Contribution of Signals Downstream From Adaptation to Saccade Programming

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Tanaka, Masaki. Contribution of signals downstream from adaptation to saccade programming. J Neurophysiol 90: 2080–2086, 2003; 10.1152/jn.00207.2003. Information about ongoing behavior is necessary for stable perception and subsequent motor planning. Although many recurrent networks are known in the motor systems, the pathways that transmit the signals for internal monitoring of behavior are not specified. The present study reports that the pathways originating from sites downstream of cerebellar adaptation provide internal signals that are used for subsequent eye-movement programming. When monkeys made two successive saccades toward the locations of previously flashed targets or initial fixation, the second saccade compensated for the adaptive changes in the primary saccade. The use of signals downstream from adaptation for saccade programming contrasts with recent findings that signals upstream from the site of saccadic adaptation, or both. The present study attempted to elucidate the relative locations of the site of saccadic adaptation, the desired eye-movement signals represented in the brain stem (Jones 1985; Leigh and Zee 1999), the eye-movement signals downstream from the site of saccadic adaptation to construct spatially accurate visual information: the perceived location of visual stimuli flashed after an adapted saccade was shifted relative to the visual stimuli that were presented at the same location before the saccade (Bahcall and Kowler 1999). Because the amounts of illusory shift were similar to those of saccadic adaptation, the desired eye-movement signals represented in the cerebral cortices or upper brain stem likely controlled the perceptual localization of visual stimuli. It remains unknown whether the same eye-movement signals are also used for subsequent movement control. Several studies have shown that the perception and action are dissociable during voluntary movements (e.g., Dunker 1929; Goodale and Milner 1992) and that the perceptual judgment based on relative locations of visual stimuli is different from that of goal-directed movements (Burr et al. 2001). For movement control, there is evidence that the cerebral cortex uses the extra-retinal, eye-movement signals to command spatially accurate saccades (Dulhamel et al. 1992; Goldberg and Bruce 1990) and that the pathways through the thalamus to the cortex are important for providing those signals (Gaymard et al. 1994; Sommer and Wurtz 2002). Because the thalamus receives ascending projections from virtually all stages of saccade processing in the brain stem (Jones 1985; Leigh and Zee 1999), the eye-movement signals could come from either downstream or upstream from the site of saccadic adaptation, or both. The present study attempted to elucidate the relative locations of the site of saccadic adaptation and the origin of the behavioral signals that are used for subsequent eye-movement programming. The data show that the signals downstream from the site of saccadic adaptation play roles in the programming of subsequent eye movements, indicating that the recurrent pathways from the brain stem saccade generator through the thalamus to the cerebral cortex transmit behavioral signals for eye-movement control.

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FIG. 1. Experimental design. A: the saccade system sends “desired displacement” signals to the brain stem. Subsequently the saccadic adaptation takes place with the help of the cerebellum. The cerebral cortices monitor recurrent signals to plan subsequent movements. B: in the double-step paradigm, 2 targets (T1 and T2) were flashed successively, then the monkey made a saccade to each. The 2nd saccade (S2) must be programmed based on the retinal location of T2 and the preceding saccade (S1). Adaptation in S1 would alter S2 if the signals downstream from adaptation are used for saccade programming but would not if upstream signals are used. C: in the re-fixation paradigm, a peripheral target (T1) disappeared when the monkey made a saccade to it (S1). The 2nd, return, saccade to the initial fixation location during adaptation of S1 differentiates 2 alternative computations. D: learning paradigm was used to induce saccadic adaptation. In this paradigm, the peripheral target (T1) jumped 3–5° horizontally when the monkey made a saccade to it. E: in the control saccade task, the target appeared 10° horizontally and stayed there for 800–1,000 ms.

METH O D S

Two female Japanese monkeys (Macaca fuscata) were used. Both animals were prepared for chronic experiments by implanting a pair of head holders and an eye coil under general anesthesia and using sterile procedures. All experimental protocols were approved in advance by the Animal Care and Use Committee of the Hokkaido University School of Medicine.

Experiments were controlled by Windows-based real-time data-acquisition system (TEMPO, Reflective Computing) running on Pentium PCs. All events were updated every 5 ms, and the visual stimuli were presented on a 21-in CRT monitor (Dell P1130, refresh rate 60 Hz) that was located 38 cm away from the eyes. Experiments were carried out in a darkened booth, but all visual stimuli were presented on a gray background (2.9 cd/m²) that subtended 54 × 42° to eliminate any persistent afterimages left on the screen. In advance of the experiments, the exact timing of target presentation relative to the vertical retrace signal was measured by using a phototransistor (Toshiba, TPS601A) attached on the screen. The time from the vertical retrace signal to the onset and offset of visual stimuli was a function of vertical location of the stimuli. Based on this relationship, the exact timing of target offset could be measured after the experiments by using the data of target location and the vertical retrace signal that were recorded during experiments.

Four oculomotor tasks were used: double-step task, re-fixation task, learning task, and control saccade task. The former two tasks were used to probe the effect of adaptation on the eye-movement programming, and the learning task was used to induce saccadic adaptation. All but the re-fixation tasks began with the appearance of a red fixation target (3.1 cd/m²) at a random location (±5°) along the horizontal meridian. In the double-step task (Hallet and Livingstone 1976), two white targets (7.3 cd/m²) were flashed successively after the fixation period of 900–1,200 ms (Fig. 1B, left). The first target appeared 10° either to the right or left of the initial fixation, and the second target appeared 4, 6, 8, or 10° above or below the first target. Typically the first and the second target were illuminated for 100 and 20 ms, respectively, but the duration varied from 90 to 120 ms and from 20 to 35 ms for the first and the second targets, respectively, depending on the animal and the direction of saccades. The monkeys were required to make two successive saccades toward the location of each target, first horizontally, and then vertically. For the re-fixation tasks, modified from previous studies (Goldberg and Bruce 1990; Mays and Sparks 1980), a green target (5.9 cd/m²) was used for both the fixation target and the saccade target to inform monkeys about the trial type. In this paradigm, the fixation target jumped 5° horizontally, then remained visible until the monkeys made a saccade toward the target (Fig. 1C, left). After the first targeting saccade was terminated, the monkeys were required to make the second, return, saccade toward the location of initial fixation without visual guidance. To induce saccadic adaptation, a conventional learning task (e., Deubel et al. 1986; Edelman and Goldberg 2002; Straube et al. 1997) was used. When the monkeys made a saccade to a white target that appeared 10° either to the right or left of the initial fixation, the target jumped 5° backward or 3–4° forward along the horizontal meridian (Fig. 1D). To obtain the data before adaptation and those during re-adaptation, the control saccade task was used. In this task, a white target appeared 10° horizontally and stayed there for 800–1,000 ms (Fig. 1E). All target spots were 0.4° squares.

In all tasks, the monkeys were required to move their eyes into a “window” that surrounded the target location at a specific time interval. During the last 300 ms of fixation period, the window was 2° square and was centered at the fixation target. After the appearance of saccade target, the monkeys were required to move their eyes into a rectangular 10 × 3° window within 300 ms. The window was extended horizontally to detect saccades with a variety of amplitudes during adaptation. In the learning task, the target jumped horizontally when eye position entered this window, then stayed there for 700–900 ms. The monkeys made a corrective saccade to the new target location within 300 ms with an accuracy of 2°. In the double-step task, the initial rectangular window on the horizontal meridian was shifted vertically to the location of the second target when the first horizontal saccade was detected. The size of the second rectangle window was 8 × 4° for the gain decrease experiments and was 6 × 4° for the gain increase experiments. The monkeys were required to make the second vertical saccade within 400 ms. In the re-fixation paradigm, the saccade target disappeared when the initial targeting saccade was detected: monkeys then were required to make the second saccade into a rectangular window around the initial fixation location within 400 ms. During the training on both the double-step and the re-fixation paradigms, the second target or the initial fixation target reappeared.
after the termination of second saccade. However, the experiments analyzed here did not provide any visual feedback after the completion of the second saccade for both paradigms (Fig. 1, B and C, left). Each correct trial was reinforced with a tone and water or apple juice reward.

Data were digitized and stored in files (sampled at 1 kHz) during experiments and were analyzed off-line using Matlab (Mathworks). Eye velocity was obtained by digital differentiation. Saccade onset was marked as the time when eye speed exceeded 80°/s on the way back to zero. Saccade termination was marked as the time when eye speed crossed 40°/s on the way back to zero. Saccade amplitude was measured as the difference in eye position 10 ms before and 50 ms after the onset and the termination of each saccade. For each double-step trial, the precise timing of target offset was computed based on target location and the timing of the vertical retrace signal that was recorded and stored in files during experiments. The fraction of the double-step trials in which the monkeys initiated a saccade before the offset of targets averaged 6.4% for 16 experiments. The data for those trials were removed from further analyses.

RESULTS

Eye movements of monkeys were examined before and during saccadic adaptation. In the first set of experiments, the double-step trials were interspersed randomly at low probabilities within the learning trials to probe the effects of adaptation. Figure 1B, right, illustrates the responses expected from two alternative computations. The first saccade (Fig. 1B, S1) has a vector based on the location of the retinal images of the first target relative to the fovea. However, since the second target disappeared before eye movements, the brain must compute the second saccade vector (Fig. 1B, S2) by subtracting the first saccade vector from the retinal location of the second target (Goldberg and Bruce 1990; Sommer and Wurtz 2002). When the gain of the first saccade is altered by adaptation, the expectation for the second saccade depends on how the brain monitors the performance of the first saccade. If the brain monitors the behavior using signals that arise downstream from adaptation, then the second saccade would have a horizontal component, to compensate for the adaptive changes in the first saccade (Fig. 1B, “downstream”). If the brain uses signals upstream from adaptation, then the second saccade would remain vertical (Fig. 1B, “upstream”).

Figure 2A plots the data obtained from an experiment that consisted of three blocks of leftward saccade trials. In the first preadaptation block, one control and two double-step trials were presented pseudorandomly for ~100 times. The second adaptation block consisted of 20% double-step trials and 80% learning trials that reduced the gains of leftward saccades. This trial configuration successfully altered the gains of the first saccades in the double-step trials (Fig. 2A, red symbols): the time course of adaptation in the double-step trials was indistinguishable from that in the learning trials (Fig. 2A, black dots). The third re-adaptation block had the same design as the first block, but the trials were repeated until the monkey was satiated with water rewards. Again, the sizes of the first saccades in the double-step trials and the control trials were altered similarly, approaching the values observed in the first block. In the course of adaptation, the second saccades compensated for the changes in the first saccade in the double-step trials. The sizes of the horizontal components of the second saccades (Fig. 2A, blue symbols) increased as the adaptation decreased the gains of the first saccades in the second block, and then they returned toward zero during re-adaptation in the third block. The precision of vertical component of second saccades depended on the vertical eccentricity of the second target but was not different between before and during adaptation for this and 9 of the 15 other experiments (2-way ANOVA, P > 0.05). The difference between vertical eye position and the location of second target immediately after the second sac-
cure averaged 0.71, 0.75, and 0.69° for the first, second, and third block of trials, respectively.

To quantify these data, Fig. 2B plots the changes in the horizontal components of the second saccades as a function of those of the first saccades during adaptation and re-adaptation compared with the mean values before adaptation. If the saccade system monitors behavior by using the actual eye-movement signals that arise downstream from adaptation, then the second saccade would compensate for the adaptive changes in the first saccade, and the data would distribute along the line with a slope of minus one. If the saccade system uses the “planned” eye-movement signals that arise upstream from adaptation and does not receive feedback about the changes in the first saccade, then the data would distribute around the horizontal line. Both the data shown in Fig. 2A (Fig. 2B, red symbols) and those obtained from another experiment that increased the gain of leftward saccades (Fig. 2B, black ×) were distributed mostly between those two lines, indicating that the second saccade partially compensated for the adaptive changes in the first saccade. The amount of saccadic compensation was estimated by computing a regression line for the data of horizontal components of the first and the second saccades throughout three blocks. The regression coefficients were −0.50 and −0.60 for the experiments shown in Fig. 2B and averaged −0.50 ± 0.07 for 16 experiments performed in both directions and monkeys (Fig. 4, left, horizontal bars). The correlation coefficients ranged from −0.74 to −0.41, and averaged −0.55 ± 0.12.

Because the amplitudes of saccades were so variable as in Fig. 2B, the amounts of saccadic compensation were also measured after smoothing out the inter-trial variability of saccades. Figure 2C plots the data the same as in Fig. 2B but was smoothed by computing the running averages of the data for every 30 consecutive double-step trials. The data points were initially close to the origin but were shifted along the oblique line as the adaptation progressed. Then they returned toward the origin at a similar rate during re-adaptation. When the amounts of saccadic compensation were estimated by fitting a regression line to the smoothed data throughout three blocks, the regression slopes were −0.54 and −0.77 for the experiments shown in Fig. 2, B and C, and averaged −0.67 ± 0.14 for the 16 experiments. The regression coefficients were greatly improved after smoothing the data and averaged −0.88 ± 0.08. Thus the second saccade in the double-step paradigm compensated for more than half of the adaptive changes in the first saccade.

A number of studies have shown that the visual stimuli presented around the time of saccade are mislocalized (e.g., Burr et al. 2001; Honda 1989; Lappe et al. 2000; Martin and Pearce 1965; Ross et al. 1997). Because the second target appeared immediately before the initiation of the first saccade in the double-step paradigm, the effects of saccade on the perceptual localization might have confused the present results. Further, the estimate of extra-retinal signals would be better in tasks that use fewer targets and hence are less sensitive to the processing of visual spatial memory (Skavenski 1990). To exclude the possible effects of perceptual mislocalization and to examine saccadic compensation in different conditions, a second set of experiments was performed. In the re-fixation paradigm (Fig. 1C), the brain needed to compute a saccade that was opposite in direction to the preceding saccade.

Figure 1C, right, illustrates predicted outcomes based on two alternative computations using different sources of behavioral monitoring signals. If the saccade system uses signals that arise downstream from adaptation, then the second saccade would compensate for the adaptive changes in the preceding saccade, and would land precisely at the location of initial fixation (Fig. 1C, downstream). If the saccade system uses signals that arise upstream from adaptation, then the size of second saccade would remain unchanged during adaptation (Fig. 1C, upstream).

Experiments were carried out in three blocks. The first preadaptation block contained ~100 repeats of two control saccade trials and one re-fixation trial that were presented pseudorandomly. The second adaptation block contained 250–350 repeats of four learning trials, one control trial in the direction opposite to adaptation, and one re-fixation trial. The third re-adaptation block had the same configuration as the first block, but included as many repeats as possible. Figure 3A plots the data from an experiment that decreased the gain of rightward saccades. The means of first saccades in the re-fixation trials (Fig. 3A, red symbols) changed over time courses similar to those in the learning trials (black dots, top). The gains of leftward saccades in control trials remained around unity throughout the experiment (Fig. 3A, black dots, bottom). However, the gains of the second, return, saccades in the re-fixation trials (blue symbols) were altered to be similar to the first rightward saccades. The changes in sizes of both the first and the second saccades during adaptation and re-adaptation are plotted in Fig. 3B, for the experiment shown in Fig. 3A (red symbols) and for another experiment that increased the gains of rightward saccades (black ×). As before, solid lines indicate predictions based on two alternative computations. The data obtained from both experiments distributed closer to the line with a unity slope, indicating that the saccade system took account of adaptive changes in the first saccades. The slopes of regression lines fitted to the sizes of the first and second saccades in all re-fixation trials for these experiments were 0.67 and 0.71, and those for 16 experiments that are plotted in Fig. 4 (right, horizontal bars) averaged 0.67 ± 0.09. The correlation coefficients ranged from 0.46 to 0.84 and averaged 0.69 ± 0.12. To eliminate the inter-trial variation and to show the consistency of the amount of saccadic compensation during adaptation, Fig. 3C plots the same data as in B but were smoothed by computing the running averages of the data for every 30 consecutive re-fixation trials. After smoothing the data, the regression slopes were 0.76 and 0.91 for the experiments shown in Fig. 3, B and C, and averaged 0.79 ± 0.19 for the 16 experiments. The regression coefficients averaged 0.86 ± 0.12.

To interpret these data, two additional sets of separate experiments were performed. First, since all visual stimuli were presented on a gray background (methods), the monkeys might remember the location of initial fixation relative to the contour of the screen. However, the additional re-fixation experiments in which the background (54 × 2°) appeared only after the first saccade showed similar results. The regression coefficients of those gain-decrease experiments performed on both monkeys averaged 0.65 ± 0.10 (n = 4) and were not different from the data for the experiments with a static background throughout the trials (unpaired t-test, t = 0.21, 10 df, P = 0.84). A second and more important control examined whether the
difference in the amount of saccadic compensation for the changes in the first saccades between paradigms was inherited from the difference in task difficulty: the saccadic compensation in the double-step paradigm might be normally less than that in the re-fixation paradigm. To test this possibility, the adaptive changes in saccades were mimicked by presenting the first target 6°, 8°, 10°, 12°, or 14° to the right or left of initial fixation, while the second target in the double-step trials was flashed 10° horizontally and 4°–10° vertically. When the amount of saccadic compensation was measured by computing the regression lines for the data of the first and the second saccade amplitudes, the correlation coefficients ranged from −0.99 to −0.90, and the absolute values of regression coefficients obtained from five experiments for each monkey averaged 0.81 ± 0.05 (n = 20) and 0.96 ± 0.05 (n = 20) for the double-step and re-fixation trials, respectively (Fig. 4, open diamonds, for each condition). Thus the saccadic compensation in the double-step trials was less in nature than that in the re-fixation trials. The difference in saccade accuracy between paradigms might be attributed to the fact that both the visual and eye-movement signals are necessary for the programming of second saccades in the double-step trials, whereas only eye-movement information would be sufficient in the re-fixation trials. The proportion of signals that are downstream from adaptation and are used for saccade programming was estimated for each monkey by dividing the mean of the regression slopes for the adaptation experiments by those for the experiments that mimicked the adaptive changes in the first saccades. The values were 66 and 59% for the double-step experiments and 72 and 69% for the re-fixation experiments. When the data of adaptation experiments that were smoothed by running averages were used for this estimation, the values were 85 and 82% for the double-step experiments and were 89 and 77% for the re-fixation experiments. Thus the majority of recurrent signals for saccade programming come from the sites downstream from saccadic adaptation.

**DISCUSSION**

The present results have shown that more than half of the behavioral monitoring signals come from subcortical structures that are located downstream from the site of saccadic adaptation. Proprioceptive inputs from extra-ocular muscles could play a role. However, previous studies have shown that the saccade system does not compensate for the eye movements...
evoked by the trochlear nerve (Sparks and Mays 1983) or abducens nucleus (Schiller and Sandell 1983) stimulation and that proprioceptive inputs are not necessary in compensating for saccades evoked from the SC (Guthrie et al. 1983). Instead, the adaptive changes are likely monitored by ascending pathways that transmit internal signals related to actual eye displacement and/or post-saccadic eye position through the thalamus to the cerebral cortex. This idea is supported by anatomical evidence showing that many subcortical eye-movement centers downstream from the cerebellar adaptation and upstream from the ocular motoneurons send ascending projections to the thalamus. The origins of those axons include: the paramedian pontine reticular formation (Büttner-Ennever and Henn 1976; Graybiel 1977), the nucleus prepositus hypoglossi (Kotchabhakdi et al. 1980; McCrea and Baker 1985), the interstitial nucleus of Cajal (Kokkoroyannis et al. 1996), the vestibular nuclei (Asanuma et al. 1982a), and the deep cerebellar nuclei (Asanuma et al. 1983b; Lynch et al. 1994). Further, some physiological studies have identified neuronal activity related to saccades or eye position in the intralaminar nuclei (Schlag-Rey and Schlag 1984; Wyder et al. 2003) and adjacent mediodorsal nucleus (MD) (Sommer and Wurtz 2002; Tanibuchi and Goldman-Racine 2003) of the thalamus.

Why does the saccade system take account of only part of the adaptive changes? Imperfect compensation for adaptive changes might be attributed to inaccuracy in the ascending information as suggested by other studies (Bockisch and Miller 1999; Dassonville et al. 1992). Alternatively, the remaining signals for behavioral monitoring might come from the sites upstream from adaptation, such as the SC or saccade-related cortical areas. The latter view is consistent with recent findings that the signals in the SC are sent to the frontal eye field through the MD and that this pathway transmits ~20% of recurrent signals that are used for subsequent eye movement programming (Sommer and Wurtz 2002). In addition, a recent psychophysical study has shown that the signals upstream from adaptation are important for perceptual localization of visual stimuli that are presented before and after saccade (Bahcall and Kowler 1999). While the difference between perceptual localization and saccade could be partly due to the fact that the subjects used information about relative versus absolute locations of visual stimuli in those experiments, the results indicate that the quality of eye-movement signals used for these systems is different. Thus commands for eye movement are likely monitored through multiple recurrent networks to enable precise movements and perception. The separation of pathways contributing to action or perception might be related to the previous findings that the amount of mislocalization of visual stimuli presented around the time of a saccade depends on whether the subjects are asked to report the relative locations of visual stimuli or to point to the location of previously flashed visual stimulus (Burr et al. 2001). Detailed analysis of eye-movement signals in different pathways in the thalamus will be needed to understand how different recurrent networks contribute to precise movement and perception.

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DISCLOSURES

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