Trial-by-Trial Updating of the Gain in Preparation for Smooth Pursuit Eye Movement Based on Past Experience in Humans

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Tabata H, Miura K, Kawano K. Trial-by-trial updating of the gain in preparation for smooth pursuit eye movement based on past experience in humans. J Neurophysiol 99: 747–758, 2008. First published December 12, 2007; doi:10.1152/jn.00714.2007. To understand how the CNS uses past experiences to generate movements that accommodate minute-by-minute environmental changes, we studied the trial-by-trial updating of the gain for initiating smooth pursuit eye movements and how this relates to the history of previous trials. Ocular responses in humans elicited by a small perturbing motion presented 300 ms after appearance of a target were used as a measure of the gain of visuomotor transmission. After the perturbation, the target was either moved horizontally (pursuit trial) or remained in a stationary position (fixation trial). The trial sequence randomly included pursuit and fixation. The amplitude of the response to the perturbation was modulated in a trial-by-trial manner based on the immediately preceding trial, with preceding fixation and pursuit trials decreasing and increasing the gain, respectively. The effect of the previous trial was larger with shorter intertrial intervals, but did not diminish for at least 2,000 ms. A time-series analysis showed that the response amplitude was significantly correlated with the past few trials, with dynamics that could be approximated by a first-order linear system. The results suggest that the CNS integrates recent experiences to set the gain in preparation for upcoming tracking movements in a changing environment.

INTRODUCTION

Motor control is influenced by context in everyday life. For example, it seems to be more difficult for a baseball player to hit a 60-mph pitched ball when it follows a 90-mph pitch, compared with successive 60-mph pitches. Actually, it was experimentally reported that the pitching history significantly influences the hitting ability (Gray 2002). This suggests that motor generation is affected by recent experiences. The studies by using relatively simpler movements have shed light on the neural basis of the effect of event history on motor generation. In human subjects, it is well known that smooth eye movements, or so-called anticipatory drift, are elicited toward the direction of the expected target motion, even when the direction of this motion is not predictable (Kowler et al. 1979a,b). Under unpredictable conditions, the magnitude of the anticipatory drift is influenced by the previous tracking direction (Badler and Heinen 2006; Heinen et al. 2005; Kowler et al. 1984). Such effects of past experiences on motor generation have also been reported in other motor behaviors, such as saccadic eye movements (Dorris et al. 1999; Fecteau and Munoz 2003; McPeek et al. 1999; Paré and Munoz 1996), canceling of eye movements (Emeric et al. 2007; Kornyo et al. 2003), and grip force (Witney et al. 2001). These data provide evidence that the CNS stores recent experiences and utilizes them to modulate the next movement. The evidence implies an underlying mechanism in the brain that generates the appropriate behavior in accommodating minute-by-minute environmental changes.

Smooth pursuit eye movements are generated to allow smooth tracking of a small, moving spot. Two types of processes are thought to be involved in the smooth pursuit system: one that transforms visual motion information into motor command for smooth eye movement and another that controls the gain of this transformation (Churchland and Lisberger 2002; Goldreich et al. 1992; Grasse and Lisberger 1992; Krauzlis and Miles 1996; Schwartz and Lisberger 1994). The gain of visuomotor transmission can be measured by observing ocular responses to brief motion (perturbation) of the tracking target (e.g., Schwartz and Lisberger 1994). Recent evidences suggest that the gain of visuomotor transmission increases in preparation for pursuit in advance of actual target movement. Ocular responses to target perturbation during fixation become larger in monkeys or humans with repeated smooth pursuit compared with repeated performance of either fixation or saccade (Kodaka and Kawano 2003; Tabata et al. 2004), and the amplitude of the perturbation response in monkeys is correlated with the magnitude of the initial pursuit response (Tabata et al. 2005, 2006).

The observation of perturbation responses during fixation allows study of the effects of past events on motor generation, since it is possible to measure the gain of visuomotor transmission independent of subsequent eye movements. Continuous recording of the responses to the same perturbation throughout all trials makes it possible to trace the response modulation directly. By applying this method, we have found that the preparatory gain increased or decreased within several trials when the required eye movement in a block of trials was switched between saccade and pursuit (Tabata et al. 2005). However, it is still unclear how the preparatory gain relates to the history of previous trials in a trial-by-trial fashion. To explore the mechanism, we applied this method to observe the trial-by-trial gain modulation when the subject performs the random trial sequences consisting of fixation and 20°/s pursuit trials. Based on the relationship between the input to the brain (trial sequence) and the output (perturbation response), we tried to estimate how the pursuit system stores the event history. We found that the past few trials influenced the
amplitude of the perturbation response and the temporal property of the effect was roughly approximated by a first-order linear system. Based on the experimental results, we hypothesized that the memory of previous trials is stored using a mechanism just like a leaky integrator and is used to set the gain of visuomotor transmission.

METHODS

Subjects, stimulus representation, and data collection

Experiments were performed based on the ethical standards established in the 1964 Declaration of Helsinki and were approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. The subjects were six men and one woman, ages 25 to 55 yr, with normal or corrected-to-normal vision and clinically normal eye movements; two of them (A and F) were among the authors of this paper and the others were unaware of the purpose of the experiment. All subjects gave written informed consent according to institutional guidelines.

During the experiments, each subject sat on a chair in a dark room with his/her eyes near the center of a field coil system (Enzanshi-Kogyo). The subject's head was supported by chin and forehead rests such that the eyes were 50 cm from a screen (90° × 90°). A green light-emitting diode (LED) spot (0.5°) for stationary fixation and a red LED spot (0.5°) as a target for pursuit/fixation, which was controlled by mirror galvanometers, were back-projected onto the screen. The LED spot (0.5°) for stationary fixation and a red LED spot (0.5°) as a target for pursuit/fixation, which was controlled by mirror galvanometers, were back-projected onto the screen. The target was kept stationary for 100 ms after the perturbation, and then either remained stationary for a further 800 ms (fixation trial; Fig. 1B) or started moving at 20°/s rightward/leftward and was extinguished 800 ms after the motion onset (pursuit trial, Fig. 1B). The intertrial interval (ITI) was either 2,000 or 500 ms, depending on the purpose of the experiment. The subject was instructed to continue gazing at the target regardless of its motion, then to track it in the pursuit trial and fixate on it in the fixation trial. The event sequence of pursuit and fixation trials was fixed. One methodological advantage of observing the perturbation responses is that the gain of visuomotor transmission can be measured independent of subsequent eye movements. This method allows a direct comparison of the responses to perturbations with the same amplitude using different eye movement conditions (fixation vs. pursuit). Since we sought to observe the effect of pursuit or fixation in previous trials, and not the direction of pursuit, the direction of the target motion in pursuit trials was selected randomly for every trial and the eye velocity was averaged when the previous trial was a pursuit, irrespective of the pursuit direction.

To study the dynamic properties of gain modulation, we used a sequence of stimuli consisting of 50 pursuit or fixation trials (25 trials each). We refer to the trial sequence as a subblock. The order of the trials (fixation or pursuit) was random within the constraint; thus the sequence had no significant autocorrelation (ranging from −0.2 to 0.12), such that the chosen sequence had temporal properties similar to those of white noise. Since the cross-correlation

Experimental paradigm

Each trial began when the subject moved his/her gaze to the fixation spot (Fig. 1A). The subject had to gaze at the spot (randomly chosen in every trial) from 1,000 to 1,500 ms; the fixation spot would then be turned off and a target would appear in the same position. The subject continued to gaze at the target, which moved briefly (perturbation; one cycle of a 10-Hz sine wave, peak-to-peak 0.3°, ± 10°/s) 300 ms after its appearance. The direction of the velocity change (i.e., rightward or leftward) was fixed for each subject and we selected the direction that produced stronger responses based on preliminary experiments (leftward for subjects A, D, F, and G; rightward for subjects B, C, and E). The target was kept stationary for 100 ms after the perturbation, and then either remained stationary for a further 800 ms (fixation trial; Fig. 1B) or started moving at 20°/s rightward/leftward and was extinguished 800 ms after the motion onset (pursuit trial, Fig. 1B). The intertrial interval (ITI) was either 2,000 or 500 ms, depending on the purpose of the experiment. The subject was instructed to continue gazing at the target regardless of its motion, then to track it in the pursuit trial and fixate on it in the fixation trial. The event sequence of pursuit and fixation trials was fixed. One methodological advantage of observing the perturbation responses is that the gain of visuomotor transmission can be measured independent of subsequent eye movements. This method allows a direct comparison of the responses to perturbations with the same amplitude using different eye movement conditions (fixation vs. pursuit). Since we sought to observe the effect of pursuit or fixation in previous trials, and not the direction of pursuit, the direction of the target motion in pursuit trials was selected randomly for every trial and the eye velocity was averaged when the previous trial was a pursuit, irrespective of the pursuit direction.

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FIG. 1. A: schematic diagram of visual stimuli. Each rectangle depicts a snapshot of the screen at a particular moment during the trial. A cross indicates the fixation spot; closed circles indicate the target for pursuit or fixation. B: representative target and eye position (top) and velocity profiles (bottom) for subject B. Black and gray lines represent the target and eye profiles, respectively; the left and right columns show data for the fixation and pursuit trials, respectively. A positive deflection indicates a leftward movement. See Fig. 2A for the magnified perturbation responses.
between the white-noise input and the output from an unknown linear system indicates the impulse response of the system, the dynamics of the gain modulation were estimated based on the cross-correlation between the time series of the amplitude of the perturbation response and the chosen trial sequence. Two types of sequences were used: time series 1 and 2. The order of trials in time series 2 was the opposite of that in time series 1, so both sequences had the same autocorrelation. Time series 2 was used for validation of the results obtained from time series 1. The sequence was repeated each day of the experiment; therefore the subject had to perform the first trial of the sequence soon after its end trial. Eye movements were recorded 20–40 min a day. We will refer to the first, second, third, and nth subblocks in each day as subblocks 1, 2, 3, and n, respectively. The subjects were not told that the trial sequences were identical and did not know that they were repeating the same trial sequence. The first sequence of each day (subblock 1) was removed from the analysis because we wanted to examine the effect of previous trials on the upcoming trial. The data for individual subject were accumulated at least 24 repetitions, a mean of 48 repetitions of the subblock, over 3–7 noncontiguous days.

Data analysis

To investigate the effect of previous trials (pursuit vs. fixation) on the gain of visuomotor transmission, we computed average eye velocity profiles and determined the peak-to-peak value and the mean response amplitude from these profiles. The peak-to-peak value is the difference between peak and trough values (Fig. 2A, thick black line). The mean response amplitude was calculated during 80 ms, starting 100 ms after the perturbation onset. The peak-to-peak value and mean response amplitude were found to be closely correlated ($R = 0.83$) and only peak-to-peak data were used in all subsequent analyses.

Since the direction of perturbation was the same throughout the experiment for a given subject, anticipatory drift toward the direction of the perturbation might be elicited in advance of the perturbation response. To determine whether such anticipatory drift was significant, we also computed “baseline” eye velocity measurements averaged during 200 ms, starting 100 ms before onset of the perturbation. The mean baseline measurement (0.21 ± 0.12°/s) was significantly different from 0. However, we did not find a clear correlation between the baseline data and the history of events (fixation vs. pursuit). Thus previous experience has less of an effect on anticipatory drift than on the visually driven response, and therefore we focused on the perturbation responses and not on anticipatory drift.

The experiment was designed to minimize the effect of the previous pursuit direction (see Experimental paradigm), but the baseline measurement in all subjects was found to be larger when the previous pursuit direction was the same as the direction of the perturbation (data not shown). This is consistent with previous reports regarding anticipatory drift (Badler and Heinen 2006; Heinen et al. 2005; Kowler et al. 1984). However, the effect of the previous pursuit direction on the visually driven component was unclear. In all subjects, the mean measurements were larger when the previous pursuit direction was the same as the direction of the perturbation than when it was opposite. However, the peak-to-peak measurements did not exhibit such a tendency, possibly due to the inclusion of eye velocity resulting from anticipatory drift, in addition to a pure ocular response to the target perturbation. The anticipatory drift might be canceled out by subtracting the trough from the peak eye velocity. Further experiments are necessary to clarify the relationship between the preceding pursuit direction and the gain of visuomotor transmission.

In the present study, to characterize the temporal property of the trial-by-trial gain modulation, we calculated the cross-correlation between the time series of the trial sequence ($y[n]$) and the perturbation response ($x[n]$) ($n = 1, 2, 3, \ldots, 50$). The trial sequence was represented by a value of 0 for fixation trial and 1 for pursuit trial. The cross-correlation with time lag $k$ was computed based on the equation $R_{xy}(k) = C_{xy}(k)/\sqrt{C_{xx}(0)C_{yy}(0)}$, where $C_{xy}(k)$ is covariance defined as $C_{xy}(k) = (1/N) \sum_{n=1}^{N} (x[n] - \bar{x})(y[n + k] - \bar{y})$, where $\bar{x} = (1/N) \sum_{n=1}^{N} x[n]$, $\bar{y} = (1/N) \sum_{n=1}^{N} y[n]$, $N = 50$, and $n + k = \text{mod}(n + k - 1, 50) + 1$ for $n + k \leq 0$, $n + k > 50$.

![FIG. 2. A: velocity profiles of ocular responses (top, subject B, ITI = 2,000 ms) to perturbation (bottom). Top: the gray lines show the response of every trial ($N = 2,008$); the black solid line shows the mean eye velocity. Three measurements are shown: mean, peak-to-peak, and baseline. B: the velocity profiles in which the immediate previous trials were pursuit or fixation are indicated by the black solid and black dashed lines, respectively. The gray solid line shows the mean eye velocity of all trials.](http://jn.physiology.org/doi/abs/10.1152/jn.00749.2008)
RESULTS

Effect of the preceding trial on preparatory gain modulation

The subjects were required to keep their eyes on a small target and to execute either pursuit when the target moved rightward or leftward (pursuit trial) or fixation when the target remained stationary at the center of the visual field (fixation trial) (Fig. 1A). The trials in an experimental block consisted of a random sequence of an equal number of pursuit and fixation trials. For every trial, the amplitude of the ocular response to a brief movement of the target (perturbation, cf. Fig. 2A) 300 ms after target appearance was measured to evaluate the gain of visuomotor transmission in preparation for pursuit. Sample position and velocity profiles of the eye (gray line) and the target (black line) are shown in Fig. 1B. After the perturbation, the subject was required to maintain fixation on the stationary target in the fixation trial or to pursue the target in the pursuit trial. By comparing the ocular responses evoked by the perturbation, the preparatory gain was estimated irrespective of subsequent eye movements.

The ocular responses of subject B in all trials are shown in Fig. 2A (N = 2,008). The mean eye velocity profiles of responses preceded by either one pursuit or fixation trial are shown in Fig. 2B (black solid and dashed lines, respectively). Following pursuit and fixation, respectively, the peak responses occurred 147 and 146 ms after perturbation onset and the trough responses occurred 201 and 202 ms after perturbation onset. The temporal properties of the waveforms were almost the same, but the response amplitudes were clearly different. The peak-to-peak measurements were 1.54°/s when the previous trials were pursuit and 1.41°/s when they were fixation. The difference between responses under the two conditions was statistically significant (t-test, P < 0.0001). A modulation index (mi) was computed based on the equation: mi = (r − 〈r〉)/〈r〉, where 〈r〉 and r are values averaged over all trials and those with a previous pursuit or fixation trial, respectively. In subject B, 〈r〉 was 1.47. Accordingly, the indices were 0.046 and −0.045 when the previous trial was pursuit and fixation, respectively (data for all subjects in Table 1). The absolute values of the indices ranged from 0.045 to 0.163. Although the trial-by-trial modulation of the response was small, we also found that the indices were significantly larger when the previous trial was pursuit than when it was fixation (paired t-test, P < 0.01). Thus ocular responses to the perturbation increased when the subject executed pursuit in the immediate past trial and decreased after fixation.

Effect of trial history on preparatory gain

To investigate the dynamic properties of trial-by-trial gain modulation, we continuously traced the amplitude of the perturbation response. The bold black line in Fig. 3A shows the time series of the peak-to-peak eye velocity of the perturbation response (with SE shown as gray thin lines) when subject B was repeatedly exposed to the trial sequence time series 1 (ITI = 2,000 ms). Although the absolute values of the response fluctuation were not large, these data clearly show the nonrandom temporal fluctuation of the trial-by-trial gain modulation. In agreement with the average eye velocity profiles in Fig. 2B, the ocular response increased when the subject executed pursuit in a previous trial (orange column) and decreased in a fixation trial (green column). Thus the gain of visuomotor transmission in preparation for upcoming movement varied in accordance with the past trial.

To quantify the relationship between the time series of trials and perturbation responses, the cross-correlation between these variables was calculated (Fig. 3B; also see METHODS). The trial sequence was represented by a value of 0 for a fixation trial and 1 for a pursuit trial (Fig. 3A, bottom). The magnitude of the perturbation response had the strongest positive correlation with the most recent past event and the correlation with past events decreased with increasing temporal separation from the perturbation response. In subject B, correlation with the previous three trials was significant (P < 0.05, Fig. 3B, asterisk). The mean correlation coefficient showed a regressive exponential decay in all subjects (Fig. 3C). The time constant of the best-fitted exponential function was 2.06 trials, consistent with the data analyzed for each subject. The number of past trials with a statistically significant correlation was distributed between 1 and 5 and the time constant of the exponential function fitting the correlation coefficients ranged from 1.4 to 3.5 trials (Table 1, subjects A–G). Thus the most recent past trials played an essential role in determining the level of gain in preparation for the upcoming pursuit. In addition, the single-exponential

### TABLE 1. Summary of results for time series 1 (ITI = 2,000 ms)

<table>
<thead>
<tr>
<th>Subject</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<th>F</th>
<th>G</th>
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<tbody>
<tr>
<td>Modulation index</td>
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</tr>
<tr>
<td>Pursuit</td>
<td>0.090</td>
<td>0.046</td>
<td>0.101</td>
<td>0.058</td>
<td>0.163</td>
<td>0.097</td>
<td>0.072</td>
</tr>
<tr>
<td>Fixation</td>
<td>−0.086</td>
<td>−0.045</td>
<td>−0.100</td>
<td>−0.055</td>
<td>−0.118</td>
<td>−0.088</td>
<td>−0.063</td>
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<td></td>
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</tr>
<tr>
<td>Significant numbers</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>τ</td>
<td>3.5</td>
<td>2.4</td>
<td>2.2</td>
<td>2.1</td>
<td>2</td>
<td>1.9</td>
<td>1.8</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>K</td>
<td>0.27</td>
<td>0.47</td>
<td>0.63</td>
<td>0.52</td>
<td>0.72</td>
<td>0.65</td>
<td>0.87</td>
</tr>
<tr>
<td>a</td>
<td>0.89</td>
<td>0.26</td>
<td>0.40</td>
<td>0.41</td>
<td>0.85</td>
<td>0.69</td>
<td>0.38</td>
</tr>
<tr>
<td>r</td>
<td>1.44</td>
<td>1.50</td>
<td>1.34</td>
<td>1.87</td>
<td>1.67</td>
<td>2.60</td>
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</tr>
<tr>
<td>R²</td>
<td>0.86</td>
<td>0.69</td>
<td>0.78</td>
<td>0.83</td>
<td>0.52</td>
<td>0.79</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Pursuit and fixation indicate modulation indices whose previous trials were pursuit and fixation, respectively. Significant numbers indicate how many past trials were significantly correlated with the ocular response (P < 0.05), τ corresponds to the time constant of an exponential function fitted to the cross-correlation of the past 10 trials. K and a are parameters in the model used to fit the data. F is peak-to-peak ocular response averaged over all trials and is calculated from the experimental data. R² is the coefficient of determination.
The amplitude of the response modulation and the possibility, we investigated whether changing the ITI affects the response. To test this hypothesis, we analyzed whether the previous trials were fixation and pursuit, respectively. The absolute values of indices for ITI = 500 ms were significantly larger than those for ITI = 2,000 ms (paired t-test, P < 0.05). The slope of the regression line was 0.391 and the line for slope = 1 (dashed line) was not included in the 95% confidence interval (0.261–0.520). These results suggest that the effect of the immediate past trial is larger for the shorter ITI. In addition, the absolute values of the indices for ITI = 2,000 ms were significantly >0 (t-test, P < 0.01). Thus the response tends to decay toward the amplitude of the response averaged over all trials with elongation of the ITI, but the effect of the previous trial does not diminish for at least 2,000 ms.

Second, to study whether changing the ITI affects the temporal dynamics of gain modulation, we traced the trial-by-trial fluctuation of the response and calculated the cross-correlation. The time series of the perturbation response for subject B on repeated exposure to the trial sequence time series 1 (ITI = 2,000 ms) is shown in Fig. 5A. Trial-by-trial fluctuations of the responses was similar to the result shown in Fig. 3A; the ocular response increased when the subject executed pursuit in the previous trial and decreased in the fixation trial. The cross-correlation between the time series of the trials and the perturbation responses indicated a significant correlation with the past three trials (P < 0.05, Fig. 5B, asterisk). The time constant of the exponential decay was 2.6 trials. Quantitative data for all subjects are summarized in Table 2 and comparison of the cross-correlation between ITI = 500 ms (black line) and ITI = 2,000 ms (gray line) is depicted in Fig. 6A. The mean of the cross-correlations with 1 to 10 past trials for all subjects is shown as a gray dashed line. For individual subjects and the five subjects (subjects B, C, E, F, and G) as earlier, but the ITI was changed from 2,000 to 500 ms.

First, to study the effect of the ITI on the amplitude of the response modulation, the modulation indices were calculated for an ITI of 500 ms (Table 2). In four of five subjects (all but subject F), the absolute values of the indices when the ITI was 500 ms were larger than those for an ITI of 2,000 ms. The scatterplot of the modulation indices is shown in Fig. 4, in which open and closed symbols indicate modulation indices whose previous trials were fixation and pursuit, respectively. The absolute values of indices for ITI = 500 ms were significantly larger than those for ITI = 2,000 ms (paired t-test, P < 0.05). The slope of the regression line was 0.391 and the line for slope = 1 (dashed line) was not included in the 95% confidence interval (0.261–0.520). These results suggest that the effect of the immediate past trial is larger for a shorter ITI. To test this possibility, we investigated whether changing the ITI affects 1) the amplitude of the response modulation and 2) the temporal dynamics of the response modulation. Time series 1 was used in five subjects (subjects B, C, E, F, and G) as earlier, but the ITI was changed from 2,000 to 500 ms.

Effect of the intertrial interval

Next, we addressed whether the effect of the immediate past trial is influenced by the blank period between trials [intertrial interval (ITI)]. If memory of the immediately preceding trial gradually diminishes during the ITI, the effect of the immediate past trial should be larger for a shorter ITI. To test this possibility, we investigated whether changing the ITI affects 1) the amplitude of the response modulation and 2) the temporal dynamics of the response modulation. Time series 1 was approximated by a first-order linear system, such as a leaky integrator.

![Diagram](image-url)

**FIG. 3.** A: time series of perturbation responses. Subject B was exposed to the trial sequence time series 1 (ITI = 2,000 ms) (N = 42). Orange and green stripes indicate pursuit and fixation trials, respectively. The time course of the perturbation responses (black line) with SE (thin lines) and the fitted model (red line) are shown. B: cross-correlation coefficients (R) between the time series of perturbation responses and trials in time series 1 (ITI = 2,000 ms) in subject B. C: dependence of group means (with SD) of cross-correlation coefficients on past trials (7 subjects). The broken line indicates the best-fit single-exponential function in the past 10 trials (e^(-\tau_Tn), \tau = 2.06).

Table 2. Summary of results for time series 1 (ITI = 500 ms) for five subjects (B, C, E, F, and G)

<table>
<thead>
<tr>
<th>Subject</th>
<th>B</th>
<th>C</th>
<th>E</th>
<th>F</th>
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<tr>
<td><strong>Modulation index</strong></td>
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<tr>
<td>Pursuit</td>
<td>0.093</td>
<td>0.353</td>
<td>0.418</td>
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<td>0.097</td>
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<td>( \tau )</td>
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<td><strong>Model parameters</strong></td>
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<tr>
<td>( K )</td>
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<td>0.49</td>
<td>0.64</td>
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<tr>
<td>( a )</td>
<td>0.70</td>
<td>0.70</td>
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<tr>
<td>( \bar{r} )</td>
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<td>1.48</td>
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<td>0.91</td>
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See Table 1 for explanation of terms and variables.
mean of all subjects, the time constants tended to be larger for the shorter ITI. However, the difference between the correlation coefficients for ITI values of 500 and 2,000 ms was not statistically significant at each point (correlations from 1 to 10 past trials, Fig. 6B, paired t-test, \( P > 0.08 \)). Therefore the effect of the immediate past trial gradually decreased during the ITI, but the decay time constant for trial-by-trial gain modulation was less dependent on the ITI.

**Effect of an alternative trial sequence**

The preceding results indicate that the effect of the ITI on the decay time constant of the trial-by-trial gain modulation was minor for the same trial sequence. The effect of a different trial sequence on the dynamic properties of gain modulation was examined in two subjects (A and C). To maintain the same autocorrelation as that of the original sequence (time series 1), a trial sequence with the reverse order was used (time series 2) with ITI = 2,000 ms. The temporal fluctuation of the perturbation response in subject A is shown in Fig. 7, A (time series 1) and B (time series 2). The cross-correlations for subject A were remarkably similar (Fig. 7C, left) and similar results were obtained for subject C (Fig. 7C, right). The quantitative data are summarized in Table 3. Thus we confirmed that for a given subject similar results could be obtained even if the temporal order of the trial sequence was reversed.

**Dynamics of trial-by-trial gain modulation**

Our results provide direct evidence that the pursuit system automatically modulates the gain of visuomotor transmission based on previous experiences (pursuit vs. fixation). The results also indicate that the effects of preceding trials decay in a roughly single-exponential manner, leading us to postulate that the system used to store memory of previous trials can be approximated by first-order linear dynamics. To test this hypothesis, we examined whether such a first-order linear model could appropriately reproduce the experimental data.

A recursive algorithm was developed to describe the underlying dynamics of trial-by-trial update of the preparatory gain (Fig. 8), based on the following equation

\[
\lambda_T = \lambda_{T-1} + K(y_{T-1} - \lambda_{T-1})
\]

The equation describes the time evolution of an internal variable \( \lambda \), where \( y_T \) represents the observation of actual events; i.e., pursuit trial \( y_T = 1 \) or fixation trial \( y_T = 0 \). \( \lambda \) represents the internal variable in which the history of trials is stored; \( \lambda \) ranges from 0 (no anticipation of pursuit) to 1 (full anticipation of pursuit) and is updated at each discrete time step based on the observation of an event at \( T \). \( K \) determines the amplitude of the modification. The update algorithm for \( \lambda \) is structured as a leaky integrator and \( K \) is inversely proportional to the time constant of the leaky integrator. We postulate that the gain controller utilizes this memory and determines the gain for initiating pursuit. If this is the case, the temporal fluctuation of the response amplitude should fit well with the model. However, in this equation \( \lambda \) ranges from 0 to 1 and scale adjustment is necessary to apply the model to actual data

\[
r_T = a(\lambda_T - 0.5) + \tilde{r}
\]

where \( a \) is the scaling factor that determines the width of the response range and \( \tilde{r} \) is the peak-to-peak eye velocity of the response averaged over all trials. This equation does not influence the dynamics of the trial-by-trial gain modulation. \( K \) and \( a \) were used as free parameters to fit the data for each subject.
First, we applied this model to fit the data for individual subjects obtained from the experiment using time series 1 (ITI = 2,000 ms) and determined the values of $K$ and $a$. The proposed model successfully reproduced the perturbation responses for subject B [subject A, subject C, subject E, subject F, subject G]. The black and gray lines represent the cross-correlation coefficients for ITI values of 500 and 2,000 ms, respectively. The black broken line indicates the best-fit single-exponential function over the past 10 trials ($e^{-ct}$, $\tau = 2.31$). The gray broken line indicates the best-fit single-exponential function for ITI = 2,000 ms.

![Fig. 6](image-url)

**FIG. 6.** A: comparison of cross-correlation ($R$) for individual subjects (B, C, E, F, G). The black and gray lines represent the cross-correlation coefficients for ITI values of 500 and 2,000 ms, respectively. B: dependence of group means (with SD) of cross-correlation coefficients on past trials (5 subjects). The black broken line indicates the best-fit single-exponential function over the past 10 trials ($e^{-ct}$, $\tau = 2.31$). The gray broken line indicates the best-fit single-exponential function for ITI = 2,000 ms.

We next applied the model to the results of the experiment using time series 1 (ITI = 500 ms) and determined the values of $K$ and $a$. The proposed model again successfully reproduced the perturbation responses in subject B [subject A, subject C, subject E, subject F, subject G]. The black and gray lines represent the cross-correlation coefficients for ITI values of 500 and 2,000 ms, respectively. The black broken line indicates the best-fit single-exponential function over the past 10 trials ($e^{-ct}$, $\tau = 2.31$). The gray broken line indicates the best-fit single-exponential function for ITI = 2,000 ms.

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however, it did not significantly affect the dynamic property of the trial-by-trial gain modulation (Fig. 6B). Therefore we can expect that the model with the same $K$ value performs well independent of ITI conditions, only by the adjustment of the scaling factor $a$. As shown in Table 4, the model with the $K$ value ($K^*$) estimated from ITI = 500 ms successfully reproduced the results of ITI = 2,000 ms (upper level; the mean $R^2$ was 0.63), and the model with the $K$ value ($K^{**}$) estimated from ITI = 2,000 ms successfully reproduced the results of ITI = 500 ms (lower level; the mean $R^2$ was 0.74). As we expected, the performance of the model was still good even if the $K$ value was fixed for both ITI conditions.

Finally, to validate the model, we used the $K$ value estimated from the results for time series 1 and applied the model to the experimental data for time series 2 (red line in Fig. 7, A and B).

Other parameters of the best-fitted model are summarized in Table 3, and the $R^2$ values were 0.77 and 0.54. The model was also confirmed to perform well for the experimental data obtained from time series 2.

**DISCUSSION**

We observed ocular responses elicited by a target perturbation of the same amplitude under conditions of during fixation, and found that the response was larger when the eye movement in the trial immediately before was pursuit compared with when it was fixation. Moreover, the eye movements in the previous few trials also influenced the perturbation responses.

**TABLE 3. Summary of results for time series 2 for two subjects (A and C)**

<table>
<thead>
<tr>
<th></th>
<th>Subject</th>
<th>A</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modulation index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pursuit</td>
<td></td>
<td>0.107</td>
<td>0.083</td>
</tr>
<tr>
<td>Fixation</td>
<td></td>
<td>−0.107</td>
<td>−0.082</td>
</tr>
<tr>
<td><strong>Cross-correlation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant numbers</td>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>$\tau$</td>
<td></td>
<td>2.9</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Model parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K$</td>
<td></td>
<td>0.27</td>
<td>0.63</td>
</tr>
<tr>
<td>$a$</td>
<td></td>
<td>0.72</td>
<td>0.27</td>
</tr>
<tr>
<td>$\bar{r}$</td>
<td></td>
<td>1.25</td>
<td>1.17</td>
</tr>
<tr>
<td>$R^2$</td>
<td></td>
<td>0.77</td>
<td>0.54</td>
</tr>
</tbody>
</table>

See Table 1 for explanation of terms and variables.

**FIG. 8.** A conceptual diagram of the proposed model. $y_T$ shows the trial type: 0 for a fixation trial and 1 for a pursuit trial. $\lambda$ is the internal variable used for storing the history of trials, which ranged from 0 (no anticipation of pursuit) to 1 (full anticipation of pursuit), and was updated at every discrete time step based on the observation of an event at $T$. $K$ indicates the size of the modification and $z$ corresponds to the $Z$-operator.
TABLE 4. Model parameters when we applied the K value estimated from one ITI condition to the data of another ITI condition

<table>
<thead>
<tr>
<th>ITI = 2,000 ms</th>
<th>B</th>
<th>C</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>K*</td>
<td>0.44</td>
<td>0.49</td>
<td>0.64</td>
<td>0.44</td>
<td>0.62</td>
</tr>
<tr>
<td>a</td>
<td>0.27</td>
<td>0.47</td>
<td>0.78</td>
<td>0.84</td>
<td>0.47</td>
</tr>
<tr>
<td>( \tilde{r} )</td>
<td>1.50</td>
<td>1.34</td>
<td>1.67</td>
<td>2.60</td>
<td>2.11</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.69</td>
<td>0.76</td>
<td>0.52</td>
<td>0.57</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ITI = 500 ms</th>
<th>B</th>
<th>C</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>K**</td>
<td>0.47</td>
<td>0.63</td>
<td>0.57</td>
<td>0.65</td>
<td>0.87</td>
</tr>
<tr>
<td>a</td>
<td>0.67</td>
<td>0.59</td>
<td>1.37</td>
<td>0.27</td>
<td>0.48</td>
</tr>
<tr>
<td>( \tilde{r} )</td>
<td>1.77</td>
<td>1.50</td>
<td>1.48</td>
<td>0.97</td>
<td>2.27</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.82</td>
<td>0.69</td>
<td>0.91</td>
<td>0.53</td>
<td>0.75</td>
</tr>
</tbody>
</table>

The results when we applied the model with the K value estimated from ITI = 500 ms to the data of ITI = 2,000 ms are shown in the top level and the results in the reverse case are shown in the bottom level.

albeit with decreasing effectiveness. Such dynamic modulation of the ocular response indicates that there is a priming effect on the visuomotor gain in preparation for the upcoming eye movement. In addition, the effect of the immediate past trial was larger for a shorter ITI, although the effect of the previous trial did not diminish for at least ITI = 2,000 ms. The results that trial-by-trial updating of the gain was approximated by a first-order linear system suggest possible underlying dynamics of the gain modulation.

Possible functional role of preparatory gain modulation in the pursuit system

The primary signal driving pursuit is target motion across the retina. This visual signal is transformed into a motor command through various cortical and subcortical neural pathways (see reviews by Keller and Heinen 1991; Krauzlis 2004, 2005; Lisberger et al. 1987; Thier and Ilg 2005). Thus the initial response to the target motion is principally governed by the visual properties such as eccentricity, velocity, and acceleration (e.g., Carl and Gellman 1987; Krauzlis and Lisberger 1994; Lisberger and Westbrook 1985; Lisberger et al. 1981; Morris and Lisberger 1987; Tychsen and Lisberger 1986). Since the amplitude of the perturbation response is correlated with the magnitude of the initial pursuit response (Tabata et al. 2005, 2006), our results suggest that the initial pursuit response is not only generated by a transformation of the visual signal into motor command, but also influenced by an internal cognitive process that dynamically modulates the gain based on recent experiences.

The dynamic modulation of visuomotor gain has been studied using comparisons of the ongoing target and ocular state. Responses to target perturbation are enhanced during tracking compared with fixation and the responses were larger for higher target/tracking velocity (Churchland and Lisberger 2001; Schwartz and Lisberger 1994). Similar observations were made when motion of the background was perturbed (Kodaka et al. 2004; Lindner et al. 2001; Schwarz and Ilg 1999; Suehiro et al. 1999). In other words, the visuomotor gain is dependent on the ongoing target/behavioral state at various levels. Our results indicate another dynamic means of control-visuomotor gain, since the gain prior to the start of pursuit may also be dynamically modulated in accordance with a recent event sequence. This flexible preparatory gain modulation may accommodate the effects of minute-by-minute environmental changes on pursuit generation.

From a computational perspective, smooth pursuit eye movements can be characterized as a negative feedback control system, and many computational models have been proposed based on this framework (e.g., Churchland and Lisberger 2001; Krauzlis and Lisberger 1989, 1994; Ringach 1995; Robinson et al. 1986). Using relatively simple dynamics, these models can reproduce the eye velocity profiles for target motions of a constant velocity. Some models include the gain element in the visuomotor pathway, and the gain is modulated in accordance with the ongoing behavioral state (Krauzlis and Lisberger 1994; Krauzlis and Miles 1996; Madelain and Krauzlis 2003). The trial-by-trial modulation of the preparatory gain reported in the present study implies that the gain controller is influenced by storage of previous events or oculomotor experiences. Since the initial value of the gain has a strong influence on the open-loop pursuit response, the preparatory gain modulation can be related to the feedforward control of pursuit. If the pursuit system adopts the forward model of the target motion (Shibata et al. 2005), the underlying mechanism to control the preparatory gain modulation will influence the forward model.

Effect of the preceding trial on the visuomotor gain

There are studies of the effects of immediate past events on the upcoming motor generation, and these effects of previous trials have been interpreted as the consequences of priming or learning, although few have addressed the question of how many preceding trials shape upcoming movement (Dorris et al. 1999; Fecteau and Munoz 2003; Heinen et al. 2005; Kowler et al. 1984). Witney et al. (2001) demonstrated that the magnitude of anticipatory grip force is affected by experiences from at least the previous three trials, but they could not directly show its on-line modulation because the fluctuation of pure anticipatory grip force could not be continuously measured. In contrast, our method in the present study allowed us to measure the gain modulation, regardless of whether pursuit is executed, permitting a continuous tracing of trial-by-trial changes in response to the same input. Using this approach, we have shown that the gain modulation is affected by the immediately preceding trials and that the dynamics of this process could be fitted to a first-order, linear, recursive algorithm. Our analysis suggests that the storage mechanism of the history of sequential events in the CNS corresponds to a leaky-integrator model with a rapid decay time constant. A similar model has been proposed to describe the behavior of monkeys performing a dynamic foraging task (Sugrue et al. 2004), and a mechanism that provides flexible and rapid mediation of motor generation may be common to various context-dependent behaviors based on short-term memory.

The K value of our proposed model shown in Eq. 1 determines the amplitude of the modification based on the error between \( \lambda \) and the actually observed event and is inversely proportional to the time constant of the leaky integrator. For smaller K values, decay of stored past experiences is slower, such that a longer trial history is maintained. In contrast, for
larger $K$ values, decay occurs rapidly, such that the effect of immediately preceding trials is larger. It is still unclear what elements of the brain or environment affect the $K$ value, and each subject may have his/her own $K$ value. However, we do not think that the $K$ value of each subject is always invariant and independent of the trial sequence. To minimize active prediction of a future event, we used a random trial sequence consisting of fixation and pursuit blocks, since the $K$ value might be influenced if the subject can predict the upcoming movement. Our proposed model should be able to trace local fluctuations in preparatory gain modulation when upcoming eye movements are unpredictable. We will further discuss this issue in the next subsection.

How does the ITI influence the effect of the preceding trial on an upcoming movement? Figure 4 shows that the absolute values of the modulation indices are smaller for the longer ITIs. In other words, the fluctuation from the mean response amplitude averaged over all trials ($\bar{r}$) is smaller for the longer ITIs. This suggests that the elongation of the ITI causes the response decay toward $\bar{r}$. However, as shown in Fig. 6B, the difference between the correlation coefficients for ITI values of 500 and 2,000 ms was not statistically significant, suggesting a minor effect of the duration of the ITI on the dynamic properties of the trial-by-trial gain modulation at least for this ITI range (500–2,000 ms). In the terms of the proposed model, the change of the ITI influences the scaling factor $a$, rather than $K$. We showed that the model with the $K$ value estimated from one ITI experiment could well reproduce the time series of the response of another ITI experiment (Table 4, $R^2 > 0.52$). The results support the idea that the change of the ITI affects mainly the scaling factor. In this interpretation, the elongation of the ITI reduces the ratio of increase or decrease of the preparatory gain modulation, and an ITI that is too long would cause $a \to 0$, i.e., the trial-by-trial response modulation could not be detectable.

To evaluate the effect of repetition of the same sequence on the preparatory gain modulation, we also examined whether repetition of the same sequence (a subblock of 50 trials) influenced the decay time constant of the correlation between the time series of the perturbation response and the trial sequence. We found that the effect was not statistically significant (repeated-measures ANOVA on the time constants in subblocks 1–6, $P = 0.35$). Therefore sequence repetition had no effect on the dynamic properties of the trial-by-trial response modulation, although a repetition of the same trial sequence has been reported to guide the development of procedural knowledge (e.g., Willingham et al. 1989).

**Block design versus random trial sequence**

In the previous study (Tabata et al. 2005), we focused on the difference of the preparatory gain in monkeys among the different blocks in which the probability of target motion was different. The study revealed that the response reached a new steady state within several trials when the block was changed. In the present study, to understand the effect of immediate past trial on the preparatory gain, we focused on the local fluctuation of the response modulation while the overall probability of target motion (either pursuit or fixation) was kept at 0.5. In this condition, subjects cannot exactly predict the upcoming trial. To compare the relationship between the characteristics of gain modulation reported in our previous study (Tabata et al. 2005) with those in the present study, we carried out a simple simulation. We tested how the model obtained in the present study performs when two blocks, each of which consisted of either 50 no-pursuit trials or 50 pursuit trials, are alternatively switched (block-design condition) as in our previous study. Note that in the previous study, a no-pursuit trial was saccade trial instead of fixation; however, for simplicity we treated the input to the model as 0. The simulation was carried out by using maximal or minimal $K$ values (i.e., 0.27 or 0.87), which we obtained in the present experiment. As a result, the time constants of the gain modulation triggered by the switch of the blocks were calculated as 3.14 and 0.49 trials for $K = 0.27$ and 0.87, respectively. In the previous study the time constants of the gain modulation were distributed from 3.9 to 6.7 trials when the required eye movement in a block of trials was switched between saccade and pursuit (Tabata et al. 2005). Thus the model proposed here predicts more rapid gain modulation than that actually observed, suggesting different mechanisms underlying the gain modulation observed in the present and previous studies. Although this dissociation might be simply due to a difference in species (humans vs. monkeys) and/or a difference in tasks (fixation vs. saccade trials), we should point out another possibility—i.e., a difference in the predictability of the next coming trial. Under the random-sequence condition, the subject is unable to predict the next coming trial, although he/she is able to predict under the block-design condition. Therefore we suggest a possibility that the effect of an immediate previous trial is larger when the next coming trial is unpredictable. In other words, the $K$ value is larger in terms of the proposed model. The pursuit system might change the degree of the modification of the preparatory gain in accordance with the environment that the brain is facing. To test this possibility, a further experiment is necessary.

Although the functional meaning of the difference of temporal property between the random condition and the block-design condition needs further studies, we think that the trial-by-trial gain modulation reported here is a fundamental mechanism to cause the increase or decrease of the gain triggered by the change of the block.

**Comparison with other studies on pursuit**

It has been suggested that the pursuit system uses short-term memory to drive anticipatory smooth eye movements. Regular, repeated presentation of target motion with an identical, constant high velocity can guide smooth eye movement in anticipation of the actual target motion (Barnes and Asselman 1991; for a review, see Barnes et al. 2002). The anticipatory velocity builds up progressively over the first three or four experiences, suggesting that the storage of velocity information occurs on a rapid timescale. In addition, even when the presentation of the stimuli is irregular, a timing cue given at a fixed time before the onset of target appearance can release the stored information, thereby triggering anticipatory smooth eye movements (Barnes and Donelan 1999).

The relationship between the storage mechanism of velocity information for the anticipatory eye movement and the trial-by-trial gain modulation reported in the present study remains to be seen. The anticipatory smooth eye movement could be
guided by the stored velocity information. In contrast, the responses we report here are evoked by the visual stimulus and we propose that short-term memory does not directly drive eye movement, but instead influences the gain of visuomotor transmission. However, it has also been reported that both anticipatory eye movements and changes in the magnitude of eye velocity during the open-loop period occur when the target motion is predictable (Kao and Morrow 1994). Thus short-term memory might provide a common influence on the preparatory gain modulation and anticipatory smooth eye movements.

Possible neural basis for trial-by-trial gain modulation

To explain the neural basis of the trial-by-trial preparatory gain modulation reported here, it is necessary to understand the relationship between memory of previous events and pursuit-related neurons. We propose two possible explanations: first, traces of recent events are left in the neurons that function in pursuit generation; and, second, the history of experiences is stored elsewhere, and these memories are decoded in conjunction with pursuit preparation and influence the activity of the pursuit-related neurons. Our data demonstrate independence between the temporal properties of preparatory gain modulation and the ITI, suggesting that the stored information is updated in a trial-by-trial (event-related) manner. Therefore neural activity in the sites that store event history data might be maintained even during the ITI. On the other hand, we have reported that the preparatory gain increase in monkeys is triggered by the appearance of the tracking target (Tabata et al. 2006). After the appearance of the target, the amplitude of the perturbation response gradually increases and reaches its peak 300–600 ms after the target appearance (in the current study, the time between target appearance and onset of the perturbation was always 300 ms). The history of the events may be used to determine the maximum value of the gain increase triggered by target appearance. If so, memory of recent experiences is stored in neural sites that are not directly related to generation of eye movements and affects pursuit-related neurons via the gain controller.

Since neural pathways related to pursuit generation are well known (see reviews by Keller and Heinen 1991; Krauzlis 2004, 2005; Lisberger et al. 1987; Thier and Ilg 2005), smooth-pursuit eye movement is one of the best model systems for studying the mechanisms of motor control. In addition, there is developing evidence that the frontal pursuit area (Tanaka and Lisberger 2001, 2002) and the supplementary eye field (Missal and Heinen 2001) participate in gain control. Tanaka and Fukushima (1998) reported that neurons in the frontal pursuit area show buildup activity, even if the upcoming pursuit direction is unpredictable. These neurons might take part in preparatory gain modulation, but there is no evidence regarding which neural sites store the history of eye movements. Here, we have proposed a simple linear model as a candidate mechanism of trial-by-trial gain modulation, and this model may be useful for analysis of modulation in neural activity. The combination of neurophysiological experiments and the results reported here should allow exploration of how the CNS stores recent oculomotor experiences and uses them to determine flexible and context-suited movements.

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