The neuronal basis of on-line visual control in smooth pursuit eye movements

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ABSTRACT

Smooth pursuit eye movements allow us to maintain the image of a moving target on the fovea. Smooth pursuit consists of separate phases such as initiation and steady-state. These two phases are supported by different visual-motor mechanisms in cortical areas including the middle temporal (MT), the medial superior temporal (MST) areas and the frontal eye field (FEF). Retinal motion signals are responsible for beginning the process of pursuit initiation, whereas extraretinal signals play a role in maintaining tracking speed. Smooth pursuit often requires on-line gain adjustments during tracking in response to a sudden change in target motion. For example, a brief sinusoidal perturbation of target motion induces a corresponding perturbation of eye motion. Interestingly, the perturbation ocular response is enhanced when baseline pursuit velocity is higher, even though the stimulus frequency and amplitude are constant. This on-line gain control mechanism is not simply due to visually driven activity of cortical neurons. Visual and pursuit signals are primarily processed in cortical MT/MST and the magnitude of perturbation responses could be regulated by the internal gain parameter in FEF. Furthermore, the magnitude and the gain slope of perturbation responses are altered by smooth pursuit adaptation using repeated trials of a step-ramp tracking with two different velocities (double-velocity paradigm). Therefore, smooth pursuit adaptation, which is attributed to the cerebellar plasticity mechanism, could affect the on-line gain control mechanism.

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1. Introduction

Eye movements are supported by interactions between visual processing and motor control systems. For example, when we precisely track a small moving object, the eye motion should match the target motion to stabilize the image of a moving object on or near the fovea. Such continuous eye movements with an active visual system are called "smooth pursuit". Smooth pursuit eye movements often require on-line gain adjustments during tracking in response to a sudden change in target motion (perturbation). Previous studies have demonstrated that visuomotor gain during smooth pursuit is regulated by an on-line (dynamic) gain control mechanism (Churchland & Lisberger, 2002, 2005; Nuding et al., 2008; Ono et al., 2010; Schwartz & Lisberger, 1994). The on-line gain control is known to regulate an internal gain parameter in pursuit, where higher target velocities yield higher gains in perturbation responses. Typically in those studies, a single cycle of

sinusoidal motion is introduced during ongoing pursuit to estimate the perturbation ocular response. The advantage of using the sinusoidal motion is to avoid triggering saccade eye movements during a sudden motion. Our studies and other laboratories have shown perturbation ocular responses without saccadic intrusions. Previous studies have suggested that cortical visual and pursuit systems are involved in the on-line gain regulation (Nuding et al., 2009; Ono et al., 2010; Tanaka & Lisberger, 2001, 2002). Cortical visual processing is necessary for initiating smooth pursuit where visual motion signals are transformed into eye movement commands (Krauzlis, 2004; Lisberger, 2010). Pursuit initiation and steady-state phases are supported by different visuomotor processing. The first 100 ms of pursuit tracking is defined as an open-loop response that occurs before the time of the visual feedback, while steady-state pursuit velocity is maintained by a feedback system (Nuding et al., 2008; Robinson, Gordon, & Gordon, 1986). The initial pursuit phase is driven strongly by retinal error signals carried by cortical neurons. The visual motion-related neuron starts discharging before pursuit onset and the discharge declines once eye velocity reaches the target (Newsome, Wurtz, & Komatsu, 1988). Then, steady-state pursuit velocity is maintained by an extraretinal (non-visual) signal (Ilg & Thier, 2003; Newsome, Wurtz, &

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Komatsu, 1988; Ono & Mustari, 2012). The extraretinal information could be associated with an efference copy of eye motion, volitional pursuit commands or prediction signals. Smooth pursuit is considered as a volitional tracking behavior, whereas the perturbation response to a sudden motion is thought to be different from volitional eye movements. This review focuses on neurophysiological aspects of the on-line visuomotor control to understand how the internal gain parameter is regulated by visual and extraretinal signals. We also argue whether the on-line gain control is influenced by smooth pursuit adaptation associated with plasticity mechanisms in the cerebellum. Understanding of neural mechanisms underlying visuomotor control during ongoing pursuit has advanced significantly in the last decade including how visual and eye motion information is processed at cortico-ponto-cerebellar pathways.

2. Visual processing in the cortical pathway for smooth pursuit

Visual motion signals are processed in the cortical middle temporal (MT) and the medial superior temporal (MST) areas to produce partially formed commands for smooth pursuit (Fig. 1). Early studies have demonstrated that MT neurons with foveal/parafoveal visual receptive fields are modulated during smooth pursuit using a small moving target (Komatsu & Wurtz, 1988; Newsome, Wurtz, & Komatsu, 1988). The response of MT neurons during pursuit is known to be visually contingent, because the neuronal response dropped when retinal image motion is reduced by target stabilization or blinking during pursuit (Newsome, Wurtz, & Komatsu, 1988). The direction selective visual motion signals in MT support pursuit initiation and dynamics in a specific direction (Groh, Born, & Newsome, 1997; Hohl & Lisberger, 2011; Komatsu & Wurtz, 1989; Lisberger & Movshon, 1999; Newsome et al., 1985). The visual motion signals carried in MT also play a role in visual motion perception (Newsome & Pare, 1988; Nichols & Newsome, 2002).

It has been shown that neurons in neighboring area MST are modulated during smooth pursuit. The lateral-anterior part of MST (MSTl) carries mainly visual motion signals, whereas the dorsal-medial part of MST (MSTd) provides extraretinal (non-visual) signals that are related to pursuit eye motion (Ferrera & Lisberger, 1997; Ilg, Schumann, & Thier, 2004; Komatsu & Wurtz, 1988; Kurkin et al., 2011; Newsome, Wurtz, & Komatsu, 1988; Thier & Erickson, 1992). These extraretinal signals carried in MSTd are revealed by extinguishing the target during pursuit when neuronal response continues with pursuit (Newsome, Wurtz, & Komatsu, 1988; Ono & Mustari, 2006, 2012) or when tracking an imaginary target (Ilg & Thier, 2003). These MST neurons also have large visual receptive fields responding to motion in preferred directions. Furthermore, lesions placed in MST/MT produce directional and retinotopic deficits in smooth pursuit eye movements (Dursteler & Wurtz, 1988; Dursteler, Wurtz, & Newsome, 1987).

Fig. 1 illustrates examples of visual motion and smooth pursuit related responses of neurons in MST during step-ramp tracking, showing direction selective activity. Multiple linear-regression modeling allows us to estimate the relative sensitivities of neuronal responses to eye or retinal error motion parameters (position, velocity and acceleration) (Das et al., 2001; Shidara et al., 1993; Sylvestre & Cullen, 1999). Averaged data of step-ramp trials are used to identify coefficients in the eye model, $FR(t + \tau) = A + BE(t) + CE'(t) + DE''(t)$ and the retinal error model, $FR(t + \tau) = A + BR(t) + CR'(t) + DR''(t)$, where $FR(t)$ is the estimated value of the unit spike density function (actual data) at time "t,". $E(t)$ denotes the eye motion (position, velocity and acceleration) at time "t," and $R(t)$ denotes the retinal error (position, velocity and acceleration) at time "t,". Coefficients in the models are

defined by terms A, B, C and D. The latency value of the unit response with respect to target onset or pursuit (eye) onset is represented by the "τ" term. Retinal error parameters were calculated as the difference between target and eye motion parameters. Note that target acceleration was assumed as $0°/s^2$, since differentiation of a step in target velocity results in zero target acceleration (Das et al., 2001; Ono & Mustari, 2009; Ono et al., 2005). The goodness of fit is determined by calculating a coefficient of determination (CD) between experimentally observed unit data and model estimated fit. We calculated a set of coefficients (A–D) and estimated coefficients of determination (CD) for a series of latencies (τ). In the final model, we used coefficients that yielded a maximum CD for specific latency values. Retinal error motion variables make the significant contributions to fits for the visual motion response (Fig. 1A), whereas eye movement variables make the significant contributions to fits for the pursuit response (Fig. 1B).

Furthermore, modeling studies have revealed that the visual motion neuron is highly dependent on a retinal error velocity component (REV). In contrast, the pursuit neuron is strongly related to an eye velocity component (Mustari, Ono, & Das, 2009; Ono & Mustari, 2012). The latency of the unit response with respect to target or pursuit onset is obtained from the model with a maximum CD. There is a major difference in the neuronal response latency between visual and pursuit neurons. The visual motion neuron has an early latency that leads pursuit onset (70 ms), whereas the pursuit eye velocity neuron lags behind pursuit onset (50 ms).

Current evidence suggests that the extraretinal (non-visual) signals carried in MSTd are related to volitional smooth pursuit commands rather than proprioceptive or other feedback signals associated with reflex driven eye movements such as vestibulo-ocular reflex (Ono & Mustari, 2006; Ono et al., 2010). Visual motion and pursuit related regions of cortical areas MT and MST must be processed further in the oculomotor regions including the pontine nuclei (Distler, Mustari, & Hoffmann, 2002; Glickstein et al., 1980; May & Andersen, 1986) and the floccular complex (Glickstein et al., 1994; Nagao et al., 1997) and vermal lobules VI and VII (Brodal, 1979, 1982; Langer et al., 1985) in the cerebellum. Here we consider whether cortical regions related to visual motion or extraretinal signals play roles in the on-line visuomotor control in smooth pursuit.

3. On-line gain regulation during smooth pursuit

A sudden change in target motion induces a corresponding perturbation response of eye motion (Churchland & Lisberger, 2002; Ono, 2013; Schwartz & Lisberger, 1994; Tabata et al., 2006). This approach evaluates how the visual input associated with a given speed and direction of image motion on the retina affects the on-line visual control in smooth pursuit eye movements. Fig. 2A illustrates an on-line gain adjustment of smooth pursuit during step-ramp tracking. A brief perturbation using a short-duration single cycle of sinusoidal motion (2.5 Hz, ±10°/s) was introduced during ongoing pursuit (ramp speed = 10°/s). Mean eye velocity traces show that the sinusoidal perturbation induces a corresponding change in eye velocity (Fig. 2A). The latency of eye motion with respect to the target perturbation is similar to the pursuit latency (<120 ms). Neuronal activities of MST neurons were recorded to determine whether the perturbation ocular response is attributed to the cortical visuomotor systems. Fig. 2B and C shows typical neuronal responses of MST neurons to the target perturbation. The visual motion related neuron (Fig. 2B) showed a significant modulation in firing rate associated with the perturbation (arrow). In contrast, the pursuit-related neuron (Fig. 2C) carrying an extraretinal signal did not show a corresponding modulation in firing