Anterior and superior lateral occipito-temporal cortex responsible for target motion prediction during overt and covert visual pursuit

Dai Kawawaki [a,b,c], Tomohiro Shibata [a,b,c,*], Naokazu Goda [d],
Kenji Doya [a,b,c], Mitsuo Kawato [a,c]

[a] *Nara Institute of Science and Technology, 8916-5 Takayama-cho, Ikoma, Nara 630-0192, Japan*
[b] *CREST, Japan Science and Technology Corporation, 2-2-2 Hikaridai, Seika-cho Souraku-gun, Kyoto 619-0288, Japan*
[c] *Computational Neuroscience Laboratories, ATR, 2-2-2 Hikaridai, Seika-cho Souraku-gun, Kyoto 619-0288, Japan*
[d] *National Institute for Physiological Sciences, 38 Nishigonaka, Myodaiji, Okazaki, Aichi 444-8585, Japan*

Abstract

In smooth-pursuit eye movements (SPEM) with gain close to one, SPEM should be controlled mainly by prediction of target motion because retinal slip is nearly zero. We investigated the neural mechanisms of visual-target prediction by the three fMRI experiments. (1) Overt pursuit task: subjects pursued a sinusoidally moving target which blinked (blink condition) or did not blink (continuous condition). (2) Covert pursuit task: subjects covertly pursued the same target with eyes gazed at fixation point. (3) Attend-to-stationary target task: subjects brought attention on a stationary target with eyes gazed at fixation point. In the overt pursuit task, the SPEM gain and the delay in the blink condition were not very different from the continuous condition, indicating good prediction of the blinking target motion. Activities in the dorsolateral prefrontal, precentral, medial superior frontal, intraparietal, and lateral occipito-temporal cortexes increased in the blink-continuous subtraction. The V1 activity decreased for this contrast. In the covert pursuit task, only the anterior/superior LOTC activity remained in the blink-continuous subtraction. In the attend-to-stationary target task, the blink-continuous subtraction elicited no activation. Consequently, the a/sLOTC activity is responsible for target prediction rather than motor commands for eye movements or just target blinking such as visual saliency.
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1. Introduction

High acuity fovea in primates requires smooth pursuit eye movements to continue looking at a target moving slowly and smoothly. The purpose of smooth pursuit eye movements is to minimize retinal slip, i.e. target velocity projected onto the retina. Retinal slip disappears once eye velocity catches up to target velocity in smooth pursuit eye movements. Nevertheless, eye movements are maintained. As a model for smooth pursuit eye movements to a target moving at constant velocity, Robinson et al. (1986) extended the positive feedback model proposed by Yasui and Young (1975) and proposed that smooth pursuit eye movements were maintained by the integration of a retinal slip velocity and the efference copy of eye velocity. This model (Robinson et al., 1986) attempted to cancel out the feedback signal in order to enable high velocity gain (i.e. the ratio of eye velocity to target velocity), and their model works as a feedforward controller. However, their feedforward pathway still contains a significant delay that prevents this model from achieving zero-lag tracking of a sinusoidal signal. For instance, the eye movement lags behind the target motion of a 1-Hz sinusoidal signal by more than 200 ms (Shibata et al., 2005). According to computational theory, target motion prediction is essential in smooth pursuit eye movements at least for sinusoidally moving targets.

Neurophysiological experiments have been conducted on monkeys to investigate the mechanisms related to an internal representation of target velocity (Sakata et al., 1983; Newsome et al., 1988; Kawano et al., 1994; Tanaka and Fukushima, 1998; Fukushima et al., 2002a, b). The task of these studies had

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* Corresponding author. Tel.: +81 743 72 5981; fax: +81 743 72 5989.
 E-mail address: tom@is.naist.jp (T. Shibata).

monkey subjects perform smooth pursuit eye movements to a target that suddenly disappeared for a moment, and the results revealed that neurons in the frontal eye field (FEF) (Tanaka and Fukushima, 1998) and the medial superior temporal (MST) (Newsome et al., 1988; Sakata et al., 1983; Kawano et al., 1994) successively discharged when a target was blanked as well as when the target was not blanked. These results suggest that the discharges of FEF and MST neurons, referred to as corollary discharges or extraretinal signals, represent information for maintaining smooth-pursuit eye movements. Especially in the task of (Fukushima et al., 2002b), the results showed that discharges of some FEF neurons of a monkey subject increased despite the eye velocity decreasing when the target was blanked compared to when the target was not blanked, indicating that discharges of some FEF neurons represent predictive information of target velocity.

There have been some neuroanatomical studies in humans using functional magnetic resonance imaging (fMRI). Barton et al. (1996) found greater activities in the lateral occipito-temporal cortex (LOTC) of human subjects when the subjects pursued a smoothly moving target on a fixed background than when they gazed at a fixed target on a smoothly moving background, despite the fact that the visual inputs from the retina was almost the same in both conditions. Dukelow et al. (2001) found that the monkey MST homologue of human subjects that lies in the LOTC was activated when the subjects performed non-visual smooth-pursuit eye movements induced by smooth finger movements in comparison with the rest condition. Lencer et al. (2004) showed that activities in the precentral cortex (PreCC; including the monkey FEF homologue), medial superior frontal cortex (MSFC), intraparietal cortex (IPC), and dorsolateral prefrontal cortex (DLPFC) in humans, increased when the subject pursued the target at constant velocity with blanking compared to when they pursued the target without blanking. These studies suggest that activity in these regions reflects an internal representation of the estimated target motion for maintaining smooth-pursuit eye movements. However, since constant velocity motion rather than sinusoidal motion was used in these experiments, their results cannot be used to assess whether brain activities reflected prediction of a target motion or just maintained the last eye velocity. Furthermore, to our knowledge, there has been no study in which the brain activity induced by saccadic eye movements was properly eliminated.

The aim of this study was to identify the human cortical regions involved in a predictive representation of target motion. For our aim, we conducted a series of fMRI tasks with simultaneous recording of eye movements. The result of recording the eye movements showed that our subjects performed predictive smooth pursuit eye movements even if the target was blinking. Furthermore, we confirmed that target motion prediction was important for smooth pursuit to sinusoidal motion by a simulation experiment based on the model proposed in Shibata et al. (2005). The fMRI result indicated that the PreCC, MSFC, IPC, LOTC, and DLPFC increased their activities when the target was blinking during smooth-pursuit eye movements compared to when the target

was presented continuously. In the series of tasks, we analyzed the effect of saccades on their activities and conducted control tasks, such as a covert pursuit task and an attend-to-stationary target task, to eliminate the possibilities of contributions by other factors than the prediction of the target. The results of our fMRI experiments suggested that the LOTC activity represented the target motion prediction during smooth-pursuit eye movements.

2. Materials and methods

2.1. Subjects

Thirty-two healthy human volunteers (29 males and 3 females) with normal vision participated in this study. All subjects gave informed consent in writing and the study was approved by the Ethics and Safety Committee of Advanced Telecommunications Research Institute International (ATR). Twenty-five subjects (23 males and 2 females) participated in the overt pursuit task. Twelve subjects (9 males and 3 females) participated in the covert pursuit task and the attend-to-stationary target task. Five subjects (3 males and 2 females) participated in all tasks.

2.2. Visual stimulus and experimental protocol

2.2.1. Overt pursuit task

The target of a laser spot (with a diameter of $0.1°$ and a luminance of 1.4 cd/cm^2) was presented on a screen ($28.7° \times 21.5°$) placed 40 cm in front of the subject's eyes. A galvanometer mirror system (Kiyohara Kougaku) for controlling the target motion was actuated at 500 Hz by a personal computer Endeavor Pro-400L (EPSON DIRECT) and VSG2/5 (Cambridge Research Systems). The MRI experiment room was fully dark.

The target moved sinusoidally along the horizontal meridian in test blocks and remained stationary in the center of the screen in rest blocks. The test block consisted of four trials. In each trial, the target was moving sinusoidally at a frequency of 0.5 Hz and amplitude of $10°$ for 4 s followed by an eye blinking period of 2 s. In the former two trials, the target was continuously lit on (continuous condition), while in the latter two trials the target was blinking repeatedly either for 100 ms on and 200 ms off or for 200 ms on and 100 ms off (blink condition). Whether the target initially moved rightward or leftward was in a pseudo-random order. In each rest block, a stationary target was presented for 24 s. In one session, the test and rest blocks repeated alternately six times and took 300 s. Five sessions, with a 1-min-break interleaved between sessions, were performed by each subject.

Subjects were asked to pursue a target with their eyes as smoothly as possible in the test blocks even if the target was blinking and asked to gaze at the stationary target in the rest blocks. The subjects were also asked to blink their eyes during the eye blink period, in which a 1000-Hz tone stimulation was presented for a moment at both the beginning and the end of each period; this was designed to avoid artifactual contaminants of eye blinks in fMRI signals.

2.2.2. Covert pursuit task

A white target (with a diameter of 0.3° and a luminance of 929.1 cd/cm^2) and a red fixation point (0.3° and 236.1 cd/cm^2) were projected by DLA-G11 (Victor) at a 60-Hz refresh rate. The screen (28.7° × 21.5° and a background luminance of 3.1 cd/cm^2) was placed 35–41 cm in front of each subject's eyes, depending on the size of the subjects' head. The target was controlled by a personal computer Endeavor Pro-400L (EPSON DIRECT) and VSG2/5 (Cambridge Research Systems).

The white target was presented at a view angle of 5° above the red fixation point at the center of the screen and was moved sinusoidally at a frequency of 0.5 Hz and amplitude of 10° along the horizontal meridian in the test blocks. The test block consisted of four trials. In the former two trials, the target was moved for 4 s with lighting continuously on (continuous condition), while in the latter two trials the target was moved for 4 s with blinking repeatedly for 100 ms on and 200 ms off (blink condition). In each trial, the eye blink period for 2 s and the randomized direction of target motion initiation were set in the same way as for the overt pursuit task. In each rest block, the white target remained stationary and was located at a view angle of 5° above the fixation point at the center of the screen for 24 s. The alternate repetitions of the test and rest blocks in a session were the same as the overt pursuit task, and three sessions were performed by each subject with a 1-min-break interleaved.

Subjects were asked to orient their attention to the white target and to pursue covertly the target motion in the test blocks, whereas they were asked to orient their attention to the stationary white target in the rest blocks. Note that they were asked to gaze at the red fixation point in both cases. The subjects were also asked to blink their eyes during the eye blink period (see the descriptions in the overt pursuit task for details).

2.2.3. Attend-to-stationary target task

A white target and a red fixation point were presented with the same equipment as that used in the covert pursuit task. The white target was presented and remained stationary at a view angle of 5° above the red fixation point at the center of the screen in test blocks. Each test block consisted of four trials. In the former two trials, the target was continuously presented and remained stationary (continuous condition), while in the latter two trials the target was blinking repeatedly for 100 ms on and 200 ms off (blink condition). In each trial, the duration of 4 s for each trial and the eye blink periods of 2 s were set in the same way as the overt and covert pursuit tasks. In each rest block, the white target was not presented while the red fixation point was presented alone at the center of the screen for 24 s. The alternate repetitions of the test and rest blocks in a session were the same as the overt and covert pursuit tasks, and three sessions were performed by each subject with a 1-min-break interleaved.

Subjects were asked to bring their attention on a white target with gazing at the red fixation point in the test blocks and asked to just gaze at the red fixation point in the rest blocks. The subjects were also asked to blink their eyes during the eye blink period (see the descriptions in the overt pursuit task for details).

2.3. Eye movement analysis

In the overt pursuit task, the horizontal eye position of subjects was recorded with the MR-Eyetracker (Cambridge Research Systems) at 500 Hz. The eye position data were filtered (30-Hz cutoff frequency), and eye velocity was calculated based on the eye position. Smooth eye velocity was extracted from the saccadic component of eye velocity by a semi-automatic computer program developed on Matlab 6.5 (The Math Works), and this was used in calculating the gain and phase delay to target velocity. Relative increase or decrease in the amount of saccadic eye movements per trial was calculated and used for a regression analysis of the fMRI data. The data of three subjects were excluded for further analysis, since they were judged to have pursued a target only by saccadic eye movements.

2.4. fMRI acquisition and analysis

All images were collected by a 1.5 T MAGNEX ECLIPSE 1.5 T Power Drive 250 (Shimazu Marconi) with a standard head coil. The head of each subject was held on by a bite-bar that was set on the head coil. In the overt pursuit task, each scan was acquired with the appropriate slice angle of each subject to include precentral sulcus, lateral occipito-temporal sulcus, and primary visual cortex (V1) [repetition time (TR) = 2000 ms, echo time (TE) = 48 ms, field of view = 192 mm, 64 × 64 matrix, voxel dimensions = 3 mm × 3 mm × 3 mm, 20 slices]. In the covert pursuit and attend-to-stationary target task, each scan covered the whole brain [repetition time (TR) = 3000 ms, echo time (TE) = 48 ms, field of view = 192 mm, 64 × 64 matrix, voxel dimensions = 3 mm × 3 mm × 6 mm, 20 slices].

fMRI time series data were analyzed by using SPM99 (The Wellcome Department of Cognitive Neurology). After correction of slice timing, realignment of head motion, and spatial normalization to the MNI (Montreal Neurological Institute) space and smoothing with a Gaussian filter of 9 mm FWHM, the data were analyzed with multiple regression analysis. Three regressors were defined in common for all tasks. The first regressor was defined as a simple boxcar function weighted 1 for test block (including the continuous and blink conditions) and 0 for rest condition. This regressor modeled increased activity during overt/covert pursuit or attending to a stationary target compared to rest block. The second regressor was defined as a function of parametric modulation weighted −1 for continuous condition, 1 for blink condition, and 0 for rest condition. This regressor represented the relative difference of activity between blink and continuous condition. In the overt pursuit task, the third regressor was defined as a function of parametric modulation weighted values depending on the relative frequency of saccadic eye movements during overt pursuit and weighted 0 for rest condition. One sample t-test was performed for each voxel by using the results of multiple regression analyses of each subject. Statistical significance ($p < 0.05$) of the result of one sample t-test was determined by the analysis based on the spatial extent of each volume of interest defined below to correct for multiple comparisons (Friston et al., 1994).

Our objective was to delineate the areas responsible for the target motion prediction during smooth pursuit eye movements. The areas related to target motion prediction were expected to be included in the areas related to smooth pursuit eye movements because the mechanism of prediction to target motion was suggested to be a subsystem of the mechanisms of smooth pursuit eye movements (Shibata et al., 2005). Therefore, the statistical test of the difference in activities between the continuous and the blink conditions was conducted using the inclusive mask with the areas that significantly increased during both the overt and the covert pursuit compared to each corresponding rest condition at two significant levels ($p < 0.05$corrected and $p < 0.001$uncorrected). Both types of inclusive masks were not only intended for checking whether the activities survive correction done strictly for multiple comparison by large areas but also whether the activities remained in more restricted areas that were related to smooth pursuit eye movements. In addition, another inclusive mask of the dorsolateral prefrontal cortex (DLPFC), defined based on anatomical evidence (Brodmann area 9/46, Buchel et al., 1998; Kim et al., 1999; Cornette et al., 2001; Schmid et al., 2001; Pierrot-Deseilligny et al., 2003), was used. This is because the DLPFC was expected to increase its activity during smooth pursuit eye movements if a task was complicated such that it included target blanking and unpredictable target motion initiation (Schmid et al., 2001; Lencer et al., 2004), while the DLPFC was not expected to increase its activity during simple smooth pursuit eye movements (Petit and Haxby, 1999; Schmid et al., 2001; Lencer et al., 2004). Furthermore, in order to investigate the relation of the MT and MST homologues with target motion

prediction, the representative voxels of each MT and MST of all subjects were determined in advance by replicating the method of Dukelow et al. (2001), except for using between-subjects statistics, i.e. random effect models of subjects.

3. Results

3.1. Behavioral analysis

Fig. 1A shows a sample time series of eye and target velocity in a test block (including the continuous condition and the blink condition). Fig. 1B shows the averaged eye velocity (thick red line) over all eye velocities (thin green lines) acquired in all of the test blocks of this subject and the target velocity (thick black line). Saccadic components were eliminated in the eye velocities. The dark shaded blocks show that the target was vanishing at that time.

Further detailed analyses of eye movements for all subjects were conducted as follows. The average and the standard deviation, over 22 subjects, of the phase delay and the gain of eye velocity to target velocity and the percentage of times that saccades were conducted during a trial were calculated. The results showed that the phase delay was 3.8 ± 20.1 ms in the continuous condition and 15.0 ± 26.4 ms in the blink condition, the gain was 81.7 ± 15.2 and $75.4 \pm 14.5\%$, respectively, and the percentage of saccades increase was 8.8 ± 3.0 and $9.8 \pm 3.2\%$, respectively. The unpaired t-test between both conditions of these measures resulted in the increase in phase delay, the decrease in gain, and the increase in percentage of saccades in the blink condition compared to the continuous condition $t(21) = 3.34$, $p < 0.01$; $t(21) = -6.47$, $p < 0.01$; $t(21) = 5.86$, $p < 0.01$, respectively].
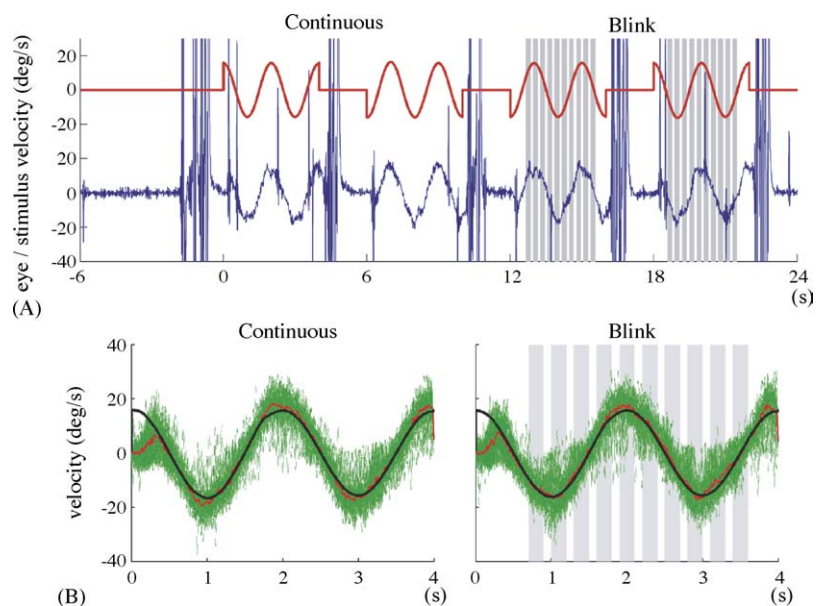

Fig. 1. Eye velocities of a typical subject. (A) A sample time series of eye and target velocity in a continuous condition (0–12 s) and a blink condition (12–24 s). Red and blue lines depict target and eye velocities, respectively. In this figure, the onset is set at the beginning of the continuous condition. Note that subjects were blinking the eyes for 2 s from each point of −2, 4, 10, 16, and 22 s in this figure. The dark shaded blocks show when the target vanished. (B) Averaged eye velocity over all test blocks of this subject (thick red line), overlapped with eye velocities in the test blocks (green lines), and target velocity (thick black line). Saccadic components were eliminated in the eye velocities.

3.2. fMRI analysis

We conducted a series of three tasks: overt, covert, and attend-to-stationary target task. An additional analysis with the MT and MST homologues was also conducted.

First, in the overt pursuit task, the PreCC, MSFC, IPC, LOTC, and V1 increased their activities significantly during smooth pursuit eye movements (test block) compared to during fixation (rest block) [$p < 0.05$, corrected] (Fig. 2A, Table 1). One sample *t*-test between the activities in the blink and continuous conditions was applied to the areas that increased significantly their activities during smooth pursuit eye movements at two significance levels. This test was also applied to the DLPFC. The results showed that the medial and lateral PreCC, MSFC, IPC, and anterior and superior LOTC increased their activities in the blink condition compared to the continuous condition [$p < 0.05$, corrected for multiple comparison for both types of inclusive masks]. The DLPFC also significantly increased its activity in the blink condition

compared to the continuous condition [$p < 0.05$, corrected] (Fig. 2 B, Table 1). In contrast, the V1 decreased its activity in the blink condition compared to the continuous condition [$p < 0.05$, corrected for multiple comparison for both types of inclusive masks] (Fig. 2C, Table 1). We further investigated whether the activities during smooth pursuit eye movements were correlated with the relative changes in saccade frequency. The result showed that the activities in the inferior and superior MSFC and IPC were correlated with relative changes in the saccade frequency [$p < 0.001$, uncorrected] (Table 2).

Second, in the covert pursuit task, the medial and lateral PreCC, IPC, anterior and posterior LOTC, and V1 significantly increased their activities during covert pursuit to the moving target (test block) compared to during attention given to the stationary target (rest block) [$p < 0.05$, corrected]. The DLPFC also increased its activity [$p < 0.001$, uncorrected] (Fig. 2D, Table 1). Along with the overt pursuit task, the difference between the activities in the blink and the continuous condition were tested in each functional area related to covert pursuit at
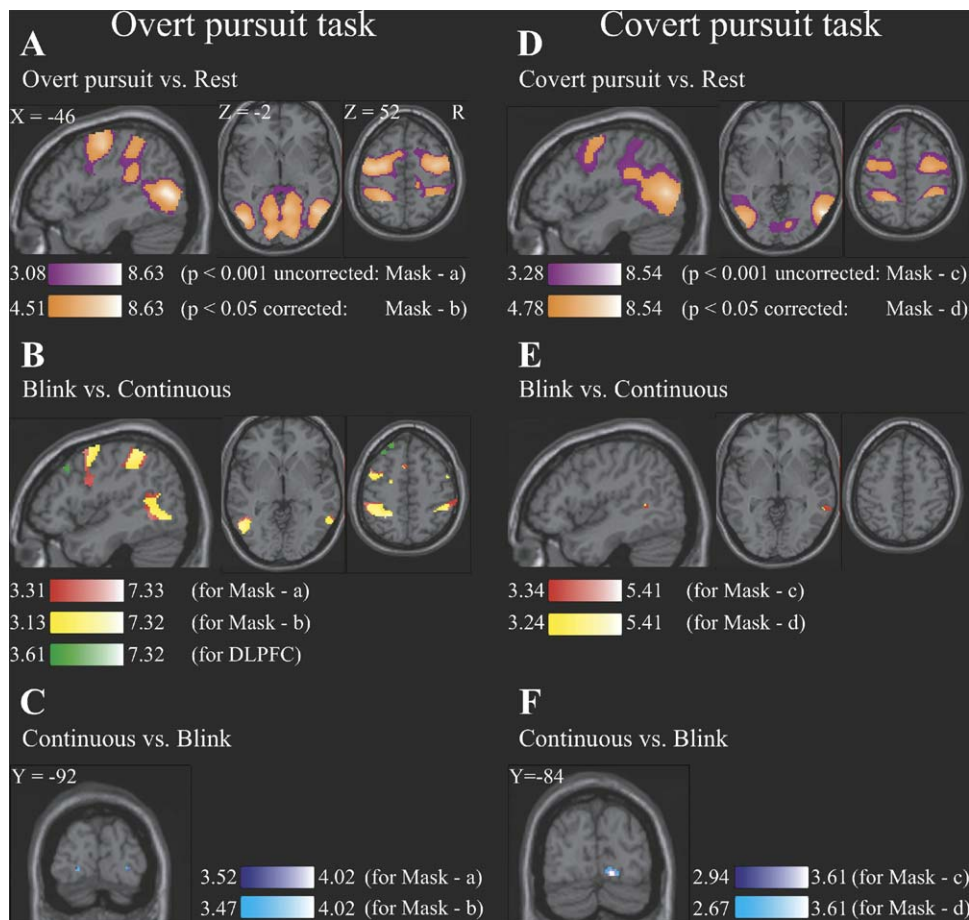

Fig. 2. (A)–(C) and (D)–(F) show the results obtained from the overt and covert pursuit task, respectively. Numerical numbers on the left and right side of each legend indicate the threshold and peak *Z*-score, respectively. (A) The PreCC, MSFC, IPC, LOTC, and V1 exhibited significantly increased activities during smooth-pursuit eye movements compared to fixation. The purple and orange regions were used as inclusive masks (Mask-a and -b, respectively) to test for differences between the blink and continuous conditions. (B) The PreCC, MSFC, IPC, LOTC, and DLPFC significantly increased their activities [$p < 0.05$, corrected for volumes defined by Mask-a (red) and Mask-b (yellow), respectively]. The green region in (B) shows significantly increased activities in the blink condition compared to the continuous condition within the DLPFC (BA 9/46, Buchel et al., 1998; Kim et al., 1999; Cornette et al., 2001; Schmid et al., 2001; Pierrot-Deseilligny et al., 2003) [$p < 0.05$, corrected]. (C) The V1 significantly decreased the activity in the blink condition compared to the continuous condition [$p < 0.05$, corrected for volumes defined by Mask-a (blue) and Mask-b (cyan), respectively]. In the same way, the results obtained from the covert pursuit task are shown in (D)–(F). See Table 1 for details.

Table 1
MNI coordinate and Z-score at peak activities in the overt pursuit, covert pursuit, and attend-to-stationary target tasks

Cortical area	Overt pursuit task								Covert pursuit task								Attend-to-stationary target task			
	Overt pursuit vs. rest				Blink vs. continuous				Overt pursuit vs. rest				Blink vs. continuous				Attention vs. rest			
	x	y	z	Z-score	x	y	z	Z-score	x	y	z	Z-score	x	y	z	Z-score	x	y	z	Z-score
V1																				
Left	−14	−92	0	7.82**	−20	−94	−6	−4.02svc	−10	−86	−10	4.96**	–	–	–	–	−12	−84	−10	3.60*
Right	10	−88	6	7.72**	24	−92	−4	−3.70svc	10	−86	−10	5.61	10	−84	−8	−3.40svc	−12	−88	−10	4.21*
Posterior LOTC																				
Left	−50	−70	6	8.63**	−52	−66	−4	6.18svc	−48	−70	6	7.55**	–	–	–	–	−46	−68	6	3.30*
Right	46	−62	4	8.52**	64	−54	0	4.85svc	52	−66	0	7.90**	–	–	–	–	46	−74	−2	3.88*
Anterior LOTC																				
Left	–	–	–	–	–	–	–	–	−64	−50	12	5.89**	−44	−52	6	3.41svc	–	–	–	–
Right	–	–	–	–	52	−40	10	3.77svc	60	−54	8	6.56**	66	−44	0	3.43svc	–	–	–	–
Superior LOTC																				
Left	–	–	–	–	−54	−60	16	5.66svc	–	–	–	–	–	–	–	–	–	–	–	–
Right	–	–	–	–	34	−72	20	4.58svc	–	–	–	–	52	−72	18	4.83svc	–	–	–	–
IPC																				
Left	−30	−50	52	7.78**	−24	−52	50	6.89svc	−36	−48	58	6.27**	–	–	–	–	−28	−58	48	4.32*
Right	40	−38	48	7.06**	28	−68	40	5.56svc	30	−52	60	6.73**	–	–	–	–	28	−56	56	4.54*
Mesial PCC																				
Left	−30	−6	54	8.14**	−38	−6	64	5.45svc	−28	−6	54	5.63**	–	–	–	–	–	–	–	–
Right	38	−6	52	8.07**	25	2	70	6.06svc	30	−10	52	5.39**	–	–	–	–	–	–	–	–
Lateral PCC																				
Left	−54	0	40	7.94**	−50	10	44	5.80svc	−50	0	40	4.96**	–	–	–	–	–	–	–	–
Right	52	0	46	7.61**	50	8	40	5.00svc	56	2	38	4.96**	–	–	–	–	46	2	34	3.38*
MSFC																				
Left/Right	−4	−2	66	7.76**	−4	14	56	5.66svc	–	–	–	–	–	–	–	–	–	–	–	–
DLPEC																				
Left	–	–	–	–	−32	36	42	5.05svc	−38	24	50	3.44**	–	–	–	–	–	–	–	–
Right	–	–	–	–	34	28	38	4.68svc	–	–	–	–	–	–	–	–	–	–	–	–

'svc' Depicts the significant level $p < 0.05$ (corrected based on interested volumes, see the text for details).
* Depicts the significant level $p < 0.01$ (uncorrected).
** Depicts the significant level $p < 0.05$ (corrected for multiple comparision).

the two significance levels [$p < 0.05$, corrected and $p < 0.001$, uncorrected]. This test was also applied to the anatomically defined area of DLPFC. The results showed that the anterior LOTC in both hemispheres and superior LOTC in the right hemisphere increased significantly their activities in the blink

Table 2
MNI coordinate and Z-score at peak voxels correlated between the activities and the percentage of saccade

Cortical area	Correlation with saccade frequency			
	x	y	z	Z-score
IPC				
Left	−54	−32	58	3.66*
Right	52	−52	46	3.29*
Inferior MSFC				
Left	10	16	40	4.11*
Superior MSFC				
Rright	10	8	74	3.64*

* Depicts the significant level $p < 0.001$ (uncorrected).

condition compared to the continuous condition [$p < 0.05$, corrected for multiple comparison for both types of inclusive masks] (Fig. 2E, Table 1), while the V1 in the right hemisphere significantly decreased its activity [$p < 0.05$, corrected for multiple comparison for both types of inclusive masks] (Fig. 2 F, Table 1).

Third, in the attend-to-stationary target task, the difference in activities was tested between the times when subjects' attention was focused on the stationary target while gazing at the fixation point (test block) and when the subject gazed at the fixation point presented alone on the screen (rest block). The results showed that the lateral PreCC in the right hemisphere, the IPC, and LOTC in both hemispheres increased their activities when the attention was oriented to the stationary target compared to simple gazing at the fixation point [$p < 0.001$, uncorrected] (Table 1). In this task, no significant changes in activities were observed between the blink and continuous conditions.

Finally, a voxel-based analysis was conducted to investigate the results of subtraction of the blink versus continuous
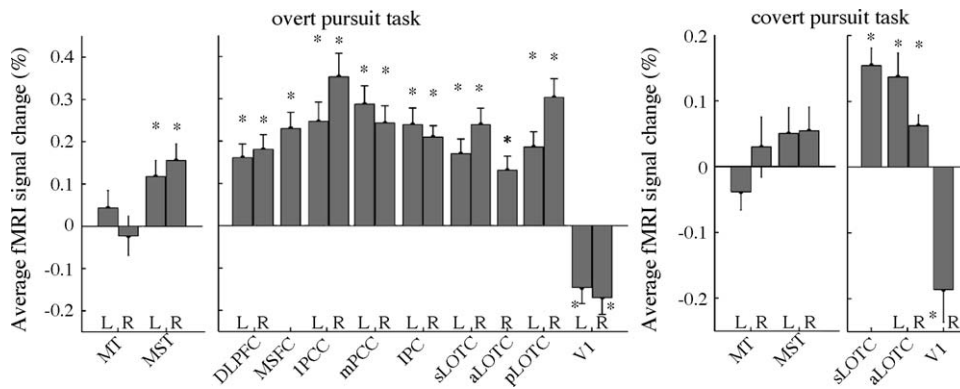
Fig. 3. In overt and covert pursuit tasks, the averaged percentage of fMRI signal changes between blink and continuous conditions at each region, over the subjects. The error bar and asterisk show S.E.M. and significant level of $p < 0.05$, respectively. The 'l', 'm', 's', 'a', and 'p' depict 'lateral', 'medial', 'superior', 'anterior', and 'posterior', respectively. See the body text for details of MT and MST homologues.

conditions in the MT and MST homologues within the LOTC. Fig. 3 depicts the average and S.E.M. of the percentage of fMRI signal changes over the subjects at the representative voxels of MT and MST homologues. In this figure, positive values were given to the areas activated larger in the blink condition compared to the continuous condition. The differences in the percentage of fMRI signal change between the blink and continuous conditions were not significant in the MT homologue [$Z = 1.03$, n.s. and $Z = -0.49$, n.s., in order of each left and right hemisphere]. On the contrary, the MST homologue showed significant increase in activity in the blink condition compared to the continuous condition [$Z = 3.06$, $p < 0.05$ and $Z = 3.89$, $p < 0.05$, respectively]. The same analysis was applied to the covert pursuit task. The activities in MT and MST homologues did not show a significant difference between the blink and continuous conditions [$Z = -1.39$, n.s. and $Z = 0.64$, n.s. in the left and right hemisphere of the MT homologue, respectively; $Z = 1.25$, n.s. and $Z = 1.46$, n.s. in the MST homologue]. Note that the x, y, and z coordinates in MNI (Montreal Neurological Institute) space of the MT homologue was $[-42, -72, 4]$ and $[44, -70, 4]$ at the left and right hemisphere in this order, and that those of the MST homologue were $[-58, -66, 10]$ and $[50, -60, 6]$, respectively. For comparison of these areas with the other areas, Fig. 3 additionally shows the average and S.E.M. of the percentage of

fMRI-signal changes over the subjects at the voxel that exhibited maximum changes in Z-score between the blink and continuous conditions in the overt and covert pursuit tasks. These Z-scores, except for the MT and MST homologues, are shown in Table 1.

4. Discussions

4.1. Prediction of the target motion

There has been much interest in how humans model and make use of the external world in the brain. To approach this question, we conducted fMRI studies mainly focusing on the maintenance phase of smooth pursuit eye movements to a sinusoidal moving target. According to the theoretical argument in Shibata et al. (2005), pursuit to a target moving at constant velocity does not require a model of target motion, but pursuit to a sinusoidally moving target without delay does require knowledge of the model of sinusoidal motion. Accordingly, we demonstrate this fact through simulations by replicating the method of Shibata et al. (2005).

Fig. 4 shows a computationally sound control model of smooth pursuit eye movements depicted in Fig. 4 in Shibata et al. (2005). The dynamics of a target motion was assumed to be a
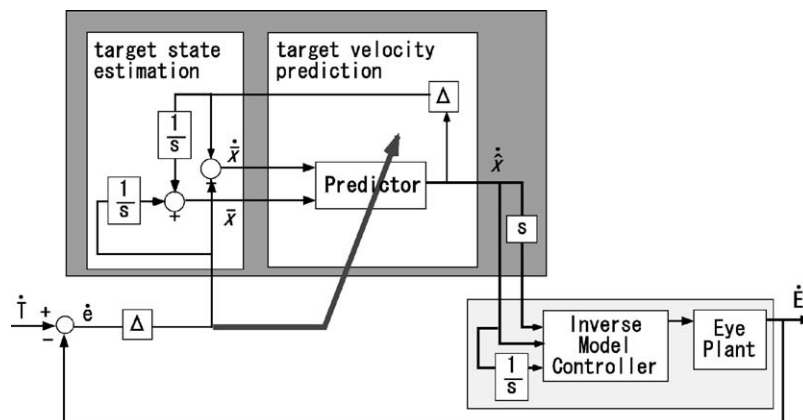

Fig. 4. The control model of smooth pursuit eye movements based on Shibata et al. (2005). The dynamics of the target motion was assumed as a second-order linear system. The dark-shaded block shows the recurrent neural network mapped on MTS. In this figure, 's' and '1/s' depict differentiation and integration, respectively.

second-order linear system that is capable of expressing sinusoidal motion as well as constant velocity motion. This system is able to predict a current target velocity from a past target state, i.e. position and velocity. This network consists of two subsystems: one is the recurrent neural network (RNN, depicted in dark shaded block) mapped onto MST, and the other is the inverse dynamics controller of the oculomotor system mapped onto the cerebellum and the brainstem. In the RNN, prediction of the current target velocity was calculated based on the retinal slip with delays of Δ time and the internal feedback of target state preserved during Δ time. The relation between the predicted target velocities $\dot{\hat{x}}$ and the estimated target state $\bar{X} = [\bar{x}, \dot{\bar{x}}]^{T}$ ($\bar{x}, \dot{\bar{x}}$ are the estimated position and velocity, respectively, and T denotes transpose) was depicted by the following equation using the appropriate network weight w^{T}: $\dot{\hat{x}}(t) = w^{T}\bar{X}(t - \Delta)$. Shibata et al. (2005) showed that the weights can be learned even when the target motion was unknown.

Simulation experiments based on the above framework were conducted with the target of a pyramidal wave motion with amplitude of $15°$ and a cycle of 6 s or a sinusoidal wave motion with amplitude of $5°$ and a cycle of 2 s. In this simulation, the weight w^{T}, however, was not updated and was fixed according to task conditions because such learning of the weight is outside the scope of this paper; w was fixed to $[0, 1]^{T}$ in the pyramidal wave condition; w was fixed to $[-0.9708, 0.9511]^{T}$ in the sinusoidal wave condition. The predicted target velocity output from the predictor was multiplied by the gain of 0.96 because actual gains of less than one were acquired in our overt pursuit task and in the results of Fukushima et al. (2002b), in which sinusoidal signals were presented. Simulation results are shown in Fig. 5. There is no difference between smooth pursuit eye movements of pyramidal target motion with (Fig. 5A) and

without (Fig. 5B) target motion prediction. For the pyramidal target motion, the velocity gain of the eye to the target was close to 1 in the continuous condition and was decreasing slightly during the target blanking period in the blank condition. In contrast, there were significant differences between smooth pursuit eye movements of sinusoidal target motion with and without target motion prediction. In Fig. 5A, the velocity gain was close to 1 and there was no phase delay, even in the blink condition, which contrasted with the results presented in Fig. 5B.

These simulation results demonstrated that target motion prediction was crucial to the pursuit of a sinusoidally moving target, which continuously changes its velocity, without phase delay. Without target motion prediction, the pursuit performance deteriorated even further when the retinal input of the target was absent. In contrast, these results suggest that research for smooth pursuit eye movements that solely utilizes pyramidal wave motion, such as Lencer et al. (2004), is not able to assess whether the subjects actually predicted the target motion. Thus, we employed a sinusoidal signal for the target motion and confirmed that our subjects performed the predictive pursuit of the sinusoidal target motion with nearly no delay, not only in the continuous condition but also in the blink condition (Fig. 1B). Although the increase in phase delay in the blink condition was significant compared to the continuous condition, the delay of 15.0 ms in the blink condition was certainly smaller than the delay of 60 ms observed in monkeys (Churchland and Lisberger, 2001; Churchland et al., 2003), approximately 200 ms in human smooth pursuit to a small spot (Madelain and Krauzlis, 2003), and at least 70 ms in human smooth pursuit to a cluster of dots (Miura et al., 2001).
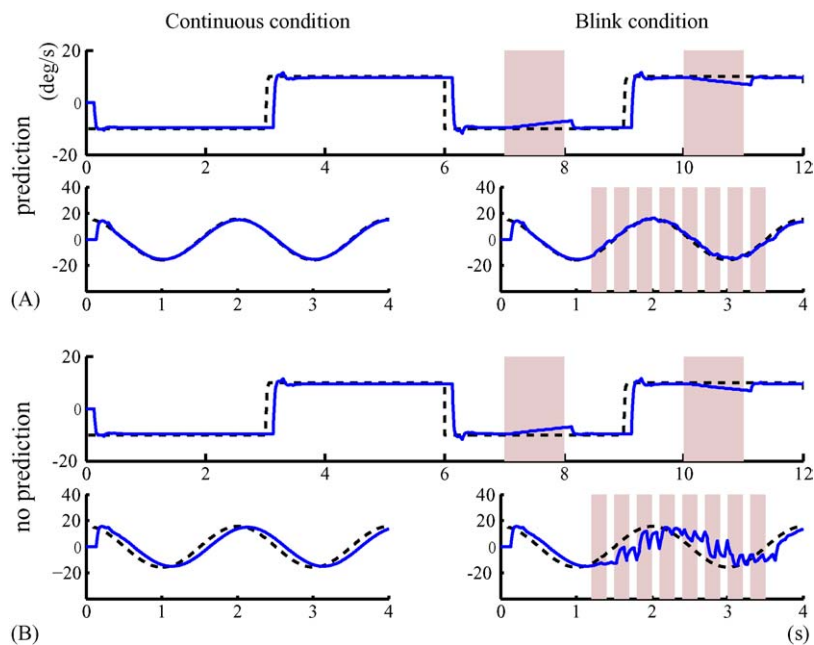

Fig. 5. The results of simulation experiment on smooth pursuit eye movements based on the model (Shibata et al., 2005) (A) and the results based on another model in which the target motion prediction was not performed (B). The upper and lower column in each category (A and B) depicts the simulation result of pursuit to pyramidal wave (amplitude: $15°$, cycle: 6 s) and sinusoidal wave (amplitude: $5°$, cycle: 2 s), respectively. Each blue and black line shows eye and target velocity, and the light red regions depict the target blinking periods.

4.2. Activities related to the target motion prediction

First, in the overt pursuit task, the PreCC, MSFC, IPC, and LOTC increased their activities during pursuit compared to fixation in line with previous studies (Petit and Haxby, 1999; Schmid et al., 2001; Lencer et al., 2004), and V1 also increased its activity (Fig. 2A). In these areas, the activities in the blink condition were statistically compared to the continuous condition in our overt pursuit task. The results showed that the PreCC, MSFC, IPC, LOTC, and DLPFC significantly increased their activities in the blink condition compared to the continuous condition, while V1 significantly decreased its activity (Fig. 2B and C). These results suggest the increased activities in the PreCC, MSFC, IPC, and DLPFC are related to the extraretinal signals such as the target motion prediction, attention, and efference copy of motor command (Schmid et al., 2001; Lencer et al., 2004) rather than the visual inputs.

This increased activity in LOTC differentiates our study from the previous study (Lencer et al., 2004) that used a similar paradigm to ours. We conjecture that this increased activity in LOTC is due to the target motion prediction based on the following reasoning. First of all, the retinal slip information was not available during the target blinking periods in the blink condition. Nevertheless, the recorded eye movements showed that the outcome of eye movements in the blink condition was almost the same as in the continuous condition. Therefore, within the neural circuit responsible for eye motor command generation, it was necessary to increase some kinds of extraretinal signals to compensate for the lack of retinal slip information. This increase in the extraretinal signals would bring an increase in the LOTC activity. Next, it is most possible that the extraretinal signals are composed of an efference copy of the oculomotor command, prediction of the target motion which continuously changes, increased attention, and other possible factors. Among these elements, only target motion prediction exists solely during the pursuit of sinusoidal motion rather than during the pursuit of constant velocity motion, which was used in Lencer et al. (2004).

Second, activities in some areas that increased during the blink condition compared to continuous condition in the overt pursuit task were not only attributable to the predictive aspect of extraretinal signals, but also to the efference copy of the oculomotor command. The covert pursuit task was conducted for studying the activity related to target motion prediction and while eliminating the effect of the oculomotor command among the extraretinal signals. In the covert pursuit task, the PreCC, IPC, LOTC, and V1 increased their activities during covert pursuit of a sinusoidally moving target compared to focusing attention on a stationary target (Fig. 2D). Possible reasons for the increased activities could be spatial attention, target motion prediction, and visual inputs. It was suggested that spatial attention plays an important role in generating eye movements; for example, Hoffman and Subramaniam (1995) show that spatial attention was inevitably oriented to the goal-position of the eyes before the saccade. It was also suggested that the processing of attention and eye movements were integrated at a neural level, since the functional areas related to the shift of

attention and the attention to motion overlapped the areas related to eye movements in fMRI experiments (Buchel et al., 1998; Corbetta et al., 1998; Nobre et al., 2000; Beauchamp et al., 2001). We concluded that our subjects performed covert pursuit by very similar neural mechanisms as overt pursuit except for refraining from moving their eyes, because our finding that the activity areas during covert pursuit were almost the same as the overt pursuit task, except for the visual cortex, was consistent with the previous studies (Fig. 2A and D in our manuscript). Therefore, it could be possible to investigate activities related to target motion prediction by comparing the blink condition with the continuous condition also in the covert pursuit task, on the same reasoning which we discussed regarding the overt pursuit task.

We showed that the bilateral anterior LOTC and superior LOTC in the right hemisphere increased their activities in the blink condition compared to the continuous condition, whereas V1 decreased its activity (Fig. 2E and F). According as we discussed in the overt pursuit task, these results suggest that the LOTC activity is related to target motion prediction rather than the visual inputs. In contrast, the increased activities in the DLPFC, PreCC, MSFC, and IPC were not observed during the blink condition compared to the continuous condition, unlike the case of the overt pursuit task. This difference indicates that the frontoparietal network for smooth pursuit eye movements during target blinking is involved mainly in the oculomotor command and its efference copy.

Third, in the attend-to-stationary target task, the PreCC, IPC, LOTC, and V1 increased their activities when the spatial attention was oriented to the stationary target while gazing at the fixation point compared to the rest condition. These increased activities related to orientation of the spatial attention and visual inputs are in line with the knowledge that the frontoparietal network and LOTC is involved in the spatial attention (Buchel et al., 1998; Corbetta et al., 1998; Kim et al., 1999; Beauchamp et al., 2001). The activities between the blink and continuous conditions were statistically compared in order to investigate whether the increased activities during the blink condition in the overt and covert pursuit task were due to the ON- and OFF-response of the visual neuron or were attributed to an enhancement in subjects' attention to the target. The results showed that no areas had significant differences between the two conditions, suggesting that the increase in LOTC activities during the target blinking in the overt and covert pursuit tasks was due to target motion prediction rather than to the effect of blinking on visual neurons or to the attention.

Additionally, in the MST homologue, though not in the MT homologue, the activity in the blink condition increased compared to the continuous condition in the overt pursuit task. Also, in the covert pursuit task, the increased activity in the MST homologue was not significant; however, compared to the MT homologue, it did show a clearer inclination in the blink condition than in the continuous condition. This result suggests the involvement of the MST homologue in target motion prediction.

The activated cortical areas related to pursuit have been referred to cortical eye fields in which the cortical areas are

networked by connecting each other (Tian and Lynch, 1996; Petit and Haxby, 1999). In this study, we took a particular emphasis on the extraretinal signals which is crucial to maintaining pursuit even when a target was blinked. By conducting a series of experiments, we tried to dissociate neural activities related to aspects such as target motion prediction, efference copy of oculomotor command, attention among the extraretinal signals, and visual inputs. According to the results, we speculate that the recurrent connection through the cortical areas would be enhanced in LOTC (especially in MST) when a target motion is being predicted for maintaining smooth pursuit and, moreover, that the IPC and PreCC receiving the predicted information of the target and the DLPFC originating the working memory and attention would support smooth pursuit eye movements having no delay and high gain.

4.3. Comparison with previous studies

4.3.1. Lateral occipito-temporal cortex

As has been discussed, the LOTC should play an important role in target motion prediction, which is consistent with previous studies as follows. Fig. 6 shows a summary of our results superimposed on a figure presented in Maquet et al. (2003) illustrating a lateral view of a glass brain with the results of previous studies related to MT/V5, smooth pursuit eye movements, biological motion, motor intention, the imitation of action, and trajectory learning (see Fig. 6 for the related references). Maquet et al. (2003) reported that 'MT/V5's were distributed in the posterior of the LOTC, whereas the regions related to biological motion were located in more anterior areas
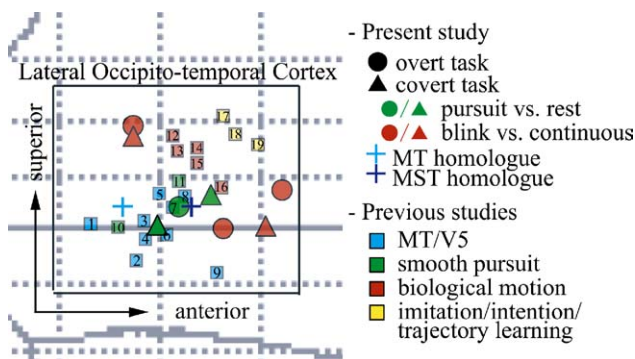

Fig. 6. Comparisons with previous studies. In the present study, peak voxels on the Z-score in the right hemisphere of LOTC are described as a combination of shapes and colors. Circles and triangles denote the overt and covert pursuit tasks, respectively, and green and red denote the peak voxel of overt or covert pursuit vs. rest and that of the blink condition vs. the continuous condition, respectively. Each MT or MST homologue is represented by a light or dark blue cross, respectively. Light blue, green, red, and yellow denote the results of previous research related to MT/V5, smooth-pursuit eye movements, biological motion, and higher-order motion (imitation of action, motor intention, and trajectory learning), respectively. See the following references for details of each numbered site: (1) Tootell et al. (1995); (2) Buchel et al. (1998); (3) Dumoulin et al. (2000); (4) Watson et al. (1993); (5) Dukelow et al. (2001); (6) Morrone et al. (2000); (7) Dukelow et al. (2001); (8) Morrone et al. (2000); (9) Friston and Buchel (2000); (10) Petit and Haxby (1999); (11) Schmid et al. (2001); (12) Bonda et al. (1996); (13) Grossman et al. (2000); (14) Vaina et al. (2001); (15) Castelli et al. (2000); (16) Puce et al. (1998); (17) Iacoboni et al. (2001); (18) Maquet et al. (2003); (19) Toni et al. (2001).

than the 'MT/V5's, and that the regions related to motor intention, imitation of action, and trajectory learning were located in the even more anterior areas. Our results showed that activities responding to the overt and covert pursuit, compared to each rest condition overlapped the anterior part of the 'MT/V5's. On the other hand, activities in the blink condition compared to the continuous condition in both the overt and covert pursuit tasks were along the regions relevant to biological motion. The alignment of functional mapping seems to be related to the difficulty level of the tasks. Subjects would be familiar with sinusoidal signals as well as biological motions that are relatively easy compared to the higher-order cognitive tasks that require subjects to develop the internal representation of appropriate actions for performing the tasks (Iacoboni et al., 2001; Toni et al., 2001; Maquet et al., 2003) in a short period, i.e. several days or hours.

In contrast, our results were partly inconsistent with Lencer et al. (2004) in the point that they reported no significantly increased activity in the LOTC in the condition when the target was blanked compared to when it was not blanked. This difference could be attributed to the following two reasons. First, the increased activity in the LOTC during the blink condition in our overt and covert tasks is assumed to be mainly caused by the target motion prediction among the extraretinal signals, such as the prediction, motor command and its efference copy, and attention. In contrast, Lencer et al. (2004) used a pyramidal wave task in which subjects were not required to predict the target motion. Our subjects performed smooth pursuit without phase delay and with high velocity gain even in the blink condition, while the eye velocities of their subjects began to decrease at about 150 ms and almost decayed at 500 ms after the target vanished. Note that 1 s of blanking period used by them would be extremely longer than period of maintaining smooth eye velocities, e.g. about 100 ms (Churchland et al., 2003), 150 ms (Kawano et al., 1994), 300–400 ms (Fukushima et al., 2002b) in monkey subjects, and about 200 ms (Madelain and Krauzlis, 2003) in human subjects. Second, they used a projector to present a target, allowing subjects to see the background and its motion caused by their eye movements. Since the neurons of the LOTC are sensitive to wide field motion stimuli (Zeki et al., 1991; Watson et al., 1993; Tootell et al., 1995; Dukelow et al., 2001), their results could be affected by such motion, depending on the eye movements. On the contrary, no background motion occurred in our study, since a laser spot moved by a galvano mirror system permitted the experiment room to be completely dark.

4.3.2. Precentral cortex

It has been shown that the PreCC includes the frontal eye field (FEF) (Luna et al., 1998; Petit and Haxby, 1999). Our results suggest that the PreCC is related to motor command, the efference copy of the motor command, and attention rather than to target motion prediction, which is supported by the report of Lencer et al. (2004) indicating that the increased activity in the FEF should be mainly attributed to the increased reliance on the efference copy because the FEF neurons presumably encode the three-dimensional representation of

smooth pursuit eye movements using efference copy (Fukush- ima et al., 2002a). Furthermore, Fukushima et al. (2002b) showed that the firing rate of some FEF neurons of a monkey subject increased during smooth pursuit eye movements when a target was blanking compared to when it was not blanking. They further showed that the FEF neurons were modulated by the changes in target velocity even when the target was blinking or blanking in their task similar to our covert pursuit task. Our results for the PreCC are consistent with their results for the FEF; the activities during the blink condition increased more than during the continuous condition in the overt pursuit task, and the activities did not significantly increase in the covert pursuit task. Although we did not measure the changes in BOLD signals modulated according to the changes in target velocity, we at least were able to measure the increased activities presumably related to an extraretinal mechanism for maintaining smooth pursuit eye movements, even when a target was blinking.

4.3.3. Medial superior frontal cortex

The areas related to smooth pursuit eye movements in the MSFC are often referred to as SEF or pre-SEF. These areas are presumably involved in the predictive mechanism of smooth pursuit eye movements (Petit and Haxby, 1999). The SEF increased the activity associated with the learning of a visuo-motor sequence and the execution of a memorized sequence, while the pre-SEF could be activated when it was necessary to plan and memorize new task sequences (Heide et al., 2001). Furthermore, Lencer et al. (2004) stated that the increase in these activities could be affected by the increased frequency of saccades during target blanking. We found that the MSFC was relevant to the overt pursuit task only, and that the MSFC was correlated with the relative change of saccade frequency, suggesting that the MSFC activity reflects the aspect of motor command execution in smooth pursuit eye movements, which is consistent with the findings from the previous studies.

4.3.4. Intraparietal cortex

It has been shown that the IPC is active during smooth pursuit eye movements (Petit and Haxby, 1999; Beauchamp et al., 2001; Schmid et al., 2001; Lencer et al., 2004). The IPC also increases its activity in the task condition with unpredictable target initiation (Schmid et al., 2001) or with a target blanked (Lencer et al., 2004), which is consistent with our result acquired in the IPC in the overt pursuit task. The increased activity in the IPC during pursuit to a blinking target in the overt pursuit task is presumably due to functions of orienting the spatial attention (Buchel et al., 1998; Corbetta et al., 1998; Gitelman et al., 1999; Kim et al., 1999; Nobre et al., 2000; Beauchamp et al., 2001) and spatial transforma- tion using efference copy (Heide et al., 2001), because an internal representation of the target motion is exclusively derived from the extraretinal signal such as spatial attention, transformation, and orientation for maintaining smooth pursuit eye movements (Lencer et al., 2004). The activity in this area was inclined to correlate with the relative change in

saccade frequency, suggesting that this area is related to saccades during smooth pursuit eye movements. Furthermore, this area increased its activity during covert pursuit and attending to the stationary target while gazing at the fixation point, suggesting that the activity is affected by the shift of attention involved in saccades (Corbetta et al., 1998; Gitelman et al., 1999; Kim et al., 1999; Nobre et al., 2000; Beauchamp et al., 2001).

4.3.5. Dorsolateral prefrontal cortex

The DLPFC has been investigated in research related to attention, working memory, and action selection guiding for goal-directed motor action. The DLPFC plays the role of the oculomotor inhibition for preparing saccades, the spatial short- term memory, and the anticipation of saccades, depending on the internal and external environment during decision making (Pierrot-Deseilligny et al., 2003). The DLPFC also plays a role in completing such complicated tasks as unpredictable initiation of a target (Schmid et al., 2001) and of target blanking (Lencer et al., 2004), both in smooth pursuit eye movements. According to the knowledge on the DLPFC, it is suggested that the increased activity in the DLPFC in the overt pursuit task plays an important role in subserving smooth pursuit eye movements during target blinking using working memory and attention. The tendency of increasing activity in this area during covert pursuit also suggests that this activity is attributed to attention.

4.3.6. V1

Within V1, a more activated region in the continuous condition than in the blink condition in the overt pursuit task was located in the occipital pole, while such region in the covert pursuit task was located in the inferior bank of the calcarine sulcus. Note that the target in the overt pursuit task was consistently lying on fovea except when it was blinking, while the target in the covert pursuit task was moving in the upper visual field. Thus, these results were consistent with those of the previous studies on the retinotopic mapping in V1.

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