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A Theory of the Dual Pathways for Smooth Pursuit Based on Dynamic Gain Control

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Abstract

The smooth pursuit eye movement (SPEM) system is much more sensitive to target motion perturbations during pursuit than during fixation. This sensitivity is commonly attributed to a dynamic gain control mechanism. Neither the neural substrate nor the functional architecture for this gain control has been fully revealed. There are at least two cortical areas that crucially contribute to smooth pursuit and are therefore eligible sites for dynamic gain control: the medial superior temporal area (MST) and the pursuit area of the frontal eye fields (FEFs), which both project to brain stem premotor structures via parallel pathways. The aim of this study was to develop a model of smooth pursuit based on behavioral, anatomical, and neurophysiological results to account for nonlinear dynamic gain control. Using a behavioral paradigm in humans consisting of a sinusoidal oscillation (4 Hz, $\pm 8^\circ/\text{s}$) superimposed on a constant velocity target motion (0–24°/s), we were able to identify relevant gain control parameters in the model. A salient feature of our model is the emergence of two parallel pathways from higher visual cortical to lower motor areas in the brain stem that correspond to the MST and FEF pathways. Detailed analysis of the model revealed that one pathway mainly carries eye velocity related signals, whereas the other is associated mostly with eye acceleration. From comparison with known neurophysiological results we conclude that the dynamic gain control can be attributed to the FEF pathway, whereas the MST pathway serves as the basic circuit for maintaining an ongoing SPEM.

INTRODUCTION

Humans and other primates are capable of pursuing slowly moving visual objects with their eyes. The aim of these smooth pursuit eye movements (SPEMs) is to minimize the error between the image of an object of interest and the retinal area of high acuity vision, the fovea (for reviews see Krauzlis 2004; Lisberger et al. 1987). The pursuit system is a controlled feedback system because the motor output (eye movement) alters the sensory input (retinal image). A consequence of this closed-loop control scheme is that the retinal error by itself is not sufficient to drive the system because its value approaches zero during

successful SPEM. Several models have been proposed that utilize different signals to maintain the drive for the pursuit system: for example, position and acceleration of the target (Lisberger et al. 1987), perceived target velocity (Robinson et al. 1986; Yasui and Young 1975) based on an efference copy of the motor command sent to the eye muscles (von Holst and Mittelstaedt 1950), or a velocity storage mechanism implemented as a local cortical feedback loop (Tabata et al. 2002).

Dynamic gain control

A special property of the smooth pursuit system is the dynamic gain control mechanism. This gain control regulates the feedforward gain of the pursuit system in dependence on the actual tracking velocity, where higher tracking velocities yield higher gains. Implicit evidence for such a mechanism was first given by Robinson (1965), where spontaneous oscillations were observed during pursuit, but not during fixation of a stationary target. Luebke and Robinson (1988) observed a difference in the onset and offset of SPEM and concluded that different systems contribute to fixation and pursuit (fixation is not pursuit at velocity zero). Schwartz and Lisberger (1994) then measured the ocular responses to constantly moving targets in macaque monkeys with a perturbation in target trajectory, i.e., one cycle of a high-frequency sinusoidal oscillation. Monkeys showed an increased eye velocity response with respect to the perturbation that depended monotonically on the underlying constant speed of target and tracking motion. Gain control also occurs in human smooth pursuit eye movements as has been revealed by similar perturbation experiments (Churchland and Lisberger 2002). Keating and Pierre (1996) used a somewhat different approach, using a continuous high-frequency hum superimposed on the constant-velocity target to test the gain of the system in macaque monkeys and developed a conceptual model of a gain control mechanism in smooth pursuit.

Acceleration saturation

Another nonlinear effect that governs smooth pursuit behavior is the saturation of maximum eye acceleration during smooth pursuit initiation, also termed the *main-sequence of smooth pursuit* (see, e.g., Robinson et al. 1986). During pursuit of step-ramp targets at different velocities, this results in an increasing latency of the first eye velocity overshoot during SPEM onset for increasing target velocities. At first glance, this is contradictory to dynamic gain control, which increases the gain and therefore reduces the latencies at higher tracking velocities. However, both effects have been reported independently of each other and no model has dealt with the simultaneous occurrence of both nonlinear effects.

Cortical contribution to smooth pursuit

Neural signals related to the motion of an object's image on the retina are found in the middle temporal area (MT) of the superior temporal sulcus in primates (Newsome et al. 1988). These cells constitute the primary motion processing stage, receiving afferent signals from the dorsal pathway via the retina, lateral geniculate nucleus (LGN), and from directionally selective cells of primary visual cortex (V1) (Movshon and Newsome 1996; Wurtz et al. 1990). MT neurons are selective for the direction and the speed of motion and can be physiologically and anatomically subdivided into cells that are responsive to small-

sized moving stimuli and cells responding only in the presence of a large moving field (Born and Tootell 1992). MT sends strong projections to the medial superior temporal area (MST) where a similar differentiation can be observed. Cells in the lateral aspect of MST (MSTl) prefer small-sized moving stimuli, whereas cells in the dorsal part (MSTd) respond best to large-field stimuli (Newsome et al. 1988). Furthermore, cells in MSTl convey extraretinal signals related to slow eye and head movements and might therefore play a role in estimating the target movement in world-centered coordinates (Ilg et al. 2004; Thier and Ilg 2005). Signals related to slow eye movements are also found in MSTd, but their discharge follows the onset of the eye movement 50 to 100 ms (Newsome et al. 1988; Squatrito and Maioli 1997). The activity is maintained during SPEM despite blinking or stabilization of the target (see, e.g., Ono and Mustari 2006) and may thus constitute an efference copy of the eye motor command. The preference for large-field stimuli and the additional extraretinal components make the MSTd neurons an eligible candidate for the compensation of self-induced visual motion (Newsome et al. 1988; Page and Duffy 2003; Shenoy et al. 2002; Thier and Ilg 2005).

Another cortical area that is crucially involved in SPEM is the frontal eye field (FEF), which is also involved in the generation of saccadic eye movements (for review see Krauzlis 2005). The first investigators to report the importance of the FEF in SPEM were Lynch (1987) and Keating (1991). FEF has strong reciprocal connections with MST (Fukushima 2003; Lynch and Tian 2006; Tusa and Ungerleider 1988) and lesions therein abolish predictive and visually guided SPEM (Keating 1991; MacAvoy et al. 1991; Shi et al. 1998). The majority of FEF neurons discharge before the onset of pursuit and thus contribute to the initiation of pursuit, which is characterized by high retinal slip and eye acceleration (for review see Fukushima 2003; Gottlieb et al. 1994).

Recently, the role of the thalamus in the control of SPEM has been reinvestigated (Tanaka 2005). Neurons in the central thalamus carry eye-velocity-related signals that are conveyed to cortical areas, such as FEF. Conversely, the central thalamus receives inputs from subcortical pursuit pathways, including the vestibular nuclei and the deep cerebellar nuclei (Tanaka 2005). This thalamocortical eye velocity feedback may be used for the control and monitoring of eye movements during ongoing smooth pursuit.

Parallel pathways

The pursuit system is characterized by parallel pathways from the cerebral cortex to the cerebellum via different pontine nuclei (for review see Krauzlis 2004; Thier and Möck 2006). One major pathway originating in MST projects to the dorso-lateral pontine nuclei (DLPN) (Distler et al. 2002), which provides smooth pursuit signals (May et al. 1988; Mustari et al. 1988; Suzuki and Keller 1984; Thier et al. 1988) to the cerebellar floccular complex (e.g., ventral paraflocculus [vPF]). Another major pathway originates in the FEF and projects strongly to the nucleus reticularis tegmenti pontis (NRTP), which provides smooth pursuit and gaze signals (Ono et al. 2004, 2005; Suzuki et al. 1999) for the oculomotor part of the cerebellar dorsal vermis (DV) (Thier and Ilg 2005). However, the functional role of these parallel cortico-ponto-cerebellar pathways is not yet fully understood and no overall computational model takes their characteristics into account.

The aim of this study was therefore to develop a nonlinear model that consolidates 1) behavioral measurements (gain control, eye acceleration saturation), 2) anatomical structure (parallel pathways, feedback via thalamus), and 3) neurophysiological data (firing rate properties of neurons in MST/DLPN and FEF/NRTP).

METHODS

Human behavioral data

SUBJECTS—Twelve healthy subjects participated (mean age: 27 ± 3.3 yr) who had normal or corrected-to-normal vision and no relevant medical or psychiatric history. All subjects but one were naïve with respect to pursuit experiments. All subjects gave their informed consent before participating in the study, which conformed to the standards set by the Declaration of Helsinki.

SETTING—The experiments were performed in a completely dark room. Subjects sat in front of a 115×112 cm (width $\times$ height) back-projection screen at a viewing distance of 71 cm and were instructed to continuously follow the moving laser dot (size 0.1°) with their eyes.

RECORDING SYSTEM—The two-dimensional (2D) eye position was recorded using a custom-made monocular video-based eye tracker (Dera et al. 2006). An on-line pupil detection algorithm, running on a separate video computer, computed the coordinates of the pupil center in each of the images sampled at 100 Hz. The resolution of this system was $<0.1^\circ$ and total accuracy was $<0.5^\circ$. Eye movement data and the timing signals of the graphic computer were recorded on a central recording system (REX; Hays et al. 1982). The eye movement data were delayed by 13 ms with respect to the stimulus recording, due to the transfer and processing time. The delay was corrected off-line. Prior to each experiment a 2D calibration was done on the basis of 18 fixations to nine target positions (at the center and at $\pm 20^\circ$ horizontal and vertical eccentricity). First, the 2D fixation positions expressed in image coordinates were detected and assigned to one of the nine target positions by using a cluster algorithm. The 2D calibrated eye position was then computed as a linear function of the image coordinates.

PARADIGM—The stimulus moved horizontally from side to side in the frontoparallel plane. The velocity profile consisted of a constant part at four different velocities (0, 8, 16, and $24^\circ/\text{s}$). A high-frequency sinusoidal oscillation with 4 Hz and $8^\circ/\text{s}$ amplitude was superimposed (see Fig. 1). For the fixation trials, three different eccentricities were chosen ($0, \pm 10, \pm 20^\circ$) and had to be fixated for 5 s each. Fifteen trials were performed for each condition (eccentricity). Because no significant differences were found, we pooled the data from the three different eccentricities. During the pursuit trials, the target moved in a visual range of $\pm 25^\circ$, starting at zero and crossing the midline three times. For each of the three pursuit velocities, 20 trials were performed. Each trial was preceded by a 1-s fixation period at the center of the screen.

DATA ANALYSIS—For data analysis, only the central $\pm 15^\circ$ of the visual field were considered. The recorded eye position traces were filtered with a Gaussian low-pass (cutoff

frequency 10 Hz) and three-point differentiated to obtain the velocity traces. Saccades were detected and removed with a slow-phase estimation algorithm as described in Ladda et al. (2007). Briefly, an estimate of the slow-phase component (SPC) was initialized to zero and iteratively improved in each step. The difference between the actual eye velocity trace and the current SPC served as an estimate of the fast-phase component (FPC). When the FPC exceeded a certain threshold ($100^{\circ}/s$ in the first step, $20^{\circ}/s$ in the second step), a saccade was detected. The SPC was then computed by linear interpolation of the eye velocity across saccades and subsequent filtering with a Gaussian low-pass (cutoff frequency: 1 Hz in the first step, 10 Hz in the second step). Each single period of the eye movement corresponding to the target oscillation was extracted and averaged. The relative modulation of the response to the oscillation for the four different velocities was estimated by fitting a sine wave in amplitude and phase to the averaged eye deviation. The coefficient of determination averaged over all fits (subjects and conditions) was 0.92 ± 0.13 (mean $\pm$ SD). The response gain was defined as the ratio of the fitted sine-wave amplitude to the amplitude of the target oscillation.

Modeling studies

All simulations were carried out using MatLab/Simulink (The MathWorks, Natick, MA) on a Linux workstation. The model included a peripheral processing stage for motion perception (modeled as a first-order low-pass with time constant $\tau_R = 100$ ms to approximate the retinal delay), an eye plant (first-order low-pass with $\tau_E = 200$ ms), and an internal model of the eye plant to estimate the eye velocity based on an efference copy of the eye motor command. The internal model was assumed to be accurate, with an additional feedback delay (approximated by a first-order low-pass with a time constant $\tau_F = 100$ ms). A premotor circuitry with a gain of 1 is included only for comparison with the original model by Robinson et al. (1986). The model parameter fitting utilized the Nelder–Mead simplex algorithm for nonlinear optimization (Nelder and Mead 1965).

Lesions of different sizes were simulated in the two-pathway model by inserting gain elements L_i in the corresponding paths that ranged from zero to one. Lesion size was thus defined as $1 - L_i$.

RESULTS

1. We first quantified the dynamic gain control effect in humans by a simple paradigm. Eye movements were recorded during high-frequency sinusoidal oscillation (4 Hz, $\pm 8^{\circ}/s$) superimposed on a constant velocity target motion (0 – $24^{\circ}/s$) of a small visual target.
2. From this, the relevant gain control parameters were determined and used for the development and fitting of the model. The model is based on a pursuit circuit that was first suggested by Robinson et al. (1986). Here, the gain control is implemented so that the feedforward gain is regulated by an efference copy of the eye motor command. We show that this model is capable of reproducing typical behavioral results associated with dynamic gain control (asymmetry in pursuit on-

and offset, increasing response to perturbations during increasing baseline velocities).

3. The model in its simplest form can be described by one nonlinear differential equation and can therefore be analyzed regarding steady-state behavior and stability using Lyapunov's stability theorem (Lyapunov 1966).
4. An equivalent reformulation of the model then provides a possible explanation for the parallel cortico-ponto-cerebellar pathways and the role of the thalamus in SPEM.
5. It is furthermore elucidated how the so-called main sequence of smooth pursuit (acceleration saturation) can be incorporated, which is apparently opposed to our implementation of dynamic gain control.
6. Finally, "lesions" in the fully determined model lead to eye movement deficits, which are in good agreement with results from actual experimental lesion studies.

Determining the gain control function in humans

The overall characteristics of the visually driven pursuit system can be understood as a negative feedback low-pass filter. An increase in the feedforward gain is equivalent with a decrease in the overall time constant and therefore a shift of the cutoff frequency toward higher frequencies. The effect of eye velocity on the feedforward gain can thus be determined by measuring the responses to high-frequency stimuli in the decay region of the transfer function at different tracking velocities. We therefore measured the responses to a high-frequency sinusoidal oscillation superimposed on a constant carrier velocity (cf. Fig. 1A). A similar paradigm has been used by Keating and Pierre (1996) to measure the gain control in monkeys, but over a smaller velocity range.

Figure 1B shows the mean response modulations of one human subject to a 4-Hz oscillation during different carrier velocities. Clearly, the response modulation increases considerably for higher carrier velocities. The response phase lag is 180° , corresponding to a delay of 125 ms that matches the latency of the pursuit eye movement system. The response gains of all measured subjects with respect to the carrier velocity are shown in Fig. 1C. Although the model proposed in the next section uses eye velocity as the determining factor for gain control, we analyzed the gain with respect to carrier velocity because the differences between carrier velocity and mean eye velocity during steady state are negligible (averaged steady-state pursuit gain over all subjects for the three different carrier velocities is 0.96, 0.97, 0.96, respectively). The increase in gain is highly significant (repeated-measures one-way ANOVA: $P < 0.001$). Furthermore, the increase is fairly linear over the measured velocity range (also see Churchland and Lisberger 2002; Keating and Pierre 1996). A linear regression analysis of the gains of all subjects yields a slope of $0.007 \text{ deg}^{-1}\text{s}$ and a bias of 0.079, which can be considered as the feedforward gain factor during fixation (dashed line in Fig. 1C). The slope of the measured response modulation can be considered as the *efficacy* of the dynamic gain control. The higher the slope, the larger the eye velocity effect on the bandwidth of the pursuit system.

Model optimization

Several models for the smooth pursuit eye movement system have been proposed that concentrate on various behavioral effects, such as spontaneous oscillations during pursuit (Robinson et al. 1986) or the effect of the system's inherent delay on the pursuit traces (Goldreich et al. 1992). Models that deal directly or indirectly with gain control assume either a “switch” in system behavior between fixation and pursuit (Goldreich et al. 1992; Grasse and Lisberger 1992; Krauzlis and Lisberger 1994) or a variable gain that is fed in independently (Carey and Lisberger 2004; Keating and Pierre 1996; Krauzlis and Miles 1996) and is related to perceived target or gaze velocity. In the present work, however, we are interested in a numerical study of the gain control mechanism by fitting the model to behavioral data.

We start with a simplified version of the original model as given by Robinson et al. (1986) (Fig. 2). Here, we assume that a nonlinear function f of the internal estimate of eye velocity $\hat{e}$ regulates the feedforward gain in a multiplicative manner

$$\dot{d} = \hat{r} f(\hat{e}) \quad (1)$$

where d denotes the primary driving signal for the pursuit system and $\hat{e}$ is the estimated retinal image motion signal.

As elaborated in the previous section, the feedforward gain increases linearly with the magnitude of eye velocity. Therefore a rectified linear function is best suited to describe the gain modulation

$$f(\hat{e}) = m|\hat{e}| + c \quad (2)$$

where the slope m and the bias c were determined by nonlinear optimization (see METHODS) to fit the gain function to the behavioral data as shown in Fig. 1C: $c = 1.1143$; $m = 0.0809$. The fitted model reproduces the behaviorally observed response modulation exactly with a mean squared error of 6.4×10^{-6} . The model response to the stimuli used in the behavioral experiment is shown in Fig. 3.

The basic assumption of the proposed gain control implementation—the weighting of the retinal image motion signal by the internal estimate of eye velocity—allows straightforward explanation of other behavioral results associated with dynamic gain control. First, consider the onset of the SPEM response to a step-ramp target. As has been pointed out by several authors, the pursuit system tends to overshoot the target velocity and shows a transient response attributed to uncompensated delays in the feedback loop (Goldreich et al. 1992; Ringach 1995; Robinson et al. 1986). Notably, during the offset of pursuit the converse behavior is observed, which is described by a smooth decline in eye velocity (Luebke and Robinson 1988). Such an asymmetry between pursuit on- and offset directly emerges from our model (arrows in Fig. 4A). At pursuit onset, increasing eye velocity leads to increasing gain signal (cf. gain signal in Fig. 4A). The increased gain causes faster attainment of

steady-state velocity and, due to the processing delay, an overshoot (first arrow in Fig. 4A). In contrast, at pursuit offset, the decreasing eye velocity feedback attenuates the retinal image motion signal, resulting in a low gain and smooth decline (second arrow in Fig. 4A). Note, however, that the overshoot occurs only when the processing delay is included in the model, whereas the asymmetry (i.e., the difference in rise- or decay time) is due to the gain control. Equivalently, the increasing responses to perturbations during different baseline velocities that were observed by Schwartz and Lisberger (1994) are reproduced correctly by the proposed model (Fig. 4B).

Simplification and stability

In its simplest form, the gain control mechanism for SPEM can be described by a simple feedback mechanism, as shown in Fig. 5A. Here, no retinal or feedback dynamics (delays) are considered. As a consequence, the internal estimate of eye velocity $\hat{e}$ is identical to the actual eye velocity e . The nonlinear function is given again by Eq. 2. For further analysis, the model can be simplified to the equivalent form shown in Fig. 5B, where the eye plant is implicated in the inner feedback loop. Then, the inner feedback loop can be substituted by the resulting transfer function (Fig. 5C)

$$H(s) = \frac{1}{\tau_E s} \quad (3)$$

In this simple but equivalent form, the model can easily be written as a single differential equation relating the target velocity input $x : = \dot{t}$ to the eye velocity output $y : = \dot{y}$ by

$$\tau_E \dot{y} = (x - y) (c + m|y|) \quad (4)$$

This nonlinear differential equation has no explicit solution, so the differential equation itself has to be analyzed. Evidently, it is a first-order low-pass filter of the form $\tau_{LP} \dot{y} = x - y$ with a time constant $\tau_{LP} = \tau_E / (c + m|y|)$. Increasing eye velocity leads to an effective decrease of the time constant while the global first-order low-pass behavior is preserved.

It follows from Eq. 4 that the static solution ($dy/dt = 0$) is always $y = x$. For a small perturbation around any possible point in state space, the system is a low-pass filter with a given time constant. Therefore the system is stable in the BIBO sense (bounded-input, bounded-output). The Lyapunov stability is derived in the APPENDIX by using an energy function of the form

$$V(\vec{x}) = \frac{1}{2} (x - y)^2 \quad (5)$$

Parallel pathways

Now the model is split in two parallel paths, by routing part of the retinal image motion information directly through the efference copy loop and part through the gain control loop.

The routing is controlled by introducing a new bias d and a gain element g , as shown in Fig. 5D. As g increases, more retinal image motion information is routed via the efference copy loop and therefore d must compensate for that. The relationship between the gain g , the correction bias d , and the direct gain control bias c from Eq. 2 can be shown as follows. Consider first the original simplified system given in Fig. 5B. The desired motor command $y_1 := \dot{y}'$ can easily be calculated as

$$\begin{aligned} y_1 &= (x-y) (c+m|y|) + y \\ &= mx|y| + xc - my|y| - yc + y \end{aligned} \quad (6)$$

The motor command $y_2 := \dot{e}'_1 + \dot{e}'_2$ in the parallel pathway model (Fig. 5D) is

$$\begin{aligned} y_2 &= g(x-y) + y + (x-y) (d+m|y|) \\ &= mx|y| + x(d+g) - y(d+g) + y - my|y| \end{aligned} \quad (7)$$

By comparison of coefficients from Eqs. 6 and 7, it follows directly for the gain element g

$$g = c - d \quad (8)$$

If this constraint is met, the models from Fig. 5, A and D are mathematically equivalent. Here, d can be considered as a correction so that the overall gain factor of the retinal slip input stays constant.

So far, we developed a dual-pathway model of smooth pursuit gain control that accounts for the anatomical topology in principle. The remaining question is whether we can identify the individual pathways and match them to the MST–DLPN–vPF and FEF–NRTP–DV pathways. A possible distinction between these pathways is given by the prominent feature that in DLPN mostly eye or gaze velocity-related signals are found, whereas NRTP codes mainly for eye acceleration (Ono et al. 2004, 2005). Furthermore, it has recently been shown that this difference can even be found in cortical areas MST and FEF, although with a larger diversity (Nuding et al. 2008). Consider now the motor command $\dot{y}'$ in the parallel pathway model (Fig. 5D). This motor command is composed of two parallel signals

$$\dot{e}' = \dot{e}'_1 + \dot{e}'_2 \quad (9)$$

We will now look at the different signal properties to match these pathways to the MST–DLPN–vPF and FEF–NRTP–DV pathways. The signals can be written as

$$\dot{e}'_1 = g(x-y) + y \quad (10)$$

$$\dot{e}'_2 = (x-y) (d+m|y|) \quad (11)$$

Together with Eq. 4, we can relate these signals to eye acceleration $\ddot{y}$

$$\dot{e}'_1 = g \frac{\tau_E \dot{y}}{c + m|y|} + y \quad (12)$$

$$\dot{e}'_2 = \tau_E \dot{y} \frac{d + m|y|}{c + m|y|} \quad (13)$$

The signal in pathway one ($\dot{e}'_1$) obviously carries a combination of eye velocity and acceleration signals, where the scaling of the eye acceleration fraction depends on actual eye velocity, due to the gain control term $c = m/y$. Taking into consideration the constraints $g = c - d$; $0 \leq d \leq c$, it becomes clear that the maximum scaling for the eye acceleration fraction is given by the time constant of the eye plant and is therefore smaller than the eye velocity proportion. Similarly, the signal in pathway two ($\dot{e}'_2$) is a scaled version of eye acceleration, where the scaling depends on the gain control parameters and the correction bias d . If, for example, $d \approx c$, the signal is eye acceleration scaled by the time constant of the eye plant. No straightforward eye velocity fraction is comprised in that signal.

From this comparison with known neurophysiological results we conclude that pathway one, which serves to estimate the target velocity in space, corresponds to the MST-DLPN-vPF pathway and that the gain control loop (pathway two) can be matched to the FEF-NRTP-DV pathway. In subsequent simulations, additional retinal and feedback dynamics are considered (see METHODS) and the correction bias d is set to $c/2$. This ad hoc assumption is justified by the fact that there is no reason to assume a significant bias in the flow of retinal image motion information. Furthermore, we checked the effects of the parameter and found no significant influence on the forthcoming results, except for extreme values at the border of the parameter domain.

Acceleration saturation

Our implementation of dynamic gain control might be in conflict with the effect of acceleration saturation during SPEM onset (see, e.g., Robinson et al. 1986). Clearly, our implementation increases the gain during SPEM onset at higher velocities, thus reducing the latencies (see transient responses in Fig. 4B). Robinson implemented this effect as a local feedback loop in the premotor circuitry (cf. Fig. 2), by generating intermediate acceleration signals and applying a saturating nonlinearity. In principle this is also viable in our model, but the models differ with respect to the assumed time constant of the eye plant (15 vs. 200 ms; the long time constant is based on measurements during passive deflections of the eye and is considered to be more realistic; for review see Glasauer 2007). The motor command in our model is therefore more correlated with eye acceleration due to the large time constant. Thus a further feedback loop in the premotor circuitry is not feasible and a direct saturation of the motor command would yield a decrease in gain for higher target velocities.

A possible site for an acceleration saturation is the second pathway ($\dot{e}'_2$) because acceleration-related signals exist there naturally. A saturating nonlinearity in that pathway decreases the maximal acceleration, but leaves the steady-state gain unchanged because the main feedback loop remains intact (cf. lesion simulation in Fig. 7). We applied a saturating

nonlinearity in the pathway and redetermined the relevant gain control parameters (m , c). As can be seen from Fig. 6, the acceleration saturation does not abolish the gain control effect, although an increase in latency of the first overshoot for increasing target velocities is observed. The acceleration saturation is neglected in the following simulations because the relevant results were not modified.

Lesion studies

Of special interest is the system's behavior after inactivation of specific branches of the system and a comparison with actual results from lesion studies. For that, we applied variable gain elements in the corresponding branches that range from zero to one, thus simulating different lesion sizes. Damage to MST ($\dot{e}_1'$) produces a deficit in the maintenance and initiation of pursuit, resulting in an increase in pursuit latency, as defined by crossing 20% of the target velocity and a reduced steady-state gain (Fig. 7, *top*). This is in agreement with classical neurophysiological studies (see, e.g., Dürsteler and Wurtz 1988).

Inactivation of FEF ($\dot{e}_2'$) reduced initial pursuit acceleration (Fig. 7, *bottom*). This has also been observed by Shi et al. (1998), but in addition, the steady-state gain was also substantially decreased. This is not reproduced by the current model, which may be attributed to the recurrent interactions between FEF and MST (Fukushima 2003; Lynch and Tian 2006; Tusa and Ungerleider 1988). A lesion in FEF may also affect eye velocity signals that are relayed to MST and may therefore impair MST function itself (see DISCUSSION). Damage to the gain control mechanism in FEF (e.g., a downscaling of the eye velocity input to the FEF) would result in an attenuation of the gain control effect. In other words, the measured gain control curves in Fig. 1C would experience a reduction in the slope.

DISCUSSION

In this study, we proposed a simple model of smooth pursuit gain control that constituted behavioral observations, anatomical constraints, and physiological data. We elaborated how the control systems model can be reconciled with known parallel cortico-ponto-cerebellar pathways of smooth pursuit (for review see Thier and Möck 2006). Clearly, the model is relatively simplistic and can be viewed as a “proof of concept.” Nevertheless, the relevant behavioral results that can be attributed to dynamic gain control were correctly reproduced with our model. Furthermore, we were able to explain the very basic response properties of neurons in the parallel pathways for smooth pursuit by analytical derivation. To our knowledge, no model has been proposed that takes into account the functional properties of gain control together with neuronal activities in the parallel pathways.

On a cortical level, there is further evidence that MST is correlated with eye velocity (Newsome et al. 1988; Ono and Mustari 2006; Squatrito and Maioli 1997; Thier and Erickson 1992; Thier and Ilg 2005), whereas FEF contributes mainly to pursuit initiation, which is characterized by high eye acceleration (Gottlieb et al. 1994; Tanaka and Fukushima 1998). In antidromic activation studies, we have recently shown that FEF neurons with eye acceleration project to the smooth-pursuit-related part of the NRTP (Ono et al. 2005).

Comparison with other models

Various models have been proposed to deal with the variety of behavioral and anatomical features of the human smooth pursuit system. Our model is closely related to the approach suggested by pioneering computational models (Robinson et al. 1986; Yasui and Young 1975), which assumed that an efference copy of the eye motor command is used to estimate the target velocity in space and to maintain an ongoing SPEM. This class of models has been termed “internal feedback models.” Another class of models—the so-called image-motion models (e.g., Churchland and Lisberger 2001; Krauzlis and Lisberger 1994)—assumes a feedforward-only architecture, where eye velocity is driven only by image velocity and acceleration. This type of models can explain several aspects related to the spontaneous oscillations during ongoing pursuit. In contrast, the tachometer feedback model (Ringach 1995) proposes an eye acceleration feedback to explain the spontaneous oscillations. These models are supposed to provide a simple functional explanation of the very complicated pursuit dynamics and are not intended to explain neuronal signal processing properties or to consider anatomical connections. Other models explicitly focused on area MST and its role in smooth pursuit maintenance (e.g., Dicke and Thier 1999; Pack et al. 2001; Tabata et al. 2002) or learning of target dynamics to drive SPEM (Shibata et al. 2005). In our model, consideration of anatomical constraints—i.e., the dual pathways of smooth pursuit—together with basic neuronal signal processing properties constitutes the crucial feature. So far, attempts to deal with the asymmetrical dynamics during pursuit on- and offset have assumed a motion transient switch or a variable gain that is fed in extrinsically. We were able to explain these dynamics by a simple multiplicative gain-control mechanism that is based on an efference copy of the eye motor command.

Multiplicative interactions

The basic functional aspect of the gain control mechanism is the multiplicative conjunction between retinal slip (feedforward) and estimated eye velocity (feedback). Apparently, this constitutes a nontrivial operation for single neurons, as well as for a whole population of neurons (Salinas and Abbott 1996). However, we could show in a preliminary modeling study that a simple, weakly nonlinear recurrent network with only additive inputs can accomplish this (Nuding et al. 2008). Furthermore, Ladda et al. (2007) derived an optimality constraint for simple velocity servos (in essence, the SPEM system) that pursue targets undergoing a natural velocity scaling. To make its position error invariant, the servo gain must be adjusted proportionally to the tangential target velocity. This condition corresponds to the dynamic gain control in our system if $f(\hat{e})$ is a rectified linear function, which we concluded based on our human behavioral experiment.

FEF and MST network

The basic architecture of the two-pathway model in Fig. 5D implies that MST receives a combination of feedforward retinal slip signals and a feedback efference copy of the eye motor command via the thalamocortical pathway (Tanaka 2005), whereas FEF activity is driven mainly by afferent signals from the primary motion detection area MT. Although Stanton et al. (2005) demonstrated the existence of MT–FEF connections, it is more likely that FEF receives input from retinal slip-sensitive neurons in MST because there are strong

connections between these areas (see INTRODUCTION). These results are compatible with our model.

The strong reciprocal connections between MST and FEF can also explain the minor inconsistencies in our model. First, we assumed independent feedback connections from the cerebellum to MST and FEF, respectively. However, the simulated transport delays from cerebellum to cortex are identical, thus allowing the possibility of a common pathway via the thalamus. Correspondingly, a lesion of the FEF pathway in our model did not result in a decrease in steady-state gain. However, according to the work on the involvement of the thalamus in SPEM (Tanaka 2005), the extraretinal signals found in MST may be routed via FEF because FEF receives abundant projections from eye-movement-related neurons in the central thalamus and there is no evidence for a direct projection from thalamus to MST. In that case, a lesion in FEF would weaken not only the FEF–NRTP–DV pathway, but also the efference copy to MST leading to a misestimate of the target velocity in space. This would in turn cause a decrease in steady-state gain with FEF lesions. Both possibilities are consistent with the hypothesis advanced by Churchland and Lisberger (2005) who suggested that the observed neuronal activities in MST could be involved in smooth pursuit gain control.

The complex reciprocal connections between MST and FEF suggest that a strict dichotomy between an acceleration and velocity pathway is unrealistic. It is clear that velocity- and acceleration-driven neurons may reside in both pathways. Our main finding was that the anatomical pathways were more correlated with eye velocity or acceleration, respectively, as has been found in several studies (Ono et al. 2004, 2005; Nuding et al. 2008). The two pathways therefore contribute acceleration and velocity signals predominantly, but not exclusively, to the motor command.

FEF and gain control

According to the developed model, the gain control mechanism is located in the acceleration branch, which corresponds best anatomically to the FEF–NRTP–DV pathway because we could show that this pathway conveys mainly eye-acceleration-related signals. This hypothesis is supported by our recent results in another study showing that smooth-pursuit-related FEF neurons carrying eye-acceleration information actually project to the NRTP (Ono et al. 2005). In that study, we used low-current stimulus pulses delivered in the rostral NRTP at the location of smooth pursuit neurons to antidromically activate FEF neurons. Neurons in the NRTP have been shown to carry eye-acceleration information related to smooth pursuit and gaze (Ono et al. 2004, 2005; Suzuki et al. 2003). We did not test whether FEF neurons with eye acceleration or eye velocity sensitivity projected to other basilar pontine sites such as the DLPN, where neurons with eye velocity but little eye acceleration sensitivity have been found (Mustari et al. 1988; Ono et al. 2004, 2005; Suzuki et al. 1990; Thier et al. 1988).

A role for the FEF in gain control has also been suggested by Tanaka and Lisberger (2001) in an electrical stimulation study. However, one must clearly distinguish between the influence of FEF in setting the static feedforward gain of the pursuit circuit and the dynamic regulation as accomplished by smooth pursuit gain control. The global behavior of the

visually driven pursuit system can be understood as a low-pass system. Increasing the static gain in such a negative feedback system is equivalent to reducing the overall time constant and therefore shifting the cutoff frequency toward higher frequencies. Thus the response to a high-frequency stimulus in the decay region of the transfer function like a perturbation is boosted. In terms of the measured gain control curves from Fig. 1C, this corresponds to an overall upward shift (cf. model bias c). Studies that deal with modifying the static gain in FEF either by lesions or by electrical stimulation provide no evidence for a change in dynamic gain control per se, given that the major gain control parameter is the efficacy, i.e., the amount of gain change that is due to a change in eye velocity (cf. model slope m). For this reason, at least two measurements at different gains are necessary to determine the slope of the gain control curves (cf. Fig. 1C). To our knowledge, there is no study dealing with that dichotomy, which is a natural consequence of our model and the proposed gain control mechanism itself.

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APPENDIX

Model stability

The model as described by the nonlinear differential Eq. 4 can be formulated in state space notation

$$\vec{\dot{x}} := \begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = \begin{bmatrix} 0 \\ 1/\tau_E (x-y) (c+m|y|) \end{bmatrix} \quad (\text{A1})$$

The inclusion of $\dot{x}$ extends the analysis to nonautonomous systems with a constant velocity input. The Lyapunov energy function is constructed as

$$V(\vec{x}) = \frac{1}{2}(x-y)^2 \quad (\text{A2})$$

which is clearly positive definite. Its derivative is

$$\begin{aligned} \dot{V} &= x \dot{x} - x \dot{y} - \dot{x} y + y \dot{y} \\ &= -x \dot{y} + y \dot{y} \\ &= (y-x) \dot{y} \\ &= (y-x) (1/\tau_E) (x-y) (c+m|y|) \\ &= -1/\tau_E (x-y)^2 (c+m|y|) \end{aligned} \quad (\text{A3})$$

For $c, m \geq 0$, the derivative is negative definite for all possible values x and y . Therefore the system is asymptotically stable in the sense of Lyapunov.

FIG. 1.

A: example target (gray) and eye (black) trace for the pursuit of a $16^\circ/\text{s}$ constant velocity target with a superimposed 4 Hz, $\pm 8^\circ/\text{s}$ oscillation. Saccades (X) were removed and excluded from averaging (raw eye velocity trace: thin black; estimated slow phase: bold black). B: mean responses of the same human subject (JL) for different baseline velocities. The baseline is subtracted to show the increase in the response modulation with increasing baseline velocity. Shaded areas around the mean traces show the SE. C: response gains of 12 human subjects. Data of subject JL displayed in A and B are marked in black. Dashed line shows the linear regression over all subjects.

FIG. 2.

Extension of the basic model by Robinson et al. (1986) to incorporate dynamic gain control. $\dot{r}$ denotes retinal error velocity, as defined by the difference between target velocity $\dot{t}$ and eye velocity $\dot{e}$, and $\hat{\dot{r}}$ is the internal estimate of retinal error velocity. Similarly, $\hat{\dot{e}}$ is the internal estimate of eye velocity as provided by the internal plant model, which receives an efference copy of the eye motor command $\dot{m}$. The shaded box represents the dynamic gain control: the feedforward retinal slip signal that constitutes the primary input to the pursuit system is multiplied with a function of estimated eye velocity, i.e., the current internal estimate of eye velocity regulates the feedforward gain of the overall system to generate the driving signal $\hat{\dot{d}}$ for the premotor circuitry.

FIG. 3.

Model responses to the stimuli used in the behavioral experiment. Labels are the same as in Fig. 1B. The differences in response modulation in comparison to the subject shown in Fig. 1B are explained by the fact that the model is fitted to the mean response modulation over all subjects, which apparently differs from individual data (cf. Fig. 1C).

FIG. 4.

Numerical simulations of the model from Fig. 2 using the fitted gain control parameters from the behavioral measurements. **A:** asymmetric response behavior with respect to the onset and the offset of a constant pursuit movement. Dashed line shows the gain as determined by the eye velocity feedback (cf. Fig. 2). Arrows indicate the asymmetry. **B:** perturbations applied during different baseline velocities cause an increase in eye deviation with increasing eye velocity.

FIG. 5.

Reformulation of the model for further analysis. *A*: this is the same model as described in METHODS, except that neither retinal nor feedback dynamics are considered. *B–D*: equivalent descriptions of the model. *B*: the eye plant is implicated in the inner feedback loop. *C*: the inner feedback loop is then substituted by the equivalent feedforward transfer function. *D*: equivalent 2-pathway formulation of the model. The shaded boxes label the distinct parallel pathways. AS is the site of the optional acceleration saturation. See text for details.

FIG. 6.

Effect of an acceleration saturation in the acceleration pathway on the eye movement during pursuit of targets with different velocities (A) and during pursuit of a piecewise constant velocity target with perturbations in target motion (B). As can be seen, the acceleration saturation does not abolish the gain control effect. *Inset* in A shows the acceleration saturation function that is applied to the signal in the gain control loop $\dot{e}_2'$ (cf. Fig. 5D).

FIG. 7.

Effects of increasing lesion size in the medial superior temporal area (MST) and frontal eye field (FEF) on the eye velocity trace. Bold trace shows control condition without lesion; thin traces show eye velocity for increasing lesion sizes. *Top*: increasing lesion size in MST leads to a reduction in the steady-state gain and an increase in pursuit latency as defined by crossing 20% of the target velocity. *Bottom*: increasing lesion size in FEF yields a decrease in the maximum acceleration during pursuit onset (shown as the fraction of maximum acceleration without lesion) as well as an increase in latency.