). We optimized the timing of T1 and T2 for each monkey to produce the fewest number of cancelled first saccades (Becker 1989). Typical T1 durations were 70-110ms. If the number of cancellations of the first saccade increased during the experiment, we increased the duration of T1. If the first saccades were hypometric by 1-2°, we increased the eccentricity of T1 by 1-2° to keep the amplitude of the first saccades constant. This adjustment was usually needed for DSTs in which the first and second saccades were in opposite directions (see below). The duration of T2 was constant at 40ms. During all DST data collections, we included ~33-50% VGT saccades to T1 as catch trials to help discourage the cancellation of the first saccades.

Adaptation of VGT saccades. The focus of this study is to examine the transfer of adaptation of VGT saccades to the second saccades of DSTs when the retinotopic target location and the DSMC of the second saccades are gradually dissociated. We used McLaughlin's adaptation paradigm (McLaughlin 1967) to decrease or increase the amplitude of 12° VGT saccades (Hopp and Fuchs 2004). Briefly, a custom behavioral control program running in Spike2 detected the occurrence of a saccade to a 12° target step (not flashed) based on a 75°/s velocity criterion. When a saccade was detected, the target jumped 4° either closer to or farther from the fixation location to gradually decrease or increase saccade amplitude, respectively. In the middle of the adaptation, we increased this intrasaccadic target jump to 6° (50% of the size of the initial target step) in an attempt to obtain as much amplitude change as possible. We performed this adaptation paradigm only in the same horizontal direction of the second saccades of DSTs.

DST with first and second saccades in opposite directions. In the first transfer test, we kept the DSMC of the second saccades constant, and varied the retinotopic position of the target. If the transfer of adaptation from VGT saccades to the second saccades of a DST depends on the DSMC, we would expect a constant transfer of adaptation regardless of the retinotopic positions of the target. In this task (Fig. 1B-D), the monkey started by fixating a target for 500-1000ms. The fixation spot (F) then disappeared and the laser spot was flashed at different eccentric locations in one visual hemifield (e.g., T1 at 3, 6, 9 or 12° to the right). After a 5 ms delay, the laser spot was flashed at a second location in the opposite hemifield (T2 at either 9, 6, 3 and 0°, respectively, to the left of F). Because the distance from T1 to T2 was always leftward 12°, the second saccade was always ~12° leftward. The 5 ms delay was added to prevent the monkey from seeing the movement of the laser spot when the extinguished target jumped from T1 to T2. The monkey made sequential saccades to the location of the first and second target flashes in the dark. We did not employ a delayed task, so the first saccades occurred within the normal VGT saccade reaction times of each monkey. If the gaze landed and stayed for at least 500 ms within the extinguished target T2 window (±2.5°), the monkey received a reward, and the target was turned on again. If the monkey failed to execute these two saccades correctly, the trial was aborted and the target was turned off for 2000-2500 ms before the next trial started. We call DSTs with T1 and T2 in opposite visual hemifields *DST-crossovers*. The task in which the second saccade returned the gaze to the fixation location is called *DST-refixation* (Fig. 1C). In one type of experiment, we also relit T2 during the intersaccadic interval of 12° DST-refixation saccades (Fig. 1D).

DST with first and second saccades in the same direction. In this DST-forward task (Fig. 1E), both T1 and T2 appeared in the same visual hemifield, at 3° and 6° eccentricities, respectively. The size of both the first and second saccades was ~3°. Adaptation of 12° VGT saccades transferred very little, if at all, to 3° VGT saccades (Fig. 2A, 3A, and 8B), but significantly to 6° VGT saccades (Fig. 2B, 3A, and 8B). Therefore, if the vector of the DSMC determines the transfer of VGT saccade, we would expect no or little transfer to the second saccades of a DST-forward task whose DSMC is ~3°.

Adaptation of the second saccades of DST-refixation. We adapted the amplitude of the second saccades of a DST-refixation using the same behavioral paradigm. The program waited for the occurrence of the second saccades and jumped the target closer to or farther from T1 to decrease or increase the amplitude of the second saccades, respectively (Fig. 1F). We also performed 3, 6, 9, 15, 18 and 21° DST-refixations (Fig. 1C) to test the transfer of this adaptation to other second saccades with different amplitudes. We found that adaptation of VGT saccades did not transfer to the second saccades of a DST-refixation task. Different adaptation sites may underlie this lack of transfer. Therefore, in this task we performed the opposite adaptation transfer test from the second saccades of the DST to VGT saccades. Moreover, we also compared the characteristics of the adaptation field of the second saccades and VGT saccades.

Conditions for all experiments. Before adaptation, we collected data from both VGT and DST saccades. We turned off the target for 500ms at the end of the visually guided and second saccades to minimize the dissipation of adaptation (Shafer et al. 2000). To eliminate the possible eye position effects in the transfer of adaptation (Tian and Zee 2010) between VGT and the second saccades of DSTs, we matched the starting positions of the two types of saccades. After adaptation, the same set of data was collected.

The day after each experiment, we dissipated any remaining adaptation by having the monkey make saccades in the same task without an ISS for at least 2 hours with the same amplitude as the adapted saccades or until the saccade amplitude returned to pre-adaptation values. Therefore, each experiment was not influenced by the previous one.

Data analysis

Initial offline analysis was performed using a homemade program that ran in Spike2. The program measured and calculated the position, amplitude, velocity and timing attributes of the target and eye position signals. Saccade onset and end were marked when the eye velocity crossed a 15°/s velocity threshold. When a blink occurred during a saccade, we measured the end position *after* the blink eye movement settled to a 15°/s velocity threshold. We elected to retain data with blinks because monkey M blinked during most saccades (50-60%), and blinks should not change the end position of the gaze at the end of the saccades (Goossens and Van Opstal 2000). Moreover, because we turned the target off before a pre- and post-adaptation saccade was executed in both VGT and DST tasks and kept it off for 500ms after the saccade, blinks should not induce changes of saccade metrics (Maus et al. 2017). Further analyses, including statistics, were performed using programs running in Matlab (Mathworks, Natick, USA).

We characterize the adaptation of saccades by measuring their gains.

$$Gain = \frac{Saccade\ Amplitude}{Desired\ Saccade\ Motor\ Command\ Amplitude} \tag{1}$$

For VGT saccades, the desired saccade motor command (DSMC) amplitude for each trial was the distance between the target location (Fig. 1A, T) and the eye position at the beginning of the saccade. For the second saccade of DST tasks, DSMC amplitude was defined as the distance between the T2 target location and the eye position at the end of the first saccade (Fig. 1B-F). Because the amount of adaptation differed from experiment to experiment, we normalized the amount of adaptation by computing the percent gain change between trials before (pre) and after (post) adaptation as follows:

$$\%\ Gain\ Change = \frac{Mean\ Gain_{post} - Mean\ Gain_{pre}}{Mean\ Gain_{pre}} \times 100\% \tag{2}$$

To calculate the transfer of adaptation between different saccade tasks *A* and *B*, we use the percent gain change:

$$\%\ Transfer = \frac{\%\ Gain\ Change_A}{\%\ Gain\ Change_B} \times 100\% \tag{3}$$

For example, to calculate percent transfer of adaptation from VGT saccades to the second saccades of a DST, the nominator was the percent gain change of the second saccades of a DST and the denominator was the percent gain change of VGT saccades. Percent transfer can only be ≥0%. If the sign of percent transfer was negative (e.g., a positive gain change in amplitude decrease adaptation), we considered the percent transfer to be zero. We used percent transfers for descriptive purposes. Statistical analyses (see below) were performed on either the raw gain data or percent gain changes.

To calculate the transfer of adaptation between VGT saccades and the second saccade of a DST, we matched the DSMC amplitudes of the two saccade types. Because the target step size of VGT saccades is fixed at 12°, their DSMC after consideration of the slight fixation error was ~12±0.5°. On the other hand, the DSMC of the second saccades of a DST must take into account the variability of the first saccades. Therefore, for 12° amplitudes, we accepted only second saccades whose DSMC amplitude was within 10-13°. We also limited the direction of both VGT and the second saccades of a DST to within ±15° of horizontal. Overall, <15% of trials were eliminated by these constraints.

At least 10 selected trials in each group before and after adaptation were required for further analysis. Across all experiments, the mean number of pre- or post-adaptation VGT saccades was 20.5±11.7 (mean ±SD, range: 10-65) and 20.1±12 (range: 10-79), respectively. The means of DST pre- or post-adaptation saccades were 25.2±13.7 (range: 10-67) and 31.1±28.2 (range: 10-150), respectively. The post-adaptation data were collected in the same manner as the pre-adaptation data, except for experiments shown in Figure 7, where we gathered adaptation recovery data. Here we considered the first 15 trials of adaptation recovery as post-adaptation data. The statistical significance of the transfer was computed by comparing the pre- and post-adaptation gain data using a two-tailed unequal variances Welch's *t*-test (Welch 1947). We considered $P<0.05$ to be significant.

Figure 2 near here

Results

We performed a total of 51 saccade adaptation experiments on two monkeys (L, 30 experiments; M, 21 experiments; Data from M are shown in red in the figures). We will indicate the number of experiments in each condition below.

The effects of varying T2 eccentricity, but keeping DSMC constant on the transfer of adaptation from VGT saccades to the second saccades of a DST.

In 8 experiments we adapted 12° VGT saccades and determined the transfer to the second saccades of a DST-crossover task. The DSMC of the second saccades also was held fixed at ~12°, but the T2 locations varied in eccentricity (either 3, 6 and 9°) along the direction of the adapted VGT saccades. In each experiment, we first determined the transfer of adaptation of the 12° saccade to VGT saccades of 3, 6 and 9°.

Figure 2 shows data from an exemplar experiment. The transfer of adaptation of 12° VGT saccades (-17% gain reduction) to VGT saccades of other sizes increased with target step size (Fig. 2A-C, T, -3° to -9°). The amount of gain reduction was not significant for 3° VGT saccades [$t(22.16)= -0.63$; $P= 0.54$], but showed a significant gain decrease for both 6 and 9° saccades (-8.7% and -

16.8%, respectively). These percent gain reductions corresponded to 0, 51.5 and 99% transfer, respectively.

A similar pattern of transfer and gain change was observed for the second saccades of a DST. The transfer of adaptation of 12° VGT saccades to the second saccades of a DST (~12° DSMC) also increased as T2 eccentricity (relative to F) increased from 3 to 9° (Fig. 2D-F). The percent gain changes were -3.6, -6.8 and -15.3% for T2 at 3, 6 and 9°, respectively ($P<0.001$ for all three groups). These corresponded to 21.2, 40.3 and 90.5% transfers, respectively.

Figure 3 near here

Across eight 12° VGT saccade adaptation experiments, increasing the eccentricity of the retinotopic target to 3, 6 and 9° (T for VGT and T2 for DST) increased the amount of gain change and transfer to both VGT saccades (Fig. 3A, C) and the second saccades of the DST (Fig. 3B, D). In 3 experiments, the gain of the second saccades of the DST with T2 at 3° did not change significantly (P>0.07, Fig. 3B black symbols) even though their DSMC remained ~12°. On average, transfers of 12° VGT saccade adaptation to 3, 6 and 9° VGT saccades were 6.8±13.6, 46.6±19.9 and 80.3±12.1% (mean ±SD), respectively. In comparison, the average transfers to the second saccades of a DST with T2 at 3, 6 and 9° were all significantly different with values of 12.9±11, 36.0±12.3 and 69.4±20.3%, respectively. Analysis using a two-way anova with main effects of retinotopic target (representing T and T2) and task (representing VGT and DST) indicated that the effect of the retinotopic target was very significant [$F(2)= 71.89$; $P= 2.75\times10^{-14}$], but both task [$F(1)= 1.34$; $P= 0.25$] and interaction term [$F(2)= 1.6$; $P= 0.21$] effects were not. In summary, the retinotopic coordinate of the target of the saccade strongly influences the amount of adaptation transfer to both VGT saccades and the second saccades of a DST task. The fact that the task differences did not affect the transfer suggests the DSMC had no influence on the transfer.

Adaptation transfer from VGT saccades to the second saccades of a DST-refixation task.

Figures 2 and 3 showed that as the eccentricity of T2 decreased, the transfer of adaptation of 12° VGT saccades to the second saccades of DST also decreased. Because transfer to the T2 at 3° was the least, we expect minimal transfer when T2 is 0° (DST-refixation). In those previous 8 adaptation experiments, we also tested the transfer to the second saccades of a DST-refixation (T1 at 12° eccentricity and T2 at 0°). In addition, we performed 3 additional gain decrease adaptation experiments on 12° VGT saccades in which we randomly interleaved 12° DST-refixation saccades. Figure 4A shows data from one of these three experiments. Although the gain of VGT saccades decreased by 20.14%, the slope of the gain of the interleaved second saccades of the DST-refixation task as a function of trial number was not significantly different from zero [$t(136)= -0.13$; $P= 0.9$; Fig. 4C, B2]. The slopes of the second saccade's gain vs. trial number in the other two experiments (B1 and B3) were significantly positive (0.08 and 0.1 /1000 trials, *P*<0.01). Therefore, there was no transfer of the gain reduction of VGT saccades to the interleaved second saccades of a DST-refixation task.

Figure 4 near here

In 5 experiments we performed gain increase adaptation of 12° VGT saccades, and randomly interleaved 12° DST-refixation trials. In the representative experiment illustrated in Fig. 4B, the gain of VGT saccades increased by 20.01%, but the slope of the gain vs. trial number relation of the second saccades of the DST-refixation trials was actually negative (slope: -0.048 /1000 trials, $t(71)= -2.4$; $P= 0.019$; Fig. 4C, F2). In 3 other experiments, the gain of the adapted VGT saccade increased by 19.3, 13.9 and 19.2%, but the slopes of the gain vs. trial number relation of the second saccades of the interleaved DST-refixation trials again were negative (-0.12, -0.047 and -0.042 /1000 trials, respectively; all slopes were significantly different from zero $P<0.03$). In the remaining experiment, the VGT saccade gain increased by 21.3%, but the slope of gain vs. trial number for DST-refixation trials was zero [$t(127)= -0.67$; $P= 0.5$; Fig. 4C, F4].

Figure 4C compares the gain changes of the adapted 12° VGT saccades and the second saccades of a DST-refixation across all gain decrease and increase experiments. For gain decrease adaptation, the first 8 experiments were from data shown in Fig. 2 and 3 and experiments B1-3 for additional experiments with interleaved DST trials. Only 3 of these 11 experiments showed significant adaptation transfer from VGT saccades (*P*<0.04, *). For gain increase adaptation, no experiments showed transfer of VGT adaptation to the second saccades of a DST-refixation. Three experiments showed a slight, but significant gain decrease of the second saccades (-2.29, -2.35 and -7.47% gain change, *P*<0.02).

The absence of or minimal transfer of adaptation from VGT saccades to the second saccades of a DST-refixation could be pre-programmed during the parallel programming of the first and second saccades of a DST (Becker and Jurgens 1979). Alternatively, the computation of the second saccade motor command might continue during the intersaccadic interval (ISI) of a DST and therefore could still be influenced by a visual target. If the latter were true, the transfer of VGT saccade adaptation to the second saccades would increase if the T2 target reappears during the ISI (Fig. 1D). In 6 experiments, we performed gain decrease adaptation of 12° VGT saccades (Fig. 5) and tested the transfer of adaptation to the second saccades of 12° DST-refixation trials. In half of the DST trials (circle data) we kept T2 off as in the experiments of Fig. 4. In the other half (triangle data), we turned T2 on when the first saccades of the DST ended. Before adaptation, the mean gains of the second saccades of a DST were not significantly different with T2 on or off (insets, *P*>0.072). In three experiments (A, C and F), the variance of the gain was unaffected by whether T2 was on or off (F-test, *P*>0.14); however, in the other three (B, D and E), the variance was significantly less when T2 was on (*P*<0.003).

Figure 5 near here

Finally, we calculated the mean pre-adaptation gain of the second saccades (insets), and then the percent gain change of each post-adaptation second saccade of the DST relative to the mean pre-adaptation gain (calculation as in equation 2 of Methods, except trial by trial). For each T2 condition, we performed a linear regression between percent gain change and the intersaccadic-interval (ISI) of the DST. In all experiments, the percent gain changes of the second saccades of the DST were lower when T2 was on at the end of the first saccade (Fig.5, triangles) than when it remained off (circles). The slopes of the linear regression for the T2-off condition were not significantly different from zero (P>0.13). When we turned T2 on during the ISI, the slopes of the linear regressions were negative in 5 experiments (significantly different from zero, P<0.005), and the slope in one experiment (panel C) was not different from zero [t(61)= -1.72; P= 0.09]. As the ISI increased so T2 was visible longer, the percent gain decrease approached the average percent gain decrease of the adapted VGT saccades (dashed lines). In summary, the negative slopes suggest that the processing of the retinotopic target is still underway between the end of the first saccade and the execution of the second saccades. The longer the target T2 was visible, the more transfer of adaptation occurred.

Adaptation transfer from VGT saccades to the second saccades of a DST-forward task.

Although the data shown in Figs. 2-5 indicate that the retinotopic target of a saccade influences the transfer of adaptation, a DSMC with an amplitude similar to the adapted saccades might still play a role in producing transfer. To test this possibility, we created a DST with a second saccade DSMC that was so small that little transfer would be expected from VGT saccade adaptation (recall Fig. 3), but whose retinotopic target was close to the adapted amplitude. We exploited the fact that adaptation of 12° VGT saccades transfers minimally to 3° VGT saccades (6.8% Fig. 3C), but substantially to 6° targeting saccades (46.6% Fig. 3C). Therefore, in 8 experiments we adapted 12° VGT saccades, and measured the transfer to the second saccades of a DST-forward task that generated two consecutive saccades of ~3° with T1 and T2 flashed at 3° and 6°, respectively (see Fig. 6C), in the same direction as the 12° adapted VGT saccades. We expect that if the optimum adaptation transfer requires that the DSMC amplitude be close to the amplitude of the target step of the adapted saccades, the amount of gain change of the second saccades of the DST-forward would be comparable to that to 3° VGT saccades, i.e., there would be minimum transfer.

Figure 6 near here

In the representative experiment of Fig. 6, gain decrease adaptation of 12° VGT saccades (-23.3%) caused an average 3.1% gain reduction of 3° VGT saccades (Fig. 6A, P=0.13), but an 8.4% gain reduction of 6° VGT saccades (Fig. 6B, 36.1% transfer, $P<10^{-8}$). This adaptation transferred well to the overall amplitude produced by the sum of the two saccades of a DST-forward task. The net gain of the DST-forward saccade sequence (measured at the end of the 2nd saccades relative to 6° [T2-F]) decreased significantly by 12.7% (Fig. 6C, $P<10^{-4}$). The first saccades did not contribute to the overall gain decrease because their gain did not change significantly [$t(15.97)= 1.05$; $P= 0.31$]. On the other hand, the gain of the second saccades decreased significantly by 24.1% (almost twice the 12.7% overall-gain decrease of the DST). Therefore, the gain decrease of the second saccades of the DST-forward task accounted almost entirely for the overall gain decrease in this task. In this exemplar experiment, the amplitude decrease of 3° second saccades [≈0.72° = 0.241x3°] accounted almost entirely for the overall 6° amplitude decrease of the DST-forward [≈0.76° = 0.127x6°].

In all eight experiments, the gain changes of the second saccades of a DST-forward task were larger than those of 3° VGT saccades (-32.6±9.3% vs. -8.4±3.6%, respectively, Fig. 6D**)**. The average overall DST-forward gain change was not significantly different from that of 6° VGT saccades (-17±5.02% vs. -12.8±4.9%, respectively, $t(13.99)= 1.69$; $P= 0.11$, Fig. 6E). In all experiments, the percent gain reduction of the second saccades was larger than the percent reduction of the overall-gain (Fig 6F, all data points above unity slope line).

Moreover, these data points lay on or near a line with a slope of 0.5 in the plot that compares the percent gain change of the overall DST-forward sequence and the percent gain change of the second saccades (Fig. 6F). A linear regression on those data yielded a slope of 0.54, which was not significantly different from 0.5 [$t(6)= 1.38$; $P= 0.22$] and significantly different from unity [$t(6)= -16.95$; $P= 2.7\times10^{-6}$]. Given that the double saccade sequence of this DST-forward task covers a 6° amplitude, the regression analysis suggests that the second saccade, which only covers half of the overall amplitude (~3°), contributes most of the overall gain reduction of the DST sequence. In summary, these data further confirm that the transfer of adaptation of VGT saccades to the second saccades of a DST task depends on the retinotopic target, and not on the DSMC amplitude of the saccades.

Adaptation of the second saccades of DST-refixation and the transfer to VGT saccades.

The absence or minimal transfer of adaptation of VGT saccades to the second saccades of a DST-refixation suggests that different neuronal sites might underlie adaptation in those two saccade tasks. To examine this possibility further, we examined the reverse transfer of adaptation of the second saccades of a DST-refixation task to VGT saccades. We decreased the gain of the second saccades of a DST-refixation (T2 at 12° eccentricity, see Fig. 1F) in 5 experiments and increased it in 5, and then measured the transfer of the adaptation to VGT saccades elicited by a 12° target step (Fig. 1A).

Figure 7 near here

Figure 7 shows representative experiments for gain decrease (A) and increase (B) adaptation. When a backward ISS occurred during the second saccade of a DST-refixation, the gain of the second saccades decreased gradually from 0.96 before adaptation to 0.58 after with a rate constant of 296 trials (Fig. 7A, first panel, filled circles and fit curve at bottom). The gain of the randomly interleaved VGT saccades decreased more slowly with a linear rate of 0.14 /1000 saccades (open circles and fit line at top). Gain reduction computed before (PRE) and after (POST, the first 15 saccades of the recovery trials) adaptation showed a reduction of 26.9% for the second saccades, but the gain change for the interleaved VGT saccades was not significant (-1.51%, $t(63.98)= 1.04$; $P= 0.3$). When the backward ISSs were discontinued, the gain of the second saccades recovered with a rate constant of 184 trials (Fig. 7A, second panel at bottom).

Forward ISSs gradually increased the gain of the second saccades of a DST-refixation task from 1.13 before the adaptation to 1.53 with a rate constant of 352 trials (Fig. 7B, first panel, filled circles and fit curves at bottom). On the other hand, the slope of the gain change of the randomly interleaved VGT saccades was not significant (open circles and fit line at top, $t(127)= -1.13$; $P= 0.26$). Although the amount of gain increase after adaptation (POST, the first 15 saccades of the recovery trials) was 26.6% for the second saccades, VGT saccades showed no significant gain change (0.63%, $t(43.37)= -0.51$; $P= 0.61$). When forward ISSs were discontinued, the gain of the second saccades decreased to PRE levels with a rate constant of 230 (Fig. 7B second panel at bottom).

Across 5 gain decrease experiments (Fig.7C), the average gain of the second saccades of the DST-refixation task decreased by 27±6.1%, and the average gain of VGT saccades decreased by only 2.6±2.5% (average: 9.6% transfer); the decrease was significant ($P<0.001$, *) in only two experiments. On average, the rate constant of the adaptation was 238±131 trials. The average slope for the interleaved 12° VGT saccades was -0.0082±0.13 /1000 saccades (3 slopes were negative, -0.051, -0.14 and -0.1, $P<0.001$, and two were positive, 0.11 and 0.14, $P<0.03$). In 4 experiments we recovered the second saccade gain and their average rate constant was 101±57 trials. In summary, there was little, if any transfer, of adaptation from gain decrease adaptation of the second saccades of a DST-refixation task to VGT saccades.

Across the five gain increase experiments (Fig. 7D), the average gain of the second saccades of a DST-refixation task increased by 28.1±7.9%, and the average gain of VGT saccades increased by only 2.9±2.8% (average: 10.3% transfer). Three experiments showed a very small, but significant transfer ($P<0.002$). Three adaptations (B2-4) could be fit well with exponential functions with rate constants of 111, 352 and 194 trials. The rate constants for recovery were 82, 230 and 132 trials, respectively. Adaptations B1 and B5 were fit with linear functions with slopes of 0.56 and 0.76 /1000 saccades, respectively. The recovery of B5 adaptation had a rate constant of 95 trials. The average slope for the interleaved 12° VGT saccades was 0.071±0.08 /1000 saccades. In summary, there was minimal transfer from gain increase adaptation of the second saccades of a DST-refixation task to VGT saccades.

Difference of amplitude transfer fields after adaptations of the second saccades of DST-refixation and VGT saccades.

The minimal transfer of adaptation between the second saccades of a DST-refixation task and VGT saccades supports the idea that they might have different adaptation sites or pathways. If this is true, their adaptation fields also are likely to be different. The amount of transfer of adaptation of VGT saccades decreases as the amplitude of the target that elicits the saccade deviates from that used to produce the adaptation. This so-called adaptation field exhibits a sharp decline of transfer for saccades to smaller target steps, and a more gradual decline for saccades to larger target steps (Frens and van Opstal 1994; Noto et al. 1999).

Figure 8 near here

We confirmed these previous studies in five 12° VGT saccade adaptation experiments (Fig. 8A-B). For large target step sizes of 9, 12, 15, 18 and 21°, the percent gain changes were not significantly different (*one-way anova*, $F(4)= 1.58$; $P= 0.22$). The percent gain change for a 3° target step was significantly less than those produced by the 9-21° steps, and the percent gain change for a 6° target step was significantly less than those produced by 9-18° steps ($P<10^{-5}$, multiple comparison with Bonferroni correction). On average the transfers for target step sizes of 9, 15, 18 and 21° were >70%, but <40% for target amplitudes of 3 and 6°.

In contrast, after adaptation of the second saccades (DSMC ~12°) of a DST-refixation task, the amplitude adaptation field of the second saccades (6 experiments) usually did not exhibit a declining transfer for smaller DSMC amplitudes. For example, the average gain change for a 3° DSMC amplitude still was significant (Fig. 8C, -17.9±11.6% on average, one-sample *t*-test: $t(5)= -3.77$; $P= 0.013$); however, in two individual experiments, it was not. The average transfer for 3° was 80.2±51.1% (Fig. 8D). The average transfers to a 6° DSMC were >100% (Fig. 8D, filled black circles), whereas VGT saccade adaptation transfer to 6° was only 38.1±12.3% (open circles). Across all 7 DSMC amplitudes, the gain changes were not significantly different (*one-way anova*, $F(6)= 1.21$; $P= 0.33$) and averaged >75% transfer. Analysis using two-way anova with main effects of retinotopic target size (representing T and T2) and task (representing VGT and DST) for trials in the 3, 6, 9 and 12° groups indicated that the effects of the retinotopic target ($F(3)= 5.85$; $P= 0.0023$), task ($F(1)= 36.92$; $P= 5.5\times10^{-7}$) and interaction term ($F(3)= 2.96$; $P= 0.045$) were significant. For trials in 12, 15, 18 and 21° groups, only the main effect of task was significant ($F(1)= 8.07$; $P= 0.0073$), and both retinotopic target ($F(3)= 1.3$; $P= 0.29$) and the interaction term ($F(3)= 0.11$; $P= 0.95$) were not. In summary, adaptation of the second saccades of a DST-refixation task generalizes over wider range of second saccade amplitudes, and its transfer pattern to the smaller second saccades is different from that of VGT saccades.

Discussion

Our primary goal was to determine whether a visual retinotopic target signal or a signal related to the motor command to acquire the target (DSMC) is the dominant contributor to saccade adaptation. We performed several experiments to dissociate these signals, and measured the effects of the dissociation on adaptation transfer.

Adaptation transfer depends on the visual target not the saccade command

First, we decreased the gain of VGT saccades and determined the transfer to the second saccade of a double step task in which the saccade crossed the midline. The DST-crossover task enabled us to hold the DSMC of the second saccade fixed at ~12°, but to vary the eccentricity of T2 (either 3, 6 and 9°). If adaptation transfer depends on T2, it should increase with T2 eccentricity. On the other hand, if the DSMC determines the transfer, the transfer should be high and constant regardless of T2 eccentricity. The DST-crossover tasks produced a partial transfer to the second saccades, which depended on the eccentricity of target T2 even though the DSMC was constant (Fig. 3). The percent transfer was lowest for a 3° T2 and highest for a 9° T2 (Fig.3D). A statistically similar dependence on target eccentricity (T) occurs for smaller VGT saccades themselves after a larger VGT saccade has been adapted (Fig. 3C).

This finding, that the visual target not the DSMC drove transfer, was further supported by the results of a DST-refixation task in which the second saccade always returned to the initial fixation location (F). After VGT saccades underwent either gain decrease or increase adaptation (Fig. 4A, B, respectively, lower open circles and fits), there was essentially no gain transfer to the second saccades of the DST-refixation where T2 was constant at zero (Fig. 4A, B, upper filled circles; 4C). For VGT amplitude decrease adaptation, the second saccades of 8 of 11 experiments did not exhibit a significant gain decrease. For VGT amplitude increase adaptation, the second saccades of none of the experiments exhibited a significant transfer of gain increase. This finding supports the importance of the eccentricity of T2 for adaptation transfer.

VGT saccade adaptation also does not transfer to the second saccades of a DST-refixation task in humans. Pélisson et al. (2010) reported that after gain adaptation of VGT saccades, the second saccades of a DST-refixation task exhibited either no significant gain change after amplitude increase adaptation (their Fig. 4C, forward column) or a very little, but significant, gain change after amplitude decrease adaptation (their Fig. 4C, backward column). Based on the different results of transfer between gain increase and decrease adaptations, they suggested that the two adaptations might not involve a common pathway. On the other hand, our results show that essentially neither gain increase nor decrease VGT saccade adaptation transfer to the second saccades. Moreover, we showed that there was a dependence of transfer on target eccentricity that was similar to that for the adaptation transfer to VGT saccades of other sizes. Finally, we added the observation that re-illumination of T2 between the first and second saccade also influences saccade adaptation transfer. Indeed, the longer T2 is illuminated during the ISI, the greater the adaptation transfer to DST second saccades (Fig. 5). Therefore, in contrast the previous study on humans, our data provide a more comprehensive description of the relation of adaptation transfer for a variety of target eccentricities and add the fact that T2 is influential throughout the entire course of double step paradigm.

In our gain decreasing paradigms**,** the DSMC of the second saccades of the DST was the same as that of the adapted VGT saccades. To disambiguate the possible effect on adaptation transfer of the DSMC for the second saccades and that for VGT saccades, we used a DST-forward task that required a second saccade that was so small that little transfer would be expected from VGT saccade adaptation (recall Fig. 3), but whose retinotopic target was close to the adapted amplitude (Fig. 6A-C). The gain reduction of the second saccades of the DST-forward task accounted for almost the entire reduction of the overall DST-forward displacement (Fig. 6F), a further confirmation that the visual target and not the DSMC drives saccade adaptation.

The characteristics of adaptation of the second saccades of a DST

The lack of transfer of VGT saccade adaptation to the second saccades of a DST task when T2 is completely dissociated from the DSMC as in DST-refixation task suggests that adaptation of the second saccades of a DST-refixation task would also not transfer to VGT saccades. An ISS backward or forward step of the target during the second saccade of a DST-refixation task produced gradual robust decreases and increase of gain, respectively (Fig. 7A, B, filled circles). However, interleaved VGT saccades exhibited only modest changes, if any (Fig. 7A, B, open circles). Pre- and post-adaptation comparisons also indicated minimal transfers to VGT saccades (Fig. 7C & D).

We and others (Levy-Bencheton et al. 2016) showed that an ISS delivered during the second saccades of a DST task gradually changed the amplitude of the second saccades. These gradual amplitude changes likely were due to adaptation mechanisms rather than strategy because elimination of the ISS caused a gradual return of the amplitude to the pre-adaptation state (Fig. 7A,B, right panels). Taken together, our experiments suggest that the modifiable neuronal pathways underlying the adaptation of VGT saccades and the adaptation of the second saccades of a DST-refixation task are independent.

This suggestion is further supported by the fact that the adaptation fields of VGT saccades and the second saccades of a DST-refixation have different shapes. The transfer of adaptation of VGT saccades to smaller VGT saccades decreased with smaller amplitude target steps (Fig. 8A and B). On the other hand, adaptation of the second saccades of a DST-refixation transferred uniformly to a broad range of saccades with larger and smaller amplitude motor commands (Fig. 8C and D).

Comparison with previous studies that dissociated the visual target and DSMC using DSTs with two target steps but at different angles

The transfer characteristics of VGT saccade adaptation to the second saccades of a DST have also been examined in 3 other studies with a different target configuration. In those studies, the positions of the fixation point, and the locations of T1 and T2 were at the points of a triangle rather than co-linear. Two studies concluded that saccade adaptation occurred at the motor level because they observed significant transfer to the second saccades of a DST after they dissociated the retinotopic target T2 from its DSMC vector (Frens and van Opstal 1994; Wallman and Fuchs 1998). However, the observed transfer could have been due to the adaptation field, which can extend more than ±45° (Soetedjo et al. 2009), because the directional angle dissociation of their T2 and DSMC vectors was <60° and 37°, respectively. In the third study (Quaia et al. 2010), the angle between T2 and the second saccade vectors was close to 90°; therefore, the two vectors lay outside the adaptation field and the second saccades directed toward the T2 target with its vector aligned with the adapted saccades still showed significant transfer. This condition was similar to our DST-forward experiments. On the other hand, when the vectors of T2 and the second saccades were reversed, there was no adaptation transfer. This condition was similar to our DST-refixation experiments. In conclusion, the results of our study using a co-linear target configuration agree with those using the triangular configuration when its vector separation of T2 and DSMC was wider than the directional adaptation field. The steep decline of VGT adaptation transfer to smaller saccades (see Fig. 8A and B) allows the co-linear configuration to titrate the contribution of T2 eccentricity to the transfer and to dissociate easily the influence of T2 and the DSMC.

How does the visual target T2 affect adaptation transfer to the second saccades of a DST?

The results in Figs. 2-6 suggest that VGT saccade adaptation modifies either the representation of the visual target or the interpretation of the visual target to be incorporated into the programming of the second saccades of a DST. The expression of this modification on behavior is not limited to saccades, but also extends to visual perception. After a VGT saccade adaptation, monkeys exhibited a shift of object localization when they touched it on a screen while maintaining fixation (Gremmler et al. 2014). The direction of the shifts corresponded to whether the adaptation was an amplitude decrease or increase. Similar shifts of visual object localization after saccade adaptation occur in humans using a computer mouse pointer while maintaining fixation (Zimmermann and Lappe 2010); however, the effects seem to occur only for amplitude increase adaptation. The shape of the mis-localization field was similar to that of the adaptation field (Awater et al. 2005; Collins et al. 2007).

Our results cannot distinguish whether VGT saccade adaptation modifies the representation or the interpretation of the visual target. If the visual representation of the target were modified by saccade adaptation, visual activity of neurons in the saccade-related areas should change during adaptation. As far as we are aware, only one study (Steenrod et al. 2013) examined this possibility and reported that both visual and saccade-related activity of neurons in the lateral intraparietal area did not change during either memory guided or VGT saccade adaptations. Moreover, the three studies (Frens and Van Opstal 1997; Quessy et al. 2010; Takeichi et al. 2007) that examined possible changes in SC neuron saccadic burst activity during saccade adaptation did not mention any changes of visual activity related to target steps.

We feel that modification of the interpretation of the visual target signal is more likely to underlie the mechanisms of VGT saccade adaptation. The circuitry and mechanisms underlying VGT saccade adaptation is rather well understood. Briefly, the brainstem saccade burst generator (Scudder et al. 2002) delivers a burst of neuronal activity to the extraocular muscles. The SC sends a command signal related to the target step both directly to this brainstem burst generator (BG) and indirectly to the BG through the oculomotor cerebellum (vermis lobules VIc and VII [OMV] and the caudal fastigial nucleus [cFN] to which they project). After gain reduction adaptation of VGT saccades, electrical stimulation of the SC site serving the adapted target vector elicits saccades of reduced size (Edelman and Goldberg 2002). During VGT saccade adaptation, the saccade-related activity of visuomotor and saccade-related burst neurons in the SC does not change (Frens and Van Opstal 1997; Quessy et al. 2010; Takeichi et al. 2007). These studies indicate that the SC saccade-related discharge is better correlated with the vector of the target step than the vector of the adapted saccades; i.e., the SC always sends a constant saccade command signal to the burst generator. Therefore, adaptation is mediated downstream by another structure.

In contrast to the unchanging burst activity in the SC during saccade adaptation, simple spike (SS) activity of Purkinje cells (PCs) in the OMV gradually changes with adaptation (Catz et al. 2008; Kojima et al. 2010). This change in SS activity is routed to the BG through cerebellar output cells in the cFN (Inaba et al. 2003; Scudder and McGee 2003). The changing SS activity is the result of the error signal between the target and the saccade end position that modulates the PC complex spike activity (Soetedjo and Fuchs 2006). Finally, several studies (Kaku et al. 2009; Soetedjo et al. 2009) identified that this error signal originates in the rostral SC where neurons change their visual activity during adaptation (Kojima and Soetedjo 2017).

Because the OMV mediates the adaptation, the command signal from the SC likely determines the transfer of adaptation to the second saccades of a DST (Edelman and Goldberg 2002; Fujita 2013). The similarity of VGT saccade adaptation fields (Fig. 8A and B) to the movement fields of SC neurons supports this idea (Noto et al. 1999; Ottes et al. 1986).

Does the SC send the same command signal for saccades of similar vectors whether they are VGT saccades or the second saccades of a DST? Remapping of the T2 visual target (Duhamel et al. 1992) could allow the SC to send a command signal appropriate for the vector of the second saccade of a DST (Sommer and Wurtz 2008). The remapping process could then shift the neuronal activity related to the T2 target to become relative to the end of the first saccade. In this scenario, the SC would send the same command signal (DSMC) for both VGT saccades and the second saccades of a DST. If such a remapping process of T2 had played a role in producing the second saccades of a DST, we would have observed full transfer of adaptation of VGT saccades in both DST-crossover and -refixation tasks and no transfer in a DST-forward task because the vector of T2 would have been the same as the vector of the target of VGT saccades. In contrast, our data are more consistent with processing the T2 signal by the adaptation mechanisms as it was presented *before* the first saccades, i.e., relative to the fixation location. This suggests that the SC could send a command signal related to the vector of T2 during the second saccades of a DST.

As far as we are aware, only one study has examined SC activity during a DST task. During the second saccades of a DST that was similar to our DST-refixation task, the saccadic bursts of SC neurons discharged at much lower rates than for VGT saccades of the same vector (Sparks and Porter 1983). Some stopped discharging for saccades all together. The decrease in rate for second saccades would be a problem if the SC used a rate code for saccade metrics. Sparks and Porter suggested that the SC output was based on its spatial map (Lee et al. 1988; Ottes et al. 1986) and therefore it would still send the appropriate DSMC vector to elicit the second saccades. However, this suggestion that the SC still retains its spatial map during the second saccades of a DST-refixation has never been tested directly. Moreover, Sparks and Porter (1983) never measured SC activity using other types of DST so they could not titrate the dissociation between the visual target T2 and the DSMC. Therefore, it is an open question whether the magnitude of the SC saccadic burst would increase if the T2 of the DST were placed in more eccentric positions in the contralateral visual hemifield while keeping the DSMC constant as for a DST-crossover task (Fig. 2-3).

Recordings during a DST-crossover paradigm might reveal whether SC activity encodes the retinotopic target T2 when the neurons burst for the second saccades. The T2 visual target can be thought of as the movement goal of the second saccades of a DST. For a different oculomotor behavior, i.e., smooth pursuit, the activity of neurons in the rostral SC is correlated with the movement goal (Krauzlis et al. 2000), which need not necessarily be visual (Hafed and Krauzlis 2008). Therefore, it is possible that the movement goal of the second saccades of a DST might be encoded by saccade-related activity of the more caudal SC neurons, where larger saccades and target eccentricities are represented. Indeed, our pilot data (Soetedjo 2016) suggest that the saccadic burst of SC neurons appears to be better correlated with T2 eccentricity than saccade amplitude. These pilot data are consistent with the observed SC saccade-related activity for saccades made to a moving target (Goffart et al. 2017; Keller et al. 1996), and supported by recent theoretical work (Optican and Pretegiani 2017).

If the SC output for the second saccades of a DST encodes the T2 visual target, a structure downstream of the SC must combine the SC T2 signal and the corollary discharge of the first saccade to produce an accurate motor command for second saccades. We think the cerebellar OMV and the cFN could perform this processing. Our pilot data show that cFN neurons discharge differently for VGT saccades and the second saccades of a DST, and the discharges during the second saccades appear to be appropriate for adjusting the SC visual target T2 signal (Soetedjo 2016).

The scenario of neuronal mechanisms that we proposed above would explain our adaptation transfer data. The SC would provide a saccadic burst that is a spatially encoded target-related signal. For example, a site in the left SC produces a saccadic burst for a rightward saccade to a 12° target step. This 12° spatial target signal will also activate a population of neurons in the nucleus reticularis tegmenti pontis (NRTP) that encodes a 12° step (Crandall and Keller 1985). The NRTP, in turn, would deliver a signal related to the 12° rightward step to the OMV via mossy fibers. This set of mossy fibers would activate specific sets of OMV granule cells, which send their parallel fibers to synapse with PCs. During adaptation of 12° VGT saccades, this particular set of parallel fiber synapses would undergo plastic changes (Fujita 2013; Ito 2000) that gradually would alter the simple spike activity. Finally, the changes in PC activity, mediated through the cFN, would adjust the activity of burst neurons in the brainstem burst generator to produce the adapted saccades.

The plastic changes that occur in the specific set of parallel fiber synapses would explain why the adaptation field of VGT saccades (Fig. 8A, B) resembles SC visuomotor fields (Noto et al. 1999; Ottes et al. 1986). Only the set of parallel fibers that originates from the SC neuron population that encodes 12° is adapted the most. For other target step vectors that activate adjacent sites in the SC, the activated parallel fibers would overlap less with the adapted 12° parallel fiber set. This would result in less adaptation transfer to saccades that are smaller or larger than 12°.

Using similar reasoning, if the SC encodes the visual target T2 for the second saccades of a DST-crossover, the active site, which depends on T2, would determine the amount of adaptation transfer to the second saccades (Fig. 2 and 3). As T2 eccentricity decreases (moves closer to the fixation location F), the active SC site would move more rostrally and be further away from the 12° site. Therefore, the transfer of adaptation decreases.

When the visual target T2 never appears in the contralateral visual hemifield as in a DST-refixation task, it is more difficult to speculate on what happens in the SC during the second saccades. The different shape of the adaptation fields of VGT saccades and the second saccades of a DST-refixation (Fig. 8) suggests that during the execution of the second saccades, the active SC population might be much broader, possibly to compensate for the low saccadic burst activity (Sparks and Porter 1983). The increase in the active population might also explain the minimal transfer of adaptation between VGT and second saccades. Further study on the SC is needed to understand the encoding of the command signal during the second saccades of a DST-refixation task.

In summary, we think that during saccade adaptation, the OMV modifies the interpretation of the visual target signal. Based on this new interpretation of the visual target, the cFN sends a corrective signal to the brainstem burst generator to change the metrics of the ongoing saccade. In addition, fastigio-thalamic-cortical projections could underlie the shift in target localization after a saccade adaptation (Baumann et al. 2015; Kyuhou and Kawaguchi 1987).

Conclusions

Before this report, it was thought that adaptation of VGT saccades transferred to any other saccades with a similar vector and, therefore, with a similar desired saccade motor command (DSMC). It did not matter which target configuration elicited them. This leads to the idea that adaptation of saccades is a motor event. In contrast, our data show that the adaptation of saccades depends on the visual goal of the movement. When the goals of two different saccade tasks are dissociated from their motor commands, generalization of adaptation between the two tasks suffers even though the intended saccades of both tasks have the same motor command. Neurophysiological studies are needed to understand the neural origin of the visual goal signal for saccade eye movements, and how it could be used in the processing of double-step saccade tasks and their adaptation.

Acknowledgements

I am grateful for the surgical assistance and the veterinary support of the staff of the Washington National Primate Research Center. I also benefited from the valuable comments of Albert Fuchs on an earlier version of the manuscript.

Grants

This study was supported by National Institute of Health (NIH) grants R01EY019258 (RS), and OD010425 (P51 for WaNPRC), and by National Science Foundation (NSF) grant number BCS-1724176 (RS). The contents of this paper are solely the responsibility of the author and do not necessarily represent the official views of NCRR, NIH or NSF.

References

Albano JE. Adaptive changes in saccade amplitude: oculocentric or orbitocentric mapping? *Vision Res*. 36: 2087-2098, 1996.

Awater H, Burr D, Lappe M, Morrone MC, and Goldberg ME. Effect of saccadic adaptation on localization of visual targets. *J neurophysiol*. 93: 3605-3614, 2005.

Bahcall DO, and Kowler E. Illusory shifts in visual direction accompany adaptation of saccadic eye movements. *Nature* 400: 864-866, 1999.

Baumann O, Borra RJ, Bower JM, Cullen KE, Habas C, Ivry RB, Leggio M, Mattingley JB, Molinari M, Moulton EA, Paulin MG, Pavlova MA, Schmahmann JD, and Sokolov AA. Consensus paper: the role of the cerebellum in perceptual processes. *Cerebellum* 14: 197-220, 2015.

Becker W. The neurobiology of saccadic eye movements. Metrics. *Reviews of oculomotor research* 3: 13-67, 1989.

Becker W, and Jurgens R. An analysis of the saccadic system by means of double step stimuli. *Vision Res*. 19: 967-983, 1979.

Catz N, Dicke PW, and Thier P. Cerebellar-dependent motor learning is based on pruning a Purkinje cell population response. *Proc Natl Acad Sci USA* 105: 7309-7314, 2008.

Collins T, Dore-Mazars K, and Lappe M. Motor space structures perceptual space: evidence from human saccadic adaptation. *Brain Res*. 1172: 32-39, 2007.

Crandall WF, and Keller EL. Visual and oculomotor signals in nucleus reticularis tegmenti pontis in alert monkey. *J neurophysiol*. 54: 1326-1345, 1985.

Deubel H, Wolf W, and Hauske G. Adaptive gain control of saccadic eye movements. *Human Neurobiol*. 5: 245-253, 1986.

Duhamel JR, Colby CL, and Goldberg ME. The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* 255: 90-92, 1992.

Edelman JA, and Goldberg ME. Effect of short-term saccadic adaptation on saccades evoked by electrical stimulation in the primate superior colliculus. *J neurophysiol*. 87: 1915-1923, 2002.

Frens MA, and Van Opstal AJ. Monkey superior colliculus activity during short-term saccadic adaptation. *Brain Res Bull*. 43: 473-483, 1997.

Frens MA, and van Opstal AJ. Transfer of short-term adaptation in human saccadic eye movements. *Exp Brain Res*. 100: 293-306, 1994.

Fuchs AF. Saccadic and smooth pursuit eye movements in the monkey. *J Physiol*. 191: 609-631, 1967.

Fuchs AF, and Robinson DA. A method for measuring horizontal and vertical eye movement chronically in the monkey. *J Appl Physiol*. 21: 1068-1070, 1966.

Fujita M. New supervised learning theory applied to cerebellar modeling for suppression of variability of saccade end points. *Neural Comput*. 25: 1440-1471, 2013.

Goffart L, Cecala AL, and Gandhi NJ. The superior colliculus and the steering of saccades toward a moving visual target. *J Neurophysiol*. 118: 2890-2901, 2017.

Goossens HH, and Van Opstal AJ. Blink-perturbed saccades in monkey. I. Behavioral analysis. *J Neurophysiol*. 83: 3411-3429, 2000.

Gremmler S, Bosco A, Fattori P, and Lappe M. Saccadic adaptation shapes visual space in macaques. *J Neurophysiol*. 111: 1846-1851, 2014.

Hafed ZM, and Krauzlis RJ. Goal representations dominate superior colliculus activity during extrafoveal tracking. *J Neurosci*. 28: 9426-9439, 2008.

Hallett PE, and Lightstone AD. Saccadic eye movements to flashed targets. *Vision Res*. 16: 107-114, 1976a.

Hallett PE, and Lightstone AD. Saccadic eye movements towards stimuli triggered by prior saccades. *Vision Res*. 16: 99-106, 1976b.

Hopp JJ, and Fuchs AF. The characteristics and neuronal substrate of saccadic eye movement plasticity. *Prog Neurobiol*. 72: 27-53, 2004.

Inaba N, Iwamoto Y, and Yoshida K. Changes in cerebellar fastigial burst activity related to saccadic gain adaptation in the monkey. *Neurosci Res*. 46: 359-368, 2003.

Ito M. Mechanisms of motor learning in the cerebellum. *Brain Res*. 886: 237-245, 2000.

Kaku Y, Yoshida K, and Iwamoto Y. Learning signals from the superior colliculus for adaptation of saccadic eye movements in the monkey. *J Neurosci*. 29: 5266-5275, 2009.

Keller EL, Gandhi NJ, and Weir PT. Discharge of superior collicular neurons during saccades made to moving targets. *J Neurophysiol*. 76: 3573-3577, 1996.

Kojima Y, Iwamoto Y, and Yoshida K. Effect of saccadic amplitude adaptation on subsequent adaptation of saccades in different directions. *Neurosci Res*. 53: 404-412, 2005.

Kojima Y, and Soetedjo R. Change in sensitivity to visual error in superior colliculus during saccade adaptation. *Sci Rep*. 7: 9566, 2017.

Kojima Y, Soetedjo R, and Fuchs AF. Changes in simple spike activity of some Purkinje cells in the oculomotor vermis during saccade adaptation are appropriate to participate in motor learning. *J Neurosci*. 30: 3715-3727, 2010.

Kommerell G, Olivier D, and Theopold H. Adaptive programming of phasic and tonic components in saccadic eye movements. Investigations of patients with abducens palsy. *Invest Ophthalmol* 15: 657-660, 1976.

Krauzlis RJ, Basso MA, and Wurtz RH. Discharge properties of neurons in the rostral superior colliculus of the monkey during smooth-pursuit eye movements. *J Neurophysiol*. 84: 876-891, 2000.

Kyuhou S, and Kawaguchi S. Cerebellocerebral projection from the fastigial nucleus onto the frontal eye field and anterior ectosylvian visual area in the cat. *J Comp Neurol*. 259: 571-590, 1987.

Lee C, Rohrer WH, and Sparks DL. Population coding of saccadic eye movements by neurons in the superior colliculus. *Nature* 332: 357-360, 1988.

Levy-Bencheton D, Khan AZ, Pelisson D, Tilikete C, and Pisella L. Adaptation of Saccadic Sequences with and without Remapping. *Front Hum Neurosci*. 10: 359, 2016.

Maus GW, Duyck M, Lisi M, Collins T, Whitney D, and Cavanagh P. Target Displacements during Eye Blinks Trigger Automatic Recalibration of Gaze Direction. *Curr Biol*. : CB 27: 445-450, 2017.

McLaughlin SC. Parametric adjustment in saccadic eye movements. *Percept Psychophys*. 2: 359-362, 1967.

Moidell BG, and Bedell HE. Changes in oculocentric visual direction induced by the recalibration of saccades. *Vision Res*. 28: 329-336, 1988.

Noto CT, Watanabe S, and Fuchs AF. Characteristics of simian adaptation fields produced by behavioral changes in saccade size and direction. *J Neurophysiol*. 81: 2798-2813, 1999.

Optican LM, and Pretegiani E. What stops a saccade? *Philos Trans R Soc Lond B Biol Sci*. 372: 2017.

Optican LM, and Robinson DA. Cerebellar-dependent adaptive control of primate saccadic system. *J Neurophysiol*. 44: 1058-1076, 1980.

Ottes FP, Van Gisbergen JA, and Eggermont JJ. Visuomotor fields of the superior colliculus: a quantitative model. *Vision Res*. 26: 857-873, 1986.

Pelisson D, Alahyane N, Panouilleres M, and Tilikete C. Sensorimotor adaptation of saccadic eye movements. *Neurosci Biobehav Rev* 34: 1103-1120, 2010.

Quaia C, Joiner WM, Fitzgibbon EJ, Optican LM, and Smith MA. Eye movement sequence generation in humans: Motor or goal updating? *J Vis*. 10: 2010.

Quessy S, Quinet J, and Freedman EG. The locus of motor activity in the superior colliculus of the rhesus monkey is unaltered during saccadic adaptation. *J Neurosci*. 30: 14235-14244, 2010.

Scudder CA, Kaneko CS, and Fuchs AF. The brainstem burst generator for saccadic eye movements: a modern synthesis. *Exp Brain Res*. 142: 439-462, 2002.

Scudder CA, and McGee DM. Adaptive modification of saccade size produces correlated changes in the discharges of fastigial nucleus neurons. *J Neurophysiol*. 90: 1011-1026, 2003.

Shafer JL, Noto CT, and Fuchs AF. Temporal characteristics of error signals driving saccadic gain adaptation in the macaque monkey. *J Neurophysiol*. 84: 88-95, 2000.

Soetedjo R. Spatial updating of saccades: What do the superior colliculus and cerebellum do? *Soc Neurosci Abstr* 2016.

Soetedjo R, and Fuchs AF. Complex spike activity of purkinje cells in the oculomotor vermis during behavioral adaptation of monkey saccades. *J Neurosci*. 26: 7741-7755, 2006.

Soetedjo R, Fuchs AF, and Kojima Y. Subthreshold activation of the superior colliculus drives saccade motor learning. *J Neurosci*. 29: 15213-15222, 2009.

Soetedjo R, Kaneko CR, and Fuchs AF. Evidence that the superior colliculus participates in the feedback control of saccadic eye movements. *J Neurophysiol*. 87: 679-695, 2002.

Sommer MA, and Wurtz RH. Brain circuits for the internal monitoring of movements. *Annu Review Neurosci*. 31: 317-338, 2008.

Sparks DL, and Porter JD. Spatial localization of saccade targets. II. Activity of superior colliculus neurons preceding compensatory saccades. *J Neurophysiol*. 49: 64-74, 1983.

Steenrod SC, Phillips MH, and Goldberg ME. The lateral intraparietal area codes the location of saccade targets and not the dimension of the saccades that will be made to acquire them. *J Neurophysiol*. 109: 2596-2605, 2013.

Straube A, Fuchs AF, Usher S, and Robinson FR. Characteristics of saccadic gain adaptation in rhesus macaques. *J Neurophysiol*. 77: 874-895, 1997.

Takeichi N, Kaneko CR, and Fuchs AF. Activity changes in monkey superior colliculus during saccade adaptation. *J Neurophysiol*. 97: 4096-4107, 2007.

Tanaka M. Contribution of signals downstream from adaptation to saccade programming. *J Neurophysiol* 90: 2080-2086, 2003.

Tian J, and Zee DS. Context-specific saccadic adaptation in monkeys. *Vision Res*. 50: 2403-2410, 2010.

Wallman J, and Fuchs AF. Saccadic gain modification: visual error drives motor adaptation. *J Neurophysiol*. 80: 2405-2416, 1998.

Welch BL. The generalisation of student's problems when several different population variances are involved. *Biometrika* 34: 28-35, 1947.

Zimmermann E, and Lappe M. Mislocalization of flashed and stationary visual stimuli after adaptation of reactive and scanning saccades. *J Neurosci*. 29: 11055-11064, 2009.

Zimmermann E, and Lappe M. Motor signals in visual localization. *J Vis*. 10: 2, 2010.

Figure Legends

Figure 1. Schematic illustration of the various saccade tasks. *A*: Visually guided task (VGT). Thick horizontal bars indicate when the target is ON (bar) or OFF (no bar). Black and grey lines indicate the position of the target spot and eye, respectively. Abbreviations: F, fixation position; T, target position; M, desired saccade motor command (DSMC). *B*: Double-saccade crossover task (DST-crossover). Abbreviations: T1, position of the first brief target; T2, position of the second brief target. T1 and T2 appear in opposite visual hemifields. *C*: Double-saccade refixation task (DST-refixation). F and T2 appear at the same positions. *D*: The same as *C* (DST-refixation) except T2 is turned ON again at the end of the first saccade and then turned OFF at the beginning of the second. *E*: Double-saccade forward task (DST-forward). T1 and T2 appear in the same hemifield. *F*: Task to elicit adaptation of the second saccades of a DST-refixation task. When the second saccade occurs, the target jumps closer to T1 and is turned ON.

Figure 2. A representative experiment of the transfer of gain decrease adaptation of 12° VGT saccades to the second saccades of a DST-crossover task. *A*-*C*: Horizontal eye position traces of 3° (*A*), 6° (*B*) and 9° (*C*) VGT saccades before (black) and after (grey) adaptation. *D*-*F*: Horizontal eye position traces of 3 different DST-crossover tasks with T2 at -3° (*D*), -6°(*E*) and -9°(*F*). T1 was positioned so that DSMC was constant ~12°.

Figure 3. The transfer of adaptation of VGT saccades to VGT saccades with different target eccentricities (*A* and *C*) and to the second saccades of DST-crossover tasks with different T2 eccentricities (*B* and *D*). *A* and *B*: % gain change vs. VGT target eccentricity (T-F) and DST T2 eccentricity (T2-F), respectively. *C* and *D*: % transfer vs. VGT target eccentricity (T-F) and DST T2 eccentricity (T2-F), respectively. Each symbol identifies data from one of eight experiments. Data in red were from monkey M.

Figure 4. Transfer of adaptation of VGT saccades to the second saccades of a DST-refixation task. *A* and *B*: Data from two representative experiments. Horizontal gain of VGT saccades (open circles) is shown below for gain decrease and increase adaptation, respectively; the gain of randomly interleaved second saccades of a DST-refixation task (filled circles) is shown above. Fits are exponential for VGT saccades and linear for the second saccades. *C*: Comparison of % gain changes of adapted 12° VGT saccades (open bars) with the associated gain changes of the second saccades of a DST-refixation task (filled bars, ~12° DSMC). The first 8 symbols represent data from the experiments in Fig. 3. B1-B3 are additional gain decrease experiments with interleaved DST trials. F1-F5 are gain increase experiments. * indicates a significant gain change, $P<0.05$, for the DST data. Data in red were from monkey M.

Figure 5. Comparison of the % gain change of the second saccades of a DST-refixation task during adaptation with T2 either OFF (circles) or ON (triangles) during the intersaccade interval (ISI). *A-F*: data from 6 experiments. Insets: average horizontal gains (±SD) before adaptation. Fits of percent gain change vs. ISI are linear. Dashed thick lines at bottom of each data set show the % gain change of 12° VGT saccades. Data in red were from monkey M.

Figure 6. Transfer of VGT saccade adaptation to the second saccades of a DST-forward task. *A-C*: an exemplar experiment. Comparison of VGT saccades of 3°(*A*) and 6°(*B*) before (black) and after (grey) adaptation of 12° VGT saccades. *C*: comparison of DST-forward saccades before (black) and after (grey) VGT saccade adaptation (T1 and T2 eccentricities are 3° and 6°, respectively). *D-F*: summary of 8 experiments. *D*: comparison of % gain change of the second saccades of a DST-forward task and 3° VGT saccades. *E*: comparison of % gain change of the overall DST-forward amplitude and 6° VGT saccades. *F*: comparison of the % gain change of the overall DST-forward amplitude and that of the second saccades. *E-F*: solid diagonal lines of slope=1.0; F: dashed line of slope=0.5. Data in red were from monkey M.

Figure 7. Transfer of adaptation of the second saccades of a DST-refixation task to VGT saccades. Effect of a horizontal gain decrease (*A*) or increase (*B*) adaptation of the second saccades of a DST-refixation task (filled circles below) on the gain of randomly interleaved VGT saccades (open circles above). Fits are

exponential for the second saccades and linear for VGT saccades. “Post” panels show recovery from adaptation. Comparison of % gain change of decrease (*C*, A1-A5) or increase (*D*, B1-B5) adaptation of the second saccades of a DST-refixation task (filled bars, ~12° DSMC) with the % gain change of 12° VGT saccades (open bars). * indicates a significant gain change, $P<0.05$, for VGT data. Data in red were from monkey M.

Figure 8. Comparison of the amplitude transfer characteristics (adaptation fields) between VGT saccade adaptation and adaptation of the second saccades of a DST-refixation task. Percent gain change (*A*) and % transfer (*B*) of VGT saccade adaptation to VGT saccades elicited by different target step amplitudes. Black circles (dashed lines) are averages. Percent gain change (*C*) and % transfer (*D*) of adaptation of the second saccades of a DST-refixation task to other second saccades with different amplitudes of saccade motor command. Black filled circles (solid line) are averages. Open circles and dashed lines are averages from *A* and *B* for comparison. Data in red were from monkey M.

Figure 1

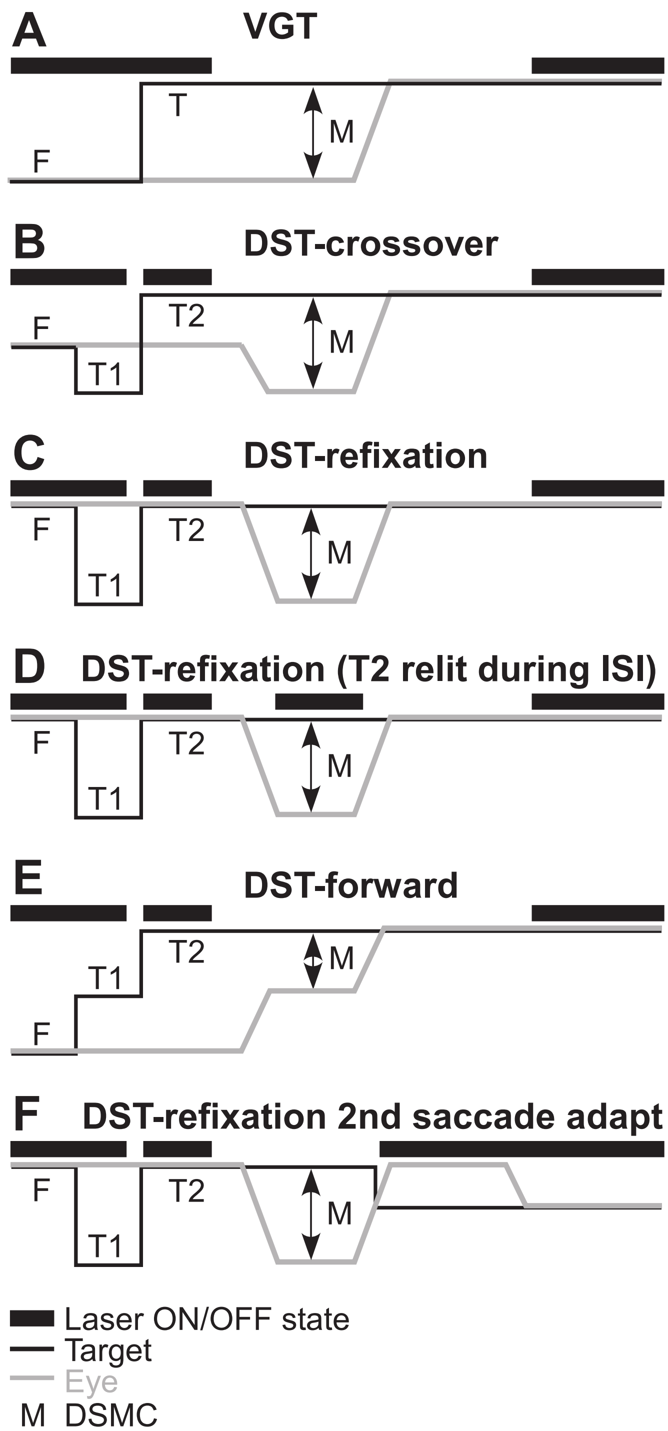
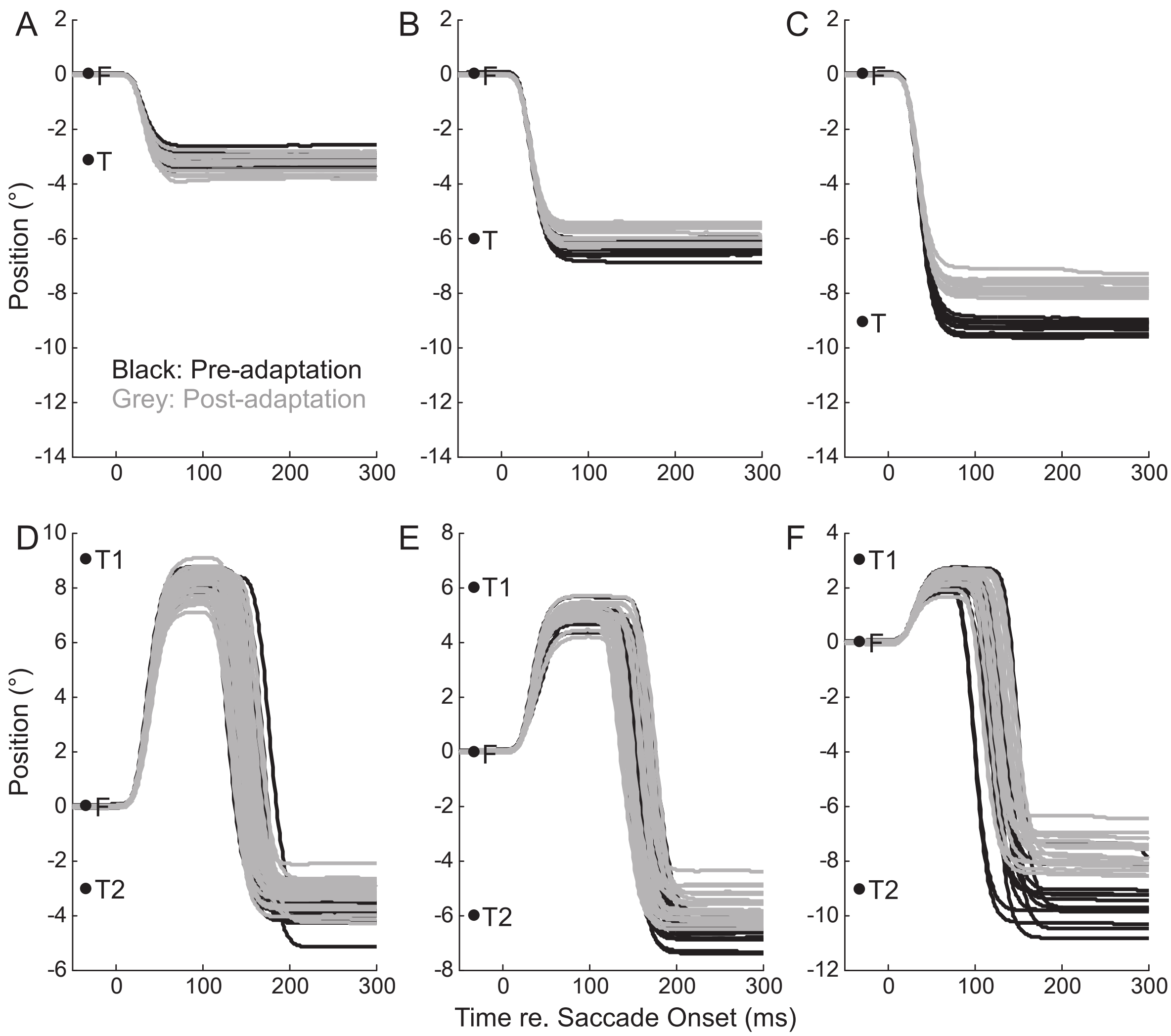

A
VGT
T
M
F
B
DST-crossover
F
T2
M
T1
C
DST-refixation
F
T2
M
T1
D
DST-refixation (T2 relit during ISI)
F
T2
M
T1
E
DST-forward
T2
M
T1
F
F
DST-refixation 2nd saccade adapt
F
T2
M
T1
Laser ON/OFF state
Target
Eye
M DSMC

Figure 2



A
B
C
D
E
F
F
T
T1
T2
Black: Pre-adaptation
Grey: Post-adaptation
Position (°)
Time re. Saccade Onset (ms)

Figure 3

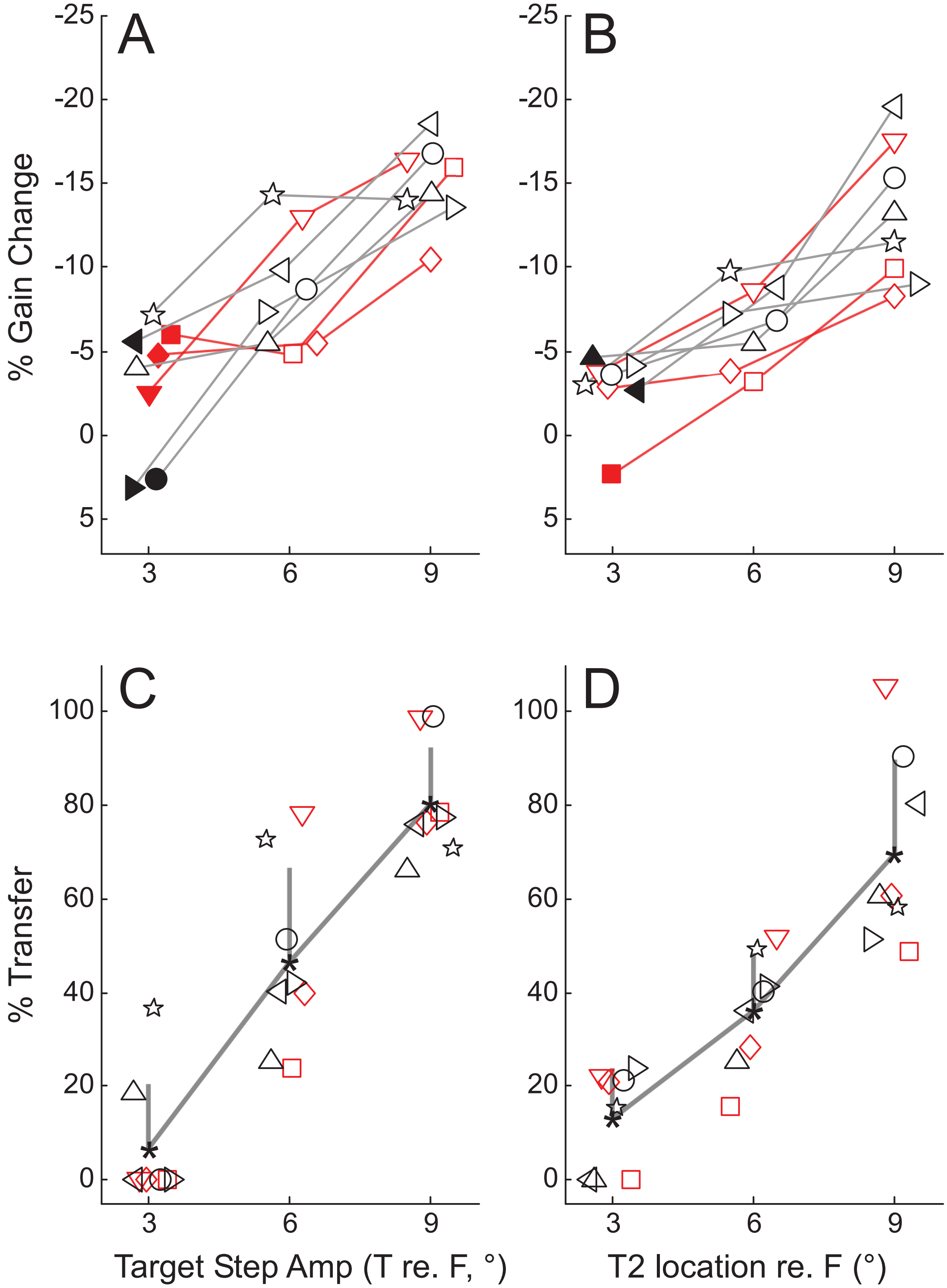
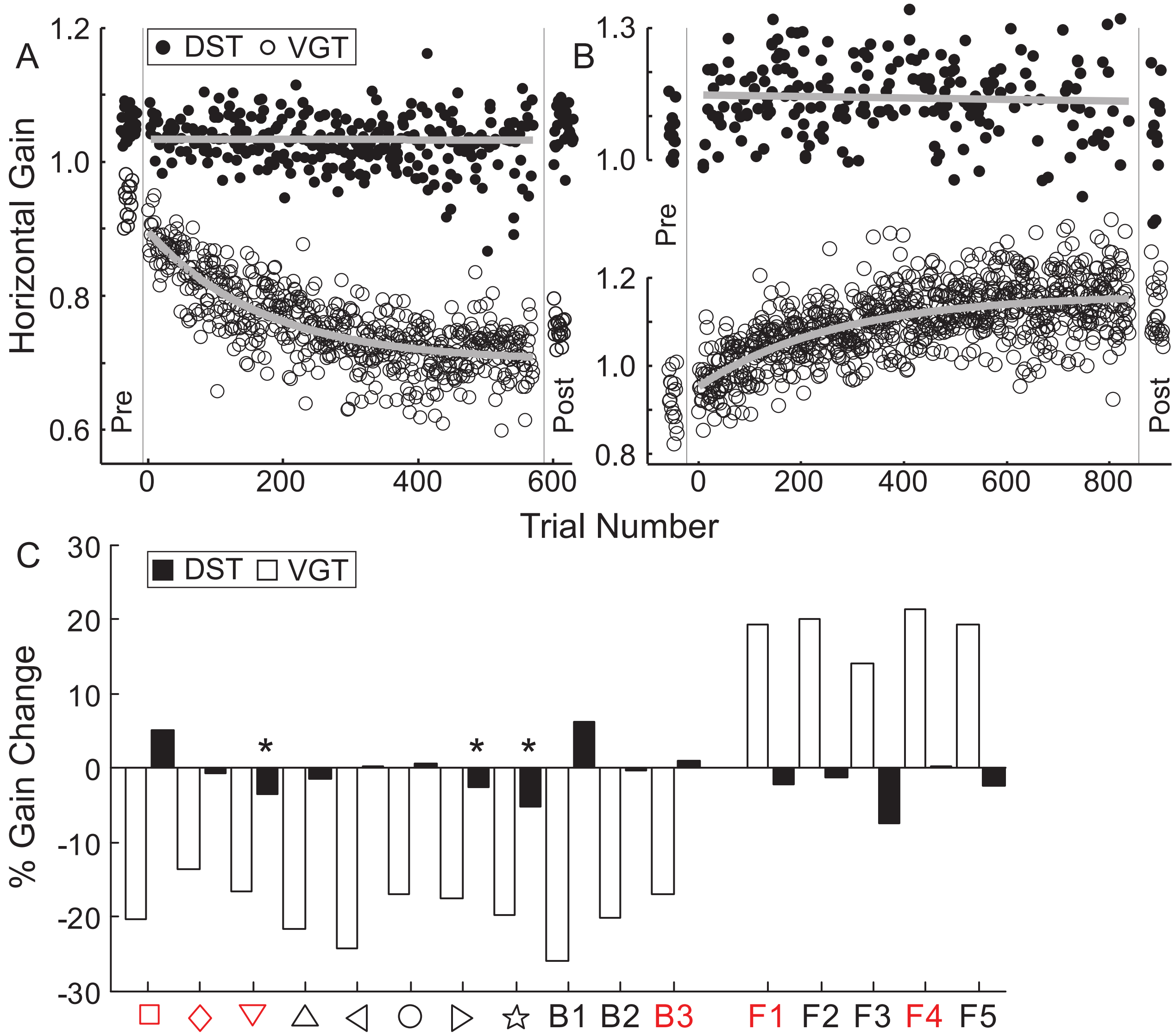
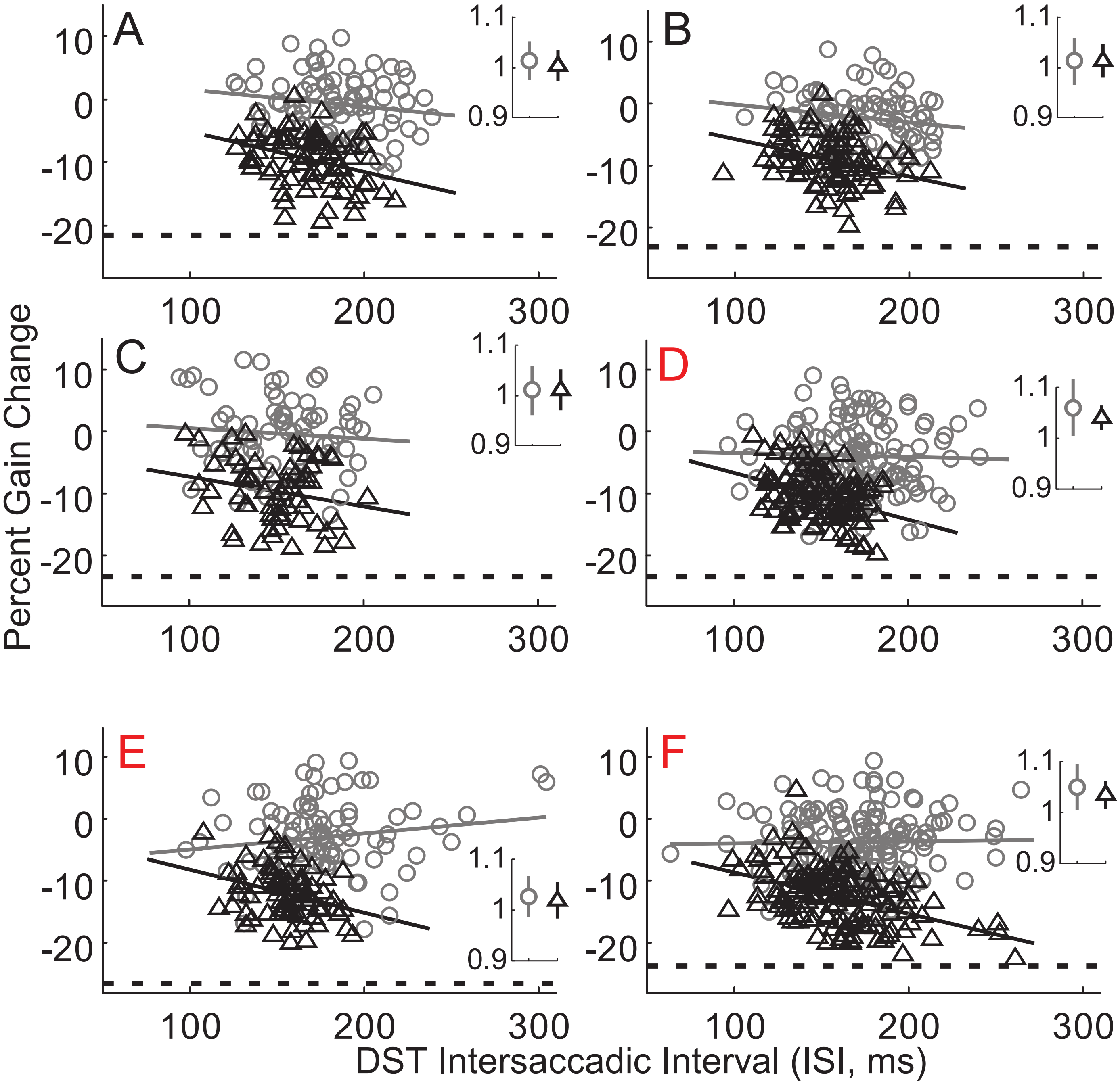

A
B
C
D
% Gain Change
% Transfer
-25
-20
-15
-10
-5
0
5
100
80
60
40
20
0
3
6
9
Target Step Amp (T re. F, °)
T2 location re. F (°)

Figure 4



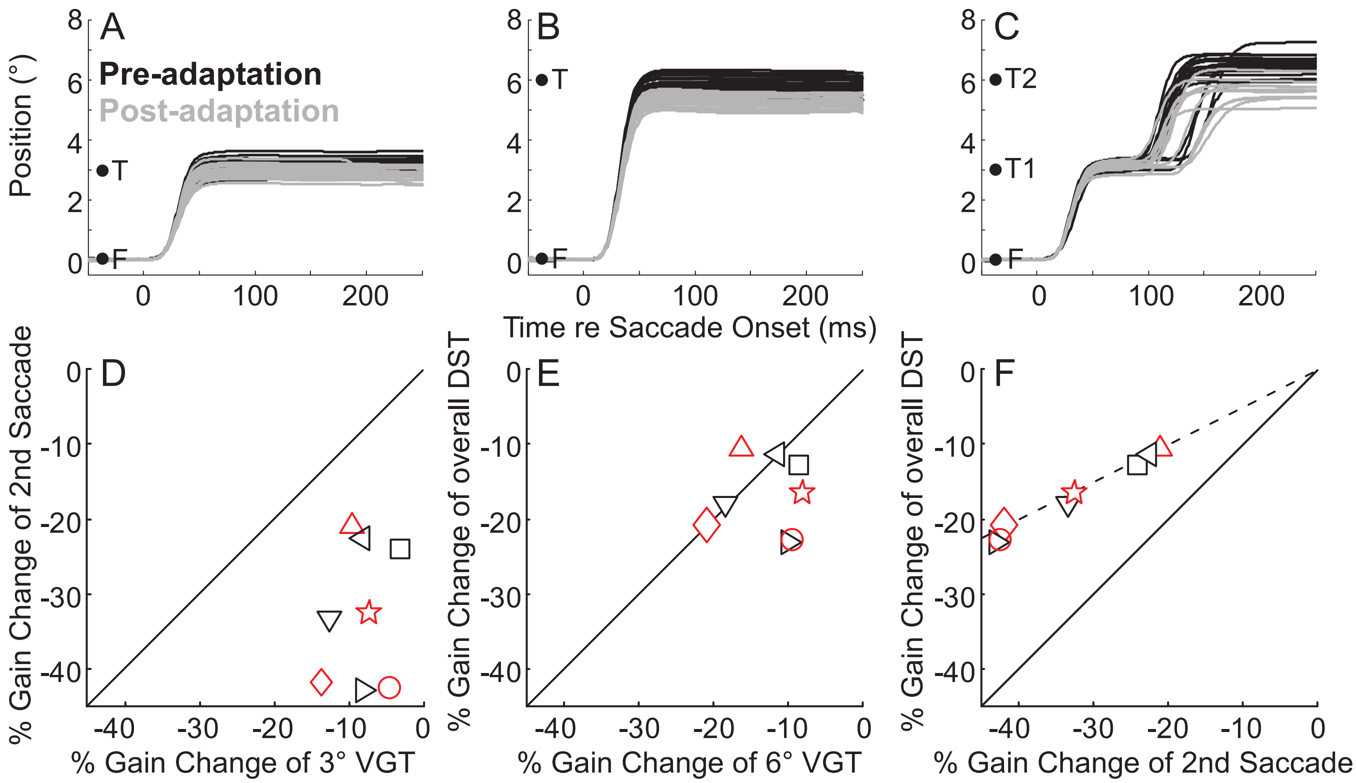
A
B
C
DST
VGT
Horizontal Gain
Pre
Post
Trial Number
% Gain Change
B1 B2 B3
F1 F2 F3 F4 F5

Figure 5



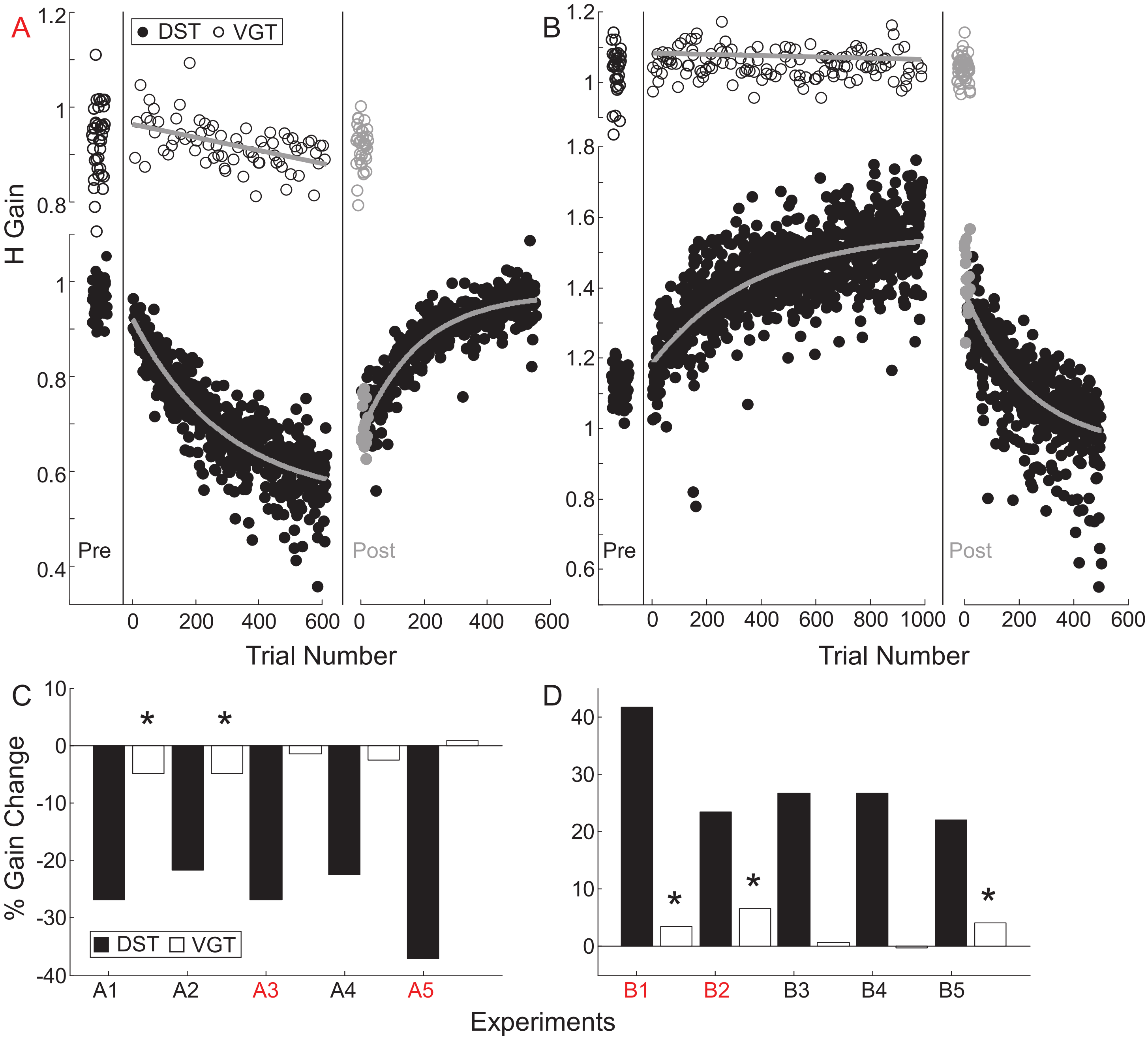
A
B
C
D
E
F
10
0
-10
-20
100
200
300
1.1
1
0.9
Percent Gain Change
DST Intersaccadic Interval (ISI, ms)

Figure 6



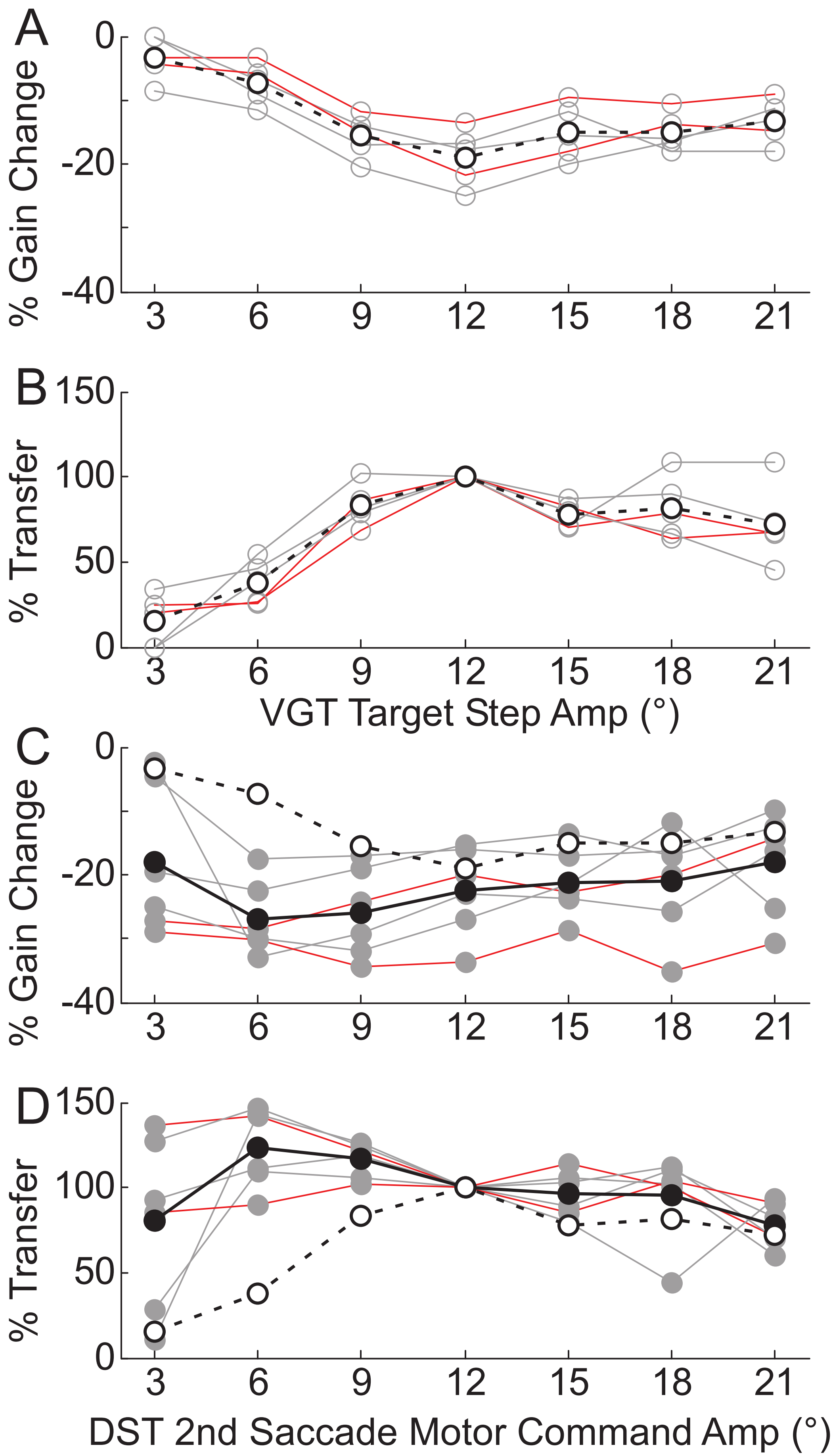
A
Pre-adaptation
Post-adaptation
T
F
B
T
F
C
T2
T1
F
Position (°)
Time re Saccade Onset (ms)
D
E
F
% Gain Change of 2nd Saccade
% Gain Change of 3° VGT
% Gain Change of overall DST
% Gain Change of 6° VGT
% Gain Change of overall DST
% Gain Change of 2nd Saccade

Figure 7



A
B
DST
VGT
H Gain
Pre
Post
Trial Number
C
D
% Gain Change
DST
VGT
A1
A2
A3
A4
A5
B1
B2
B3
B4
B5
Experiments

Figure 8



A
0
-20
-40
% Gain Change
3
6
9
12
15
18
21
B
150
100
50
0
% Transfer
3
6
9
12
15
18
21
VGT Target Step Amp (°)
C
0
-20
-40
% Gain Change
3
6
9
12
15
18
21
D
150
100
50
0
% Transfer
3
6
9
12
15
18
21
DST 2nd Saccade Motor Command Amp (°)