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Spatiotemporal properties of eye position signals in the primate central thalamus

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Abstract

Although both sensory and motor signals in multiple cortical areas are modulated by eye position, the origin of eye position signals for cortical neurons remains uncertain. One likely source is the central thalamus which contains neurons sensitive to eye position. Since the central thalamus receives inputs from the brainstem, these neurons may transmit eye position signals arising from the neural integrator or from proprioceptive feedback. However, since the central thalamus also receives inputs from many cortical areas, eye position signals in the central thalamus could come from the cerebral cortex. To clarify these possibilities, spatial and temporal properties of eye position signals in the central thalamus were examined in trained monkeys. Data showed that eye position signals were decomposed into horizontal and vertical components, suggesting that the central thalamus lies within pathways that transmit brainstem eye position signals to the cortex. Further quantitative analyses suggested that two distinct groups of thalamic neurons mediate eye position signals from different subcortical origins, and that the signals are modified dynamically through ascending pathways. Eye position signals through the central thalamus may play essential roles in spatial transformation performed by cortical networks.

Introduction

Information of orbital eye position is essential to compute egocentric, head-centred locations of visual stimuli, or to plan direction and amplitude of saccades toward auditory or somatosensory targets. Previous studies have shown that both sensory and motor signals in the cerebral cortex are modulated by eye position. In the parietal cortex, orbital eye position alters gains of visual (Andersen and Mountcastle, 1983; Galletti and Barraglini, 1989; Andersen et al., 1990; Galletti et al., 1995; Bremmer et al., 1997; DeSouza et al., 2002; Siegel et al. 2003), auditory (Stricanne et al., 1996; Fu et al., 2004) and eye movement (Andersen et al., 1990; Bremmer et al., 1997) signals, while in the frontal cortex, both motor and preparatory signals for somatic movements are modulated by eye position (Boussaoud, 1995; Mushiake et al., 1997; Boussaoud et al., 1998; Baker et al., 1999). Although importance of eye position signals for spatial transformation is obvious, and neuronal modulation by eye position is a ubiquitous finding in the cerebral cortex, the origin of eye position signals for these cortical neurons remains uncertain.

One likely source of eye position signals in the cerebral cortex is the central thalamus: a subset of neurons in and around the anterior intralaminar nuclei of the primate thalamus showed persistent activity that was modulated as a function of eye position (Schlag-Rey and Schlag, 1984; Wyder et al., 2003). For oculomotor control, it is widely accepted that command of eye position is computed by the brainstem circuitry called 'velocity-to-position integrator' that calculates the time integral of eye movement (velocity) signals (Robinson, 1981; Fukushima et al., 1992). Since neurons in the central thalamus receive inputs from brainstem nuclei consisting of the neural integrator including the nucleus prepositus hypoglossi (Kotchabhakdi et al., 1980), the interstitial nucleus of Cajal (Kokkoroyannis et al., 1996) and the vestibular nuclei (Lang et al., 1979; Magnin and Kennedy, 1979), the central thalamus may transmit a copy of subcortical eye position signals to the cerebral cortex.

However, given that most thalamocortical projections are reciprocal, eye position signals in the central thalamus could reflect signals that are processed within the cortex. Although it is not known whether neural integrators exist in the cerebral cortex, a sustained activity related to eye position has been

reported in multiple cortical areas. For examples, neurons in parietal 7a, LIP (Andersen et al., 1990), V6A (Galletti et al., 1995; Nakamura et al., 1999), and MST (Squatrito and Mioli, 1996; Bremmer et al., 1997), as well as in the frontal (Segraves, 1992; Tanaka and Fukushima, 1998) and supplementary (Schlag et al., 1992) eye fields show eye position–related activities. In the parietal cortex, the preferred directions of these eye position neurons and the above-mentioned eye position gain fields distribute all directions relative to the recorded hemisphere including oblique directions, and relationships between firing of individual neurons and eye positions containing non-linear elements for many neurons (LIP and 7a, Andersen et al., 1990; V6A, Galletti et al., 1995; Nakamura et al., 1999; MST, Bremmer et al., 1997; V3A, Galletti and Barraglini, 1989). This is in contrast to linear eye position signals in the brainstem where horizontal and vertical eye position signals are processed separately, and the optimal direction of individual neurons is found along the cardinal axis (Robinson, 1981; Fukushima et al., 1992). Differences in distribution of preferred directions and the linearity of individual neurons suggest that cortical and subcortical eye position signals are computed separately, or alternatively, subcortical eye position signals provided through the thalamus are further integrated in the cerebral cortex.

To examine the possible role of the central thalamus in relaying brainstem eye position signals to the cortex, the present study analyzed spatial and temporal properties of eye position–related neuronal activities in the central thalamus of monkeys. Unlike the two previous studies that examined thalamic eye position signals during spontaneous eye movements (Schlag-Rey and Schlag, 1984) or for a relatively small number of neurons ($n = 6$; Wyder et al., 2003), the present study used controlled experimental paradigms to quantitatively examine the activity of many thalamic neurons. Data showed that eye position signals in the central thalamus were decomposed into horizontal and vertical components, suggesting that the central thalamus lies within pathways that transmit brainstem eye position signals to the cortex. Further quantitative analyses also suggested that two distinct groups of thalamic neurons mediate eye position signals from different subcortical origins, and that eye position signals are modified dynamically through these ascending pathways.

Materials and Methods

Animal preparation

Experiments were conducted on three Japanese monkeys (*Macaca fuscata*, one male, two females, 6–12 kg). All experimental protocols were approved in advance by the Animal Care and Use Committee of the Hokkaido University School of Medicine, and were in accordance with the NIH Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Following initial chair training, a pair of head holders was implanted to the skull using titanium screws and dental acrylic under general halothane and pentobarbital anaesthesia, and using sterile procedures. A coil of stainless steel wire was implanted under the conjunctiva using separate surgical procedures to record eye movements. During subsequent training and experimental sessions, the monkey's head was secured to the primate chair, and horizontal and vertical eye position was recorded using the search coil technique. After training for oculomotor tasks, a recording cylinder was installed over a small craniotomy under the same surgical conditions. Animals received analgesia by either suppository acetaminophen or intramuscular injection of pentazocine or ketoprofen after each surgery. Topical antibiotics were administered around the implant and in the cylinder as necessary. Water intake was controlled daily so that monkeys were motivated to perform oculomotor tasks.

Visual stimulus and behavioural paradigms

Experiments were controlled by a Windows-based real-time data acquisition system (TEMPO, Reflective Computing) running on Pentium PCs. All events were updated every 5 ms, and visual stimuli were presented on a 24-inch cathode-ray tube monitor (SONY GDM-FW900, refresh rate: 60 Hz) that was located 38 cm away from the eyes, and subtended 64 x 44° of visual angle. A 0.5° square spot served as a visual stimulus. Targets of different colours (red, white, green) were used for different purposes in the trials (see below). Experiments were carried out in a darkened booth. Horizontal and vertical eye position signals were calibrated before each experiment by having monkeys fixate a stationary target spot at known visual angles. Thereafter, visual stimuli were presented in individual trials, and monkeys were rewarded

with drops of water or apple juice for maintaining eye position within a 'window' that surrounded the target position throughout each trial. A trial was aborted and followed by a newly selected trial if monkeys failed to maintain eye position within a specified window.

The present study used three saccade tasks as shown in Fig. 1. In both the memory-guided saccade task and the visually-guided saccade task, a stationary red spot (2.0 cd/m^2) was used for initial fixation, and a white spot (2.3 cd/m^2) was used to induce eye movements. In the re-fixation saccade task, a green spot (1.7 cd/m^2) was used as the fixation target and the saccade target. Direction of the target step was in any of 8 directions including four cardinal directions and four 45° oblique directions. Trials of different types and in different directions were presented in a random order within a block.

Memory-guided saccade task.　　　This task was used to search for and classify task–related neurons. During central fixation of 800–1,200 ms, a white target spot appeared at 16° in the periphery for 200 ms. Monkeys were required to remember the location of the peripheral target, and to maintain fixation at the centre of the screen for an additional 1 s. Once the fixation point disappeared, monkeys made a saccade to the remembered location within 400 ms. The peripheral target reappeared at the same location 400 ms after fixation point offset, and was visible for an additional 800–1,200 ms until the end of the trial. Size of the eye position window was 2° during initial fixation, and was 3–4° for the saccade target. The second fixation interval was introduced to examine eye position–related activities during fixation of a peripheral target, and to temporally dissociate the responses to saccades and those to rewards.

Visually-guided saccade task.　　　After a random fixation interval of 800–1,200 ms, the fixation point disappeared and a white target spot appeared 10–40° peripherally. Monkeys were required to make a saccade to the target within 400 ms. The saccade target remained stationary and visible for 1,600–2,000 ms until the end of the trial. The fixation target was presented within a range of ± 20° along the preferred axis of the neuron under study. The task was used to quantify eye position sensitivities and to examine effects of preceding saccade directions on eye position–related neuronal activity.

Re-fixation saccade task.　　This task was also used to examine the hysteretic nature of thalamic eye position signals within each trial. A green fixation target appeared at the centre of the screen for

1,100–1,600 ms. The target was displaced by 12°, and was visible for 800 ms following saccade initiation that was detected when eye position entered a ± 3° window surrounding the target. After offset of the peripheral target, monkeys were required to make a second, return, saccade to the location of the initial fixation without any visual guidance (i.e., memory-guided saccade; Tanaka, 2005a). Trials were aborted if eye position was deviated more than 3° from the central target that reappeared 400 ms after offset of the peripheral target. In successful trials, the central target remained visible for an additional 800–1,000 ms, and monkeys were rewarded at the end of the fixation interval.

Physiological procedures

A tungsten microelectrode (Frederick Haer) was lowered through a 23-gauge guide tube using a hydraulic micromanipulator (Narishige, MO-97S). At the beginning of each experimental session, location of electrode penetration was adjusted using an X-Y stage attached to the top of the cylinder, and the guide tube was advanced 10–15 mm from the surface of the intact dura. Signals through the electrodes were amplified, filtered, and monitored using oscilloscopes and an audiomonitor. Once the task–related neuronal activity was obtained, spikes of single neuron were isolated using a real time spike sorter with template-matching algorithms (Alpha Omega, MSD). The optimal direction of each neuron was determined by changing directions of targets in 45° steps. Occurrence of action potentials was time-stamped, and was saved in files with data of eye movements, location and timing of visual stimuli during the experiments.

Data acquisition and analysis

Horizontal and vertical eye position signals were directly obtained from the eye coil electronics (Enzanshi Kogyo, MEL-25). Data were digitized at 1 kHz, and were stored in appropriate files during the experiments for further off-line analysis that was performed using Matlab (Mathworks).

For each neuron, data were aligned on either the initiation of saccades or the onset and offset of visual stimuli. Saccades were detected using automated algorithms. After applying a 29-point finite impulse response filter to eye position data, horizontal and vertical eye velocities were obtained by digital

differentiation. Saccade onset was defined as the time when the net eye speed exceeded 40°/s, and offset was defined when it crossed 20°/s on the way back to zero. Data were removed from analysis if duration of saccade was shorter than 10 ms or longer than 200 ms, and if amplitude of the saccade was less than half of the magnitude of the target step. Traces of horizontal and vertical eye positions were reviewed with rasters and spike density profiles that were constructed from neuronal data. To obtain spike densities, means of the millisecond-by-millisecond occurrence of action potentials across multiple trials were convolved using a Gaussian filter. The σ of the Gaussian was 15 ms to reveal time courses of individual neuronal activity, and was 10 ms to measure latency of neuronal activity (see the following paragraph). Other quantitative measures were performed on the basis of spike counts for specific time windows. Analytical measures are reported in the relevant text in the Results.

Latencies of eye position–related and saccade–related activities were measured using the receiver operating characteristics (ROC) analysis (Green and Swets, 1966) that was previously applied to determine cortical neuronal latency (Thompson et al., 1996; Tanaka and Lisberger, 2002). Firstly, data of neuronal activity were aligned on the initiation of memory-guided saccades in the preferred direction (Fig. 5A). Then, trial-by-trial distribution of firing rates at a given time ("Test") was obtained by computing the spike density ($\sigma = 10$ ms) for each trial, and was compared with the distribution of activity 300 ms before fixation point offset ("Baseline"). The ROC curve was constructed by computing the "Hit rate" and the "False-Alarm rate" on a millisecond-by-millisecond basis for the interval starting from 300 ms prior to and 900 ms after saccades. The Hit rate represented proportion of data in the Test distribution that exceeded a given criterion, and the False-Alarm rate represented proportion in the Baseline distribution exceeding the same criterion. The level of the criterion varied from zero to a maximal value in distributions in a step of either 5 spikes/s or a smaller value so that the number of criteria was ≥ 25. Area under the ROC curve represented the choice probability indicating how well an ideal observer could discriminate these two distributions. The ROC values were plotted as a function of time (Fig. 5A), and the first time when the value exceeded 0.75 for more than 5 ms was measured as the onset of neuronal activity.

Histological procedures

Sites of recorded neurons for two monkeys were reconstructed from histological sections. The third monkey is still in use for another project. At the end of the experiments, several electrolytic lesions were made by passing negative current (10–20 µA) through the recording electrodes for 30–40 s. Monkeys were deeply anaesthetized with lethal dose of pentobarbital ($\geq$ 50 mg/kg), and were perfused transcardially with 0.1 M phosphate buffer followed by 10% formalin with 5% picrotoxine. Then, the brain was removed, blocked, and fixed with the same solution overnight. Once the brain was equilibrated with 0.1 M phosphate buffer containing 30% sucrose, histological sections (50 µm thick) were cut using a freezing microtome. Sections were stained with cresyl violet.

Results

Localization of eye position–related neurons

A total of 43 eye position–related neurons were recorded from 4 thalami of 3 monkeys. Activity of some of these neurons during smooth pursuit eye movements was analyzed in the previous study (Tanaka, 2005b). The present study focuses on the activity of these neurons during fixation and saccades, and their properties will be compared with the activity of the other 132 saccade–related neurons recorded from the same animals. Figure 2 plots locations of both types of neurons for 3 hemispheres of 2 monkeys. Most of saccade-related neurons were located in the paralaminar regions of the ventrolateral (VL) and ventroanterior (VA) nuclei, while some were recorded from the anterior group of the intralaminar nuclei and the lateral edge of the mediodorsal (MD) nucleus of the thalamus. Eye position–related neurons were found either at the dorsal surface, or $\geq$ 3 mm deep in the central thalamus, consistent with the previous study (Schlag-Rey and Schalg, 1984). Histological examination showed that the dorsal group of eye position–related neurons distributed rather sparsely and was located around the rostral part of the lateral dorsal nucleus (LD), and a few were located in the caudal part of the anteroventral nucleus (AV). Neurons belonging to the ventral group were located either within the centrolateral nucleus (CL) or the adjacent VL of the thalamus. There was a slight tendency for neurons with a preference for contralateral eye position to

be located dorsally. Most of eye position–related neurons in the ventral group discharged before saccade initiation, whereas those in the dorsal group modulated their activity following saccades. Differences in dynamics of neuronal activities between the groups are analyzed below.

Comparison of directional preferences between eye position–related and saccade–related neurons

Horizontal and vertical eye position signals are processed separately at the level of the brainstem (Robinson, 1981; Fukushima et al., 1992), while many eye position neurons in the cerebral cortex show preferences for oblique directions (Anderson et al., 1990; Galletti et al., 1995). It is therefore important to analyze the overall distribution of directional preferences of individual eye position–related neurons in the central thalamus to begin to understand the origin of these signals.

The directional preference of each thalamic neuron was examined by having monkeys perform memory-guided saccades in 8 different directions. Figure 3A shows a representative example of an eye position–related neuron that had a preference for ipsilateral eye position. The neuron discharged shortly before the initiation of rightward saccades (vertical line), and showed a sustained activity as long as the monkey fixated a peripheral target that reappeared after the termination of memory-guided saccades (diamond in each raster). For comparison, Fig. 3B plots an example of a saccade–related neuron that exhibited a strong burst of activity for saccades in the right-up or upward directions, but showed no change in activity for saccades in other directions. Among 70 saccade–related neurons that were formally tested in 8 directions, 41 neurons showed a directional modulation like the example shown in Fig. 3B. Other neurons showed a response that was insensitive to direction of saccades like the example shown in Fig. 3C. For each neuron, directional preference was assessed by fitting a Gaussian curve (least squares) to the mean of firing rates that were measured at a specific time window for trials in different directions. For eye position–related neurons, the time window was a 500-ms period starting from 300 ms after the initiation of saccades. For saccade–related neurons, the time window lasted 150 ms, and was located within the interval from 150 ms before to 300 ms after saccade initiation to obtain a maximal value across 8 saccade directions. Figures 3D and E illustrate directional tunings of the neurons shown in Figs. 3A and

B, respectively. Preferred directions of these neurons were – 7° and 61°, and are indicated by arrows. The σ values of the fitted Gaussian were 79° and 36°, corresponding to the full-width at half maximum of 186° and 85°, for the neurons shown in Figs. 3D and E, respectively.

The distribution of directional preferences of eye position–related neurons was different from that of saccade–related neurons. For 31 of 34 eye position–related neurons and 41 of 70 saccade–related neurons that were tested for 8 directions, the preferred direction was determined ($r^2 > 0.7$ for fitted Gaussian). Fig. 4A compares preferred directions and maximal activities of the two types of neurons. Data for saccade–related neurons were uniformly distributed in all directions without any bias toward cardinal axes (Rayleigh test, $P > 0.10$, mean vector length $r = 0.24$ after quadrupling the angles; Batschelet, 1981), consistent with the previous study (Wyder et al., 2003). In contrast, most eye position–related neurons had a preference for ipsilateral eye position, and distribution of vectors tended to be biased towards cardinal axes (Rayleigh test, $P < 0.001$, mean vector length $r = 0.69$ after quadrupling). To visualize the latter, deviation of each vector from cardinal axes was computed. Values could be between 0 and 45°, and the cumulative distributions of these values are plotted in Fig. 4B. While data for saccade–related neurons were uniformly distributed, those for approximately 90% of eye position–related neurons were distributed within the range less than 22.5° (vertical line), indicating that eye position signals in the central thalamus are decomposed into two cardinal axes. The deviations from the cardinal axes were statistically different between the eye position–related neurons and the saccade–related neurons (Wilcoxon rank-sum test, $P < 0.001$). In addition to distribution of preferred directions, the width of directional tuning was also different between types of neurons. Medians of σ values of the fitted Gaussian were 76.9° (mean ± SD, 81.2 ± 37.9°) and 46.7° (57.5 ± 36.4°), corresponding to the full-width at half maximum of 181.1° and 109.9° for eye position–related neurons and saccade–related neurons, respectively. These values were statistically different between types of neurons (Wilcoxon rank-sum test, $P < 0.01$).

Neuronal response latency

A previous study reported an example of eye position–related neuron in the central thalamus that

anticipated changes in eye position a few hundred milliseconds before the initiation of spontaneous saccades (Schlag-Rey and Schlag, 1984), but quantification of latencies has never been performed. To examine temporal properties of eye position signals in the central thalamus, latency of individual eye position–related neurons was measured using the ROC analysis. Figure 5A illustrates an example of an eye position–related neuron that had a preference for ipsilateral eye position, and was recorded near the dorsal surface of the thalamus. Data were aligned on the initiation of memory-guided saccades in the preferred direction, and the spike density was obtained for each trial (data not shown). The ROC values were obtained for each millisecond by comparing trial-by-trial distributions of firing rates and those for 300 ms before the offset of the fixation point. For this neuron, the ROC value exceeded 0.75 slightly after the initiation of saccades (94 ms, arrow in the bottom panel of Fig. 5A).

The ROC measures were useful not only to determine neuronal latencies, but also to statistically examine the time courses of activity modulation. Figure 5B summarizes data for 43 eye position–related neurons in the memory-guided saccade tasks. Each row of the pseudo-colour plot indicates the time course of the ROC value obtained from a single neuron, and data are sorted according to latency of neuronal activity relative to saccade initiation. For these neurons, medians of saccade latencies averaged 204.9 ± 29.2 ms and median times of target reappearance ranged from 131 to 245 ms following saccade initiation (Fig. 5B, top black bar). Data in Fig. 5B indicate that most neurons increased their activity before the reappearance of the peripheral target. Although some neurons showed a gradual decrement in activity over the period of peripheral fixation, all neurons continued firing as long as monkeys looked in the preferred direction. About half of neurons discharged before saccade initiation, and the latencies relative to saccade initiation averaged 30.2 ± 102.3 ms (median, –6 ms; $n = 43$). For comparison, neuronal latencies were also measured for saccade–related neurons using the ROC analysis. The latencies for saccade–related neurons averaged 35.6 ± 99.6 ms (median, 2 ms; $n = 132$), and a statistical test showed no significant difference in median latencies between the two neuron types (Wilcoxon rank-sum test, $P = 0.68$). For eye position–related neurons, the latencies were also examined for saccades in the direction opposite to the preferred direction. Since many neurons discharged rather weakly during the initial fixation at the centre

of the screen, the latency could be measured for 15 neurons only by taking the time when the ROC value became < 0.25. For these neurons, the latencies of neuronal modulation for saccades in opposite directions were not statistically different (paired t-test, $P = 0.10$).

As seen in Fig. 2, there were two clusters of eye position–related neurons in the central thalamus; one located near the dorsal surface and the other was deep in the central thalamus. Dynamics of neuronal discharge was different between the two groups. Most of eye position–related neurons located ventrally discharged before saccades, whereas those located dorsally discharged following saccades. Response latency averaged -34.2 ± 50.1 ms ($n = 25$; median, -41 ms) and 119.7 ± 87.9 ms ($n = 18$; median, 99 ms) for ventral and dorsal groups, respectively, and these values were statistically different (unpaired t-test, $P < 10^{-4}$). To examine whether changes in activity prior to saccade initiation were attributed to early transient associated with saccades, Fig. 5C plots the ratio of neuronal activities early and late in the response period as a function of neuronal response latency, for both ventral (blue circles) and dorsal (red triangles) groups. Early and late responses were measured for the initial 150-ms period and 300–600 ms after onset of the neuronal activity, respectively. Values averaged 1.26 ± 0.24 (median, 1.30) and 1.07 ± 0.28 (1.00) for ventral and dorsal groups, respectively, and were statistically different between the groups (unpaired t-test, $P < 0.05$), indicating that the saccade–related transient was greater for the ventral than the dorsal groups. However, the relative magnitude of the early transient did not always determine the latencies of neuronal activity. Overall, the ratios and latencies of eye position–related neurons did not correlate with each other (Spearman's rank correlation coefficient, $r_s = -0.27$, $n = 43$, $P = 0.09$). For saccade–related neurons, median of the ratio was 2.66 (7.11 ± 20.3, $n = 131$), and the two variables did not correlate with each other ($r_s = -0.14$, $P = 0.10$). Thus, the eye position–related neurons in the ventral group discharged earlier and tended to have a transient, but the existence of saccade–related burst was neither necessary nor sufficient for the eye position–related neurons to have a presaccadic activity. In addition, the relative magnitude of the early transient was not a determinant for the latencies of eye position–related neurons.

Activity modulation in the absence of foveal visual stimuli

As outlined in the Introduction, neurons in the parietal cortex show gain modulation of visual responses depending on eye position. It is therefore possible that the eye position–related activity in the central thalamus is attributed to the gain modulation of the foveal visual responses to the fixation target. However, several observations indicated this was unlikely. Firstly, most eye position–related neurons altered their activity before the reappearance of a peripheral target in the memory-guided saccade tasks, like an example shown in Fig. 3A, and as seen in the time courses of individual neuronal activity shown in Figs. 5B and D, indicating that the activity modulation around the time of saccade was not solely due to the foveal visual response. Secondly, when the data of memory-guided saccades were aligned on the target reappearance, most eye position–related neurons showed no clear change in activity following the onset of a peripheral target, and the population activity did not show any significant modulation (Fig. 5D). Finally, neurons in the central thalamus altered their activity during spontaneous eye movements depending on the orbital eye position. To examine the neuronal modulation without foveal visual inputs, the firing rate was measured for every intersaccadic intervals (> 300 ms) before the onset of the fixation point or before monkeys started initial fixation at the screen centre (eye position window 4°). Almost all eye position–related neurons showed activity modulation during spontaneous eye movements like the three examples shown in Fig. 6. Thus, neurons in the central thalamus modulated their activity depending on eye position in the absence of a fixation target, suggesting that the neuronal activities represented eye position, rather than foveal visual stimuli.

Effects of prior eye movements

Distribution of directional preferences strongly suggest that eye position signals in the central thalamus originate from the velocity-to-position neural integrator in the brainstem which processes horizontal and vertical eye position signals separately. However, further analyses showed that eye position signals in the central thalamus were dynamically modified: activity of eye position–related neurons showed a trace of preceding eye movements. To examine this hysteretic nature, sensitivity to eye position was measured by

making monkeys perform visually-guided saccades of 10 or 40° along the preferred axis. Initial fixation location for 10° saccades systematically varied within the range of ± 20°. Activity during the second fixation interval for the neuron shown in Fig. 7A steadily increased as the monkey made saccades toward the preferred direction that was contralateral to the recording site ("Toward"), and activity decreased for eye positions away from the contralateral side ("Away"). In this figure, data were aligned on the initiation of saccades (vertical lines) and were arranged so that each column plotted data for eye movements in opposite directions but within the same range of eye position. The number on each panel indicates the horizontal location of the saccade target, thus indicating the final eye position after the saccade. Time courses of neuronal activity in toward trials (upper row) showed that sustained activity during fixation after saccades decreased slightly over time, and magnitudes of neuronal responses during fixation were greater after saccades compared to before saccades. Comparison between toward and away trials showed that magnitudes of sustained activity during fixation were dependent on the direction of preceding saccades. For example, the activity during fixation at the centre of the screen after saccades in the preferred direction (*Toward*, middle column of Fig. 7A) was greater than that during fixation at the same location but following saccades in the opposite direction (*Away*, fourth column).

Since amplitude and direction of saccades prior to initial fixation were uncontrollable, a quantitative analysis was performed for the data obtained during the second fixation interval. Figure 7B plots means (± SEs) of firing rates during a 400-ms interval starting from 400 ms after the initiation of 10° or 40° saccades for the neuron shown in Fig. 7A as a function of means of eye position measured for the same period. The two curves in Fig. 7B show that activity of the neuron almost linearly correlated with horizontal eye position, whereas direction of preceding saccades biased magnitudes of the response. Activities of 18 eye position–related neurons were formally examined, and the data are summarized in Figs. 7C and D. To show effects of the preceding saccade direction, Fig. 7C compares means of neuronal activity during the second fixation at the centre of the screen (+) and ± 10° along the preferred axis (open squares and filled triangles, respectively) between trials in opposite saccade directions. Most data points distributed above the line with a unity slope, indicating that neuronal activity during fixation was greater

after saccades in the preferred direction than those in the opposite direction (paired t-test, $P < 0.001$). Sensitivity to eye position was assessed by fitting a regression line to the data of individual trials, and is summarized in Fig. 7D. Correlation coefficients averaged 0.67 ± 0.15 and 0.64 ± 0.20 for toward trials and away trials, respectively. Eye position sensitivities were measured as regression slopes that averaged 0.92 ± 0.46 (median, 0.76) and 0.61 ± 0.33 (0.56) spikes/s/° for toward trials and away trials, respectively. Effects of saccade directions on magnitude of eye position sensitivity were statistically significant (paired t-test, $P < 0.01$). To estimate the amount of modulation of eye position signals resulting from preceding saccade directions, the mean of differences in neuronal activities during the second fixation at 3 central locations ($\pm 10°$ and the centre of the screen) between trials in opposite directions was divided by eye position sensitivity obtained from the toward trials. Values averaged $6.74 \pm 6.20°$ ($n = 18$; median, 6.16°), indicating that neurons in the central thalamus encoded eye position inaccurately with a maximal error of 6° depending on direction of the preceding saccades.

The trace of preceding saccades in activity of eye position–related neurons was also observed in the re-fixation trials. Figures 8A and B show activity of a single thalamic neuron with a preference for contralateral eye position. Activity of the same neuron during spontaneous eye movements was shown previously in Fig. 6C. Neuronal activity was slightly suppressed when the monkey looked at the target that was presented ipsilaterally, and activity resumed after the second, return, saccades to the location of the initial fixation (Fig. 8A). The same neuron showed a sustained activity during fixation on the contralateral target (Fig. 8B), but ceased firing after the second saccade that brought the eyes to the central location. Neuronal responses were quantified by measuring activity during the following three 400-ms intervals which were separated by two saccades; 1) immediately before onset of the peripheral target, 2) immediately before offset of the peripheral target, and 3) starting from 400 ms after the initiation of the return saccades. Figure 8C plots means ($\pm$ SEs) of firing rates during these three intervals as a function of means of eye positions that were measured for the same intervals for the neuron shown in Figs. 8A and B. While the monkey fixated the central target accurately before and after saccades in the preferred or opposite directions, magnitudes of neuronal activities were different between the three fixation conditions,

as shown by the central data points plotted in Fig, 8C. Neuronal activity during central fixation was greater after saccades in the preferred direction than that after saccades in the opposite direction. To examine modulation in the re-fixation trials for multiple neurons, Fig. 8D compares activity during central fixation after the return saccades in the preferred direction (toward) and the opposite direction (away). Data for many neurons distributed above the line, indicating that activity of eye position–related neurons showed a trace of the direction of preceding eye movements. Although modulations of response magnitudes for individual neurons were rather weak, and were statistically significant only for a subset of neurons (27%, $n = 4$, unpaired t-test, $P < 0.05$), activity during fixation was greater after saccades in the preferred direction than that following saccades in the opposite direction for the population of neurons (paired t-test, $P < 0.01$). Thus, eye position signals in the central thalamus were dynamically modified depending on direction of the preceding eye movements.

Discussion

As a possible source of eye position signals in the cerebral cortex, the present study examined spatial and temporal properties of eye position–related neuronal activity in the central thalamus. Consistent with previous studies (Schlag-Rey and Schlag, 1984; Wyder et al., 2003), eye position–related neurons were located within or around the anterior group of the intralaminar nuclei of the thalamus. Data showed that most eye position–related neurons in the central thalamus had directional preferences along the horizontal axis, and many discharged before saccades. Histological examination showed that there were two loci of eye position–related neurons, and temporal properties of neuronal discharges for these groups were different. While the distribution of directional preferences suggested that neurons in the central thalamus received eye position signals from the brainstem and might transmit them to the cerebral cortex, the effects of prior eye movements on neuronal activity indicated that eye position signals were dynamically modified through ascending pathways before they reached the cerebral cortex.

Origins of eye position signals in the central thalamus

The present study is the first to quantitatively measure latency of eye position signals in the central thalamus. The overall distribution of response latencies of eye position–related neurons was comparable to that of saccade–related neurons, and about half of them altered their firing rates before the initiation of saccades. Further histological consideration indicated that eye position–related neurons discharging before saccades were mostly located in the paralaminar VL, and those discharging following saccades were located near the dorsal surface of the thalamus, mostly around the border of LD and AV. These results suggested that eye position–related neurons in the central thalamus might receive inputs from two different sources; eye position signals recorded deep in the central thalamus might reflect commands of eye position (i.e., efference copy), while those recorded dorsally could also reflect proprioceptive feedback from extraocular muscles. An analogous topography of neuronal activity in relation to saccade initiation was reported previously for saccade–related neurons in the central thalamus, showing higher proportion of presaccadic neurons in the paralaminar MD than in VL (Tanibuchi and Goldman-Rakic, 2005). Because about half of saccade–related neurons in VL were exclusively active for memory-guided saccades, these authors suggested that neurons in VL transmitted oculomotor feedback signals only for memory-guided saccades. In contrast, eye position–related neurons recorded from both VL and LD similarly modulated their activity for different types of eye movements, including visually-guided saccades, memory-guided saccades, spontaneous eye movements, and smooth pursuit (Tanaka, 2005b). These results suggest that the topographies of neuronal activity in relation to saccade initiation aligned mediolaterally (saccade neurons) or dorsoventrally (eye position neurons) might reflect different patterns of innervations for different types of thalamic neurons.

Since neurons in the central thalamus receive both cortical and subcortical inputs, eye position signals could come from either or both structures. As outlined in the Introduction, a remarkable feature of these cortical and subcortical eye position signals is the difference in distributions of their directional preferences: cortical neurons have preferences in all directions including oblique directions (Andersen et al., 1990; Galletti et al., 1995), or in some cases, show non-planar 'eye-position field' (Nakamura et al., 1999), whereas horizontal and vertical eye position signals are separately processed in the brainstem. To

identify the origin of eye position signals in the central thalamus, the present study examined the overall distribution of directional preferences. Results showed that most eye position–related neurons had directional preferences along the horizontal axis, and only a few neurons had preferences for oblique directions. Neurons with a vertical directional preference were also rare (10%), consistent with previous studies (13%, Schlag and Schlag-Rey 1984; 0%, Wyder et al. 2003). Although it is not known why directional preferences were biased along the horizontal axis, the scarcity of neurons with oblique directional preference suggested that eye position signals in the central thalamus are decomposed into horizontal and vertical components. In contrast, directional preferences of saccade–related signals distributed over all directions with respect to the recording site, consistent with the previous study (Wyder et al., 2003). Difference in the distributions of preferred directions suggested that these signals came from different stages in the saccade generating pathways. Some but not all of saccade–related signals must come from sites where saccade commands are organized in an eye-centred coordinate frame such as the SC, as indicated by anatomical (Benevento and Fallon, 1975; Harting et al., 1980) and recent physiological (Sommer and Wurtz, 2004) data. On the other hand, eye position signals in the central thalamus may come from sites where eye movement signals are organized horizontally or vertically, likely from the neural integrator located in the brainstem. Bilateral projections from the nucleus prepositus hypoglossi (Kotchabhakdi et al., 1980), the interstitial nucleus of Cajal (Kokkoroyannis et al., 1996), and the vestibular nuclei (Lang et al., 1979) to the central thalamus support this hypothesis. Thus, the central thalamus likely transmits eye position signals from the brainstem to the cerebral cortex, rather than receiving and processing cortical eye position signals.

Hysteresis of eye position signals

The distribution of preferred directions suggested that neurons in the central thalamus receive eye position signals derived from brainstem neural integrator. However, further quantitative analyses showed that neuronal activity did not encode accurate eye position: eye position signals in the central thalamus showed a trace of prior eye movements. For many neurons, firing rates during fixation at the same location were

greater following saccades in the preferred direction than those after saccades in the opposite direction. In other words, eye position signals *overestimated* changes in eye positions for each eye movement. This hysteretic nature of eye position signals in the central thalamus has been previously reported for spontaneous eye movements (Schlag and Schlag-Rey, 1984) as well as during smooth pursuit (Tanaka, 2005b). When the amount of hysteresis was estimated, thalamic neurons encoded eye position inaccurately with a maximal error of 6.2°, following saccades in opposite directions. A similar effect of prior eye movements on neuronal activity has also been reported in extraocular motoneurons of many species (monkeys, Eckmiller, 1974; Goldstein and Robinson, 1986; cats, Delgado-Garcia et al., 1986; rabbits, Stahl and Simpson, 1995a; goldfish, Pastor et al., 1991), neural integrator of goldfish (Aksay et al., 2003), vestibular nucleus neurons of rabbits (Stahl and Simpson, 1995b), as well as eye position–related units in the monkey cerebellum (Miles et al., 1980). However, the amount of hysteresis observed in the present study was much more than those reported in the previous studies; for monkeys, hysteresis in abducens motoneurons was 1.3° (Goldstein and Robinson, 1986), and that in the cerebellum was 3.8° (Miles et al., 1980). The present results suggested that eye position signals in the brainstem are dynamically modified through ascending pathways before they reach the cerebral cortex. The hysteretic nature of eye position signals has also been previously reported in the cortex (Nakamura et al., 1999). Unfortunately however, there are no available data for quantitative comparisons with the present data. Also, we do not know whether the cerebral cortex can reconstruct accurate eye position from the inaccurate thalamic signals by taking account of the recent history of eye movements.

Possible roles of eye position signals in the central thalamus

Previous studies have shown that signals through the thalamus to the cortex are used for monitoring of eye movements. For example, memory-guided saccades following saccades or smooth pursuit during the delay period became inaccurate for subjects with damages to the central thalamus (Gaymard et al., 1994; Bellebaum et al., 2005). Similarly, inactivation of the central thalamus of monkeys resulted in a systematic shift of saccade endpoint in the double-step paradigms (Sommer and Wurtz, 2002). Other studies

demonstrated that both saccade and perceptual systems use actual rather than desired eye movement signals during saccade adaptation to monitor eye movements (Tanaka, 2003; Awater et al., 2004), indicating that signals through the thalamus to the cortex are used for behavioural and perceptual control. These studies examined the ability to track changes in eye position for updating the spatial memory or goals of subsequent movements.

Although direction and amplitude of eye displacements can be tracked by monitoring eye velocity rather than eye position signals (White and Snyder, 2004), there are many situations where information on absolute eye position is needed. For example, eye position signals are essential to compute the head-centred location of visual stimuli for reaching movements (Boussaoud, 1995; Mushiake et al., 1997). Conversely, transformation from head- to eye-centred coordinate frames is necessary to command accurate saccades from various initial locations to an auditory (Jay and Sparks, 1984) or somatosensory (Groh and Sparks, 1996) target. Previous studies showed that, although activities of individual neurons in the parietal cortex encoded the location of visual stimuli in an eye-centred coordinate frame (Andersen et al., 1990), the accurate head-centred location of visual stimuli could be represented by the population of neurons with eye position gain field (Zipser and Andersen, 1988; Bremmer et al., 1998). In other studies, a subset of neurons in area V6 had a visual receptive field that did not move with eyes, showing the existence of the head-centred representation of visual stimuli (Galletti et al., 1993). It remains unknown whether eye position signals through the thalamus to the cortex play roles in such spatial transformations, however, the use of eye movement signals though the thalamus for spatial updating and the existence of decomposed eye position signals in the central thalamus suggest this possibility. Indeed, a previous study proposed that, on the basis of response properties of recorded neurons, eye position signals in V3A and V6/7a might come from dorsal and ventral groups of eye position neurons in the central thalamus, respectively (Galletti et al., 1995). Eye position signals through the thalamus to the cortex may play roles in spatial transformations to represent an egocentric coordinate frame that is invariant with eye position.

Notes

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Figure legends

Figure 1.   Behavioural tasks. (*A*) Memory-guided saccade task. A peripheral target was briefly flashed (200 ms) during central fixation. Animals were required to maintain fixation and to remember the location of the target, then to make a saccade to the location after the fixation point was extinguished. The peripheral target reappeared 400 ms later and remained visible for an additional 800–1,200 ms. (*B*) Visually-guided saccade task. A peripheral target appeared at the time of fixation point offset. (*C*) Re-fixation task. A peripheral target disappeared 800 ms following the initiation of visually-guided saccade. Monkeys were required to make a second, return, saccade to the location of the initial fixation without any visual guidance. FP, fixation point; Tg, peripheral target.

Figure 2.   Locations of eye position–related (♦) and saccade–related (°) neurons reconstructed from histological sections of two monkeys. Levels of frontal sections are shown as millimetres posterior to the anterior commissure (AC). AM, anteromedial nucleus (n.); AV, anteroventral n.; CM, centromedian n.; MD, mediodorsal n.; Pf, parafascicular n.; VAmc and VApc, magnocellular and parvocellular parts of ventroanterior n., respectively; VLc and VLo, caudal and oral divisions of ventrolateral n., respectively; VPLo, oral division of ventroposterolateral n.; VPM, ventroposteriomedial n.; X, area X.

Figure 3.   Directional tuning. (*A*) Example of an eye position–related neuron recorded from the right thalamus. Data are aligned on the initiation of memory-guided saccades (vertical line), sorted and grouped according to directions of eye movements that are indicated by the left-hand arrowheads. The white diamond on each raster line indicates time of target reappearance in the memory-guided saccade task. (*B*) Example of a directional saccade–related neuron recorded from the left thalamus. (*C*) A non-directional saccade–related neuron. (*D*) Polar plot indicating directional tuning of the neuron shown in A. Each data point and error bar indicates mean and 95% confidence intervals of neuronal activity for a 500-ms interval starting from 300 ms after saccade initiation. The curve indicates the best-fit Gaussian for a set of 8 data points, and the polygons at the origin represent means (solid lines) and 95% confidence interval (dashed lines) of baseline activity. Estimates of the preferred direction and the magnitude of maximal response are

represented by the arrows. (*E*) Directional tuning of the neuron shown in B. Neuronal activity was measured for a 150-ms interval. The polygon at the origin and some error bars are smaller than the size of data points.

Figure 4.   Distributions of directional preferences for eye position–related and saccade–related neurons. (*A*) Orientation and length of each vector indicate the preferred direction and the maximal response derived from the Gaussian curve fitted to the direction tuning of each position neuron (left) and saccade neuron (right). (*B*) Cumulative relative frequency of the minimal value of the differences between the orientation of each vector and 4 cardinal directions.

Figure 5.   Quantitative analysis of the neuronal response latency. (*A*) Example of latency measurement using the ROC analysis. Data are aligned on the initiation of memory-guided saccades in the preferred direction, and are sorted according to saccade latency. Spike data were filtered with a Gaussian ($\sigma = 10$ ms) for each trial, then were averaged across trials. The ROC value was computed for every millisecond by comparing trial-by-trial distribution of neuronal activity at a given time with that for 300 ms baseline interval immediately before the fixation point offset (open diamond). The time when 5 consecutive data points exceeded 0.75 was taken as the onset of the response (arrow). See Methods for details. (*B*) Each row of the pseudo-colour plots shows time course of the ROC value obtained from a single eye position–related neuron. Data are aligned on saccade initiation, and are sorted by latency of neuronal activity. The range of medians of the time of cue reappearance is indicated by the top black bar. (*C*) Absence of correlation between magnitude of initial burst of activity and neuronal response latencies. The ratio of activities during early (initial 150 ms) and late (300-600 ms) response intervals is plotted as a function of response latency relative to saccade initiation. Different symbols are used for neurons in the dorsal and ventral groups. (*D*) Time course of population activity for memory-guided saccades in opposite directions along the preferred axis. Solid and dashed traces indicate means and 95% confidence intervals, respectively. Data are aligned on fixation point offset. The peripheral target reappeared 400 ms later, and monkeys were required to make a saccade until then. Since many neurons showed only a weak activity

during the central fixation, the modulation of population activity for the direction opposite to the preferred direction was less than that for the preferred direction.

Figure 6.   Activity of three representative neurons during spontaneous eye movements. The firing rate was measured during each intersaccadic interval (> 300 ms) before onset of the fixation point or before monkeys started initial fixation. Note that eye position data clustered near the centre, because monkeys expected onset of the central fixation point during the intertrial period. Data for neurons in A and C are also shown in Figs. 3A and 8, respectively.

Figure 7.   Effects of direction of prior eye movements on activity of eye position–related neurons during fixation. (*A*) Responses of an example neuron to visually-guided saccades that were generated from different initial fixation locations. Each column plots data for saccades within the same range of eye position. The number on each column indicates the location of the saccade target and the location of final eye position. Data labelled "Toward" show time courses of spike densities for trials in the neuron's preferred direction, while data labelled "Away" indicate those in the opposite direction. All data are aligned on the initiation of saccades. Eye position traces are shown only for Toward trials. (*B*) Eye position sensitivity for the neuron shown in A. Means (± SEs) of neuronal activity are plotted as a function of the final eye position following saccades in opposite directions. Both the neuronal activity and eye position were measured for the 400-ms intervals that are indicated as horizontal black bars in A. (*C*) Effects of preceding saccade directions on neuronal responses during fixation for 18 neurons. Different symbols indicate data for different final fixation locations (filled triangles, + 10°; crosses, 0°; open squares, − 10°). Note that most of data points are above the line with a unity slope, indicating that neuronal activity during fixation was greater for Toward than Away trials. (*D*) Comparison of eye position sensitivities during final fixation following saccades in opposite directions.

Figure 8.   Response of eye position–related neurons in the re-fixation task. (*A*) and (*B*) Activity of an example neuron. Data are aligned on the initiation of the first (left panel) and the second, return, saccades (right panel). Trials are sorted according to latency of the return saccades. Note that activity during central

fixation after return saccades are greater for trials shown in A than B. Activity of this neuron during spontaneous eye movements is shown in Fig. 6C. (*C*) Means (± SEs) of neuronal activity for 400-ms periods during the 3 fixation intervals that were separated by two saccades are plotted as a function of eye position for the neuron shown in A and B. Arrows indicate increasing time. (*D*) Effects of saccade direction on neuronal activity during central fixation after the return saccades. Activity after the return saccades that brought the eyes in the preferred direction (Toward) are plotted as a function of those after saccades in the opposite direction (Away).

A   Memory saccade
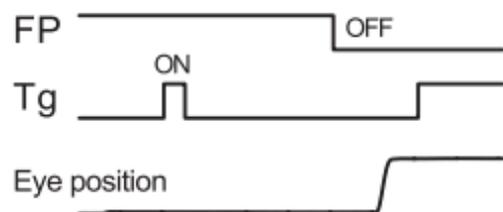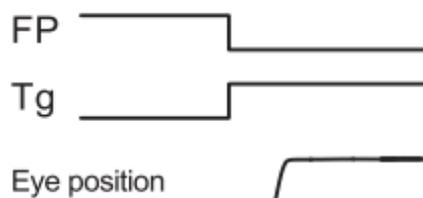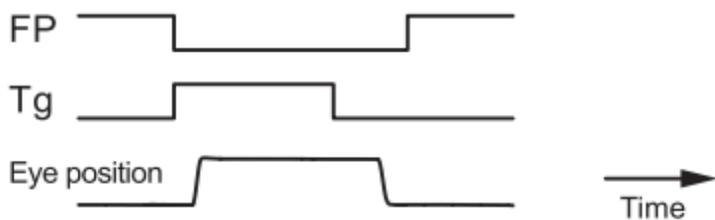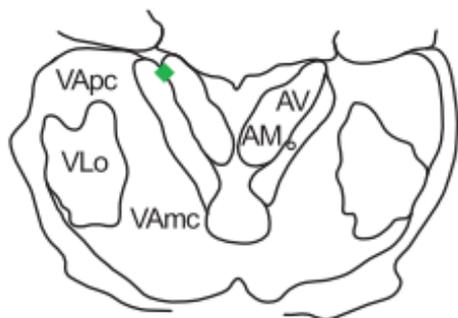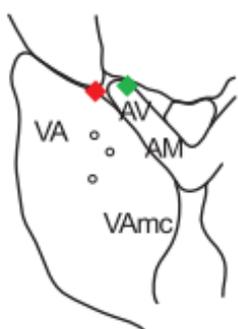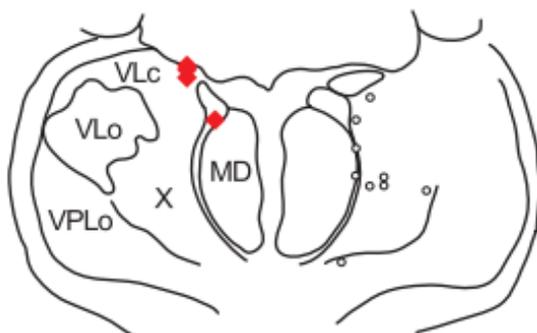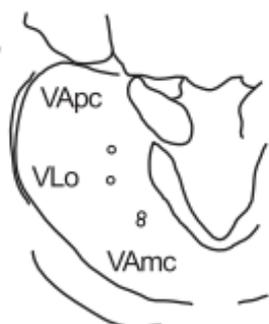
FP

Tg   ON   OFF

Eye position

B   Visual saccade

FP

Tg

Eye position

C   Re-fixation

FP

Tg

Eye position   →
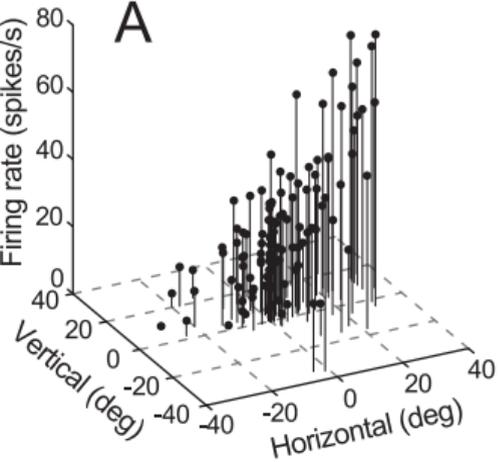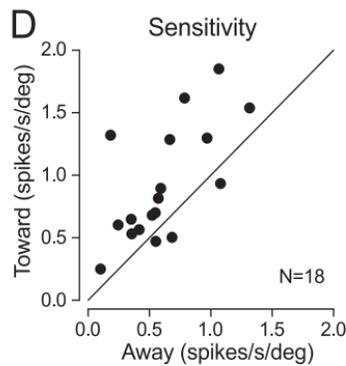   Time

Figure 1, Tanaka

Figure 2, Tanaka

200 ms/div

80 spikes/s

160 spikes/s
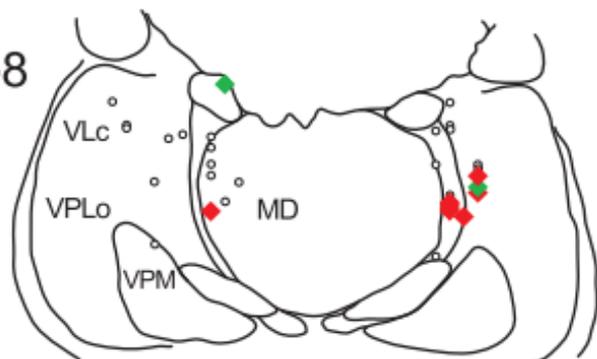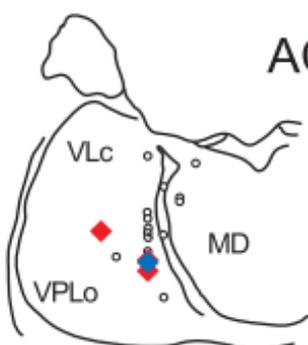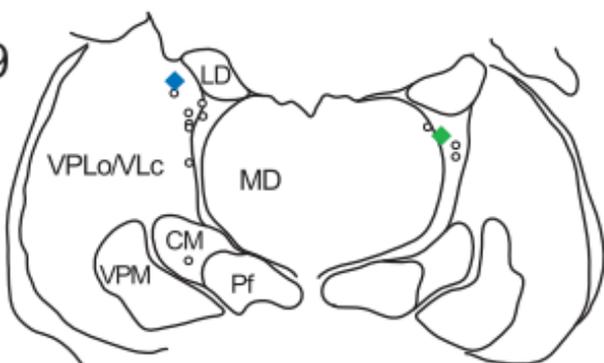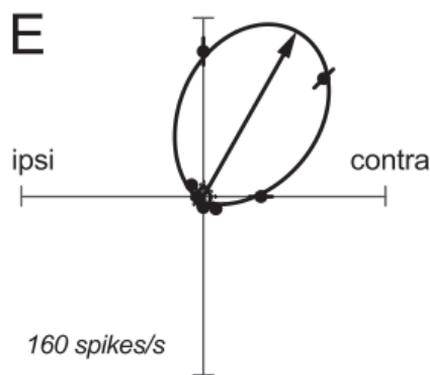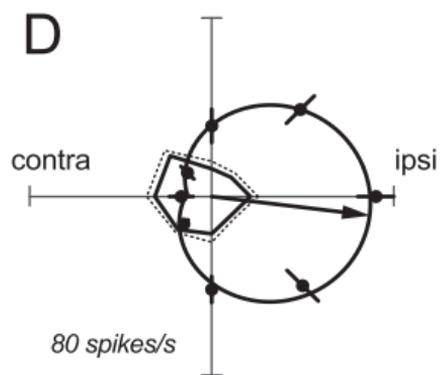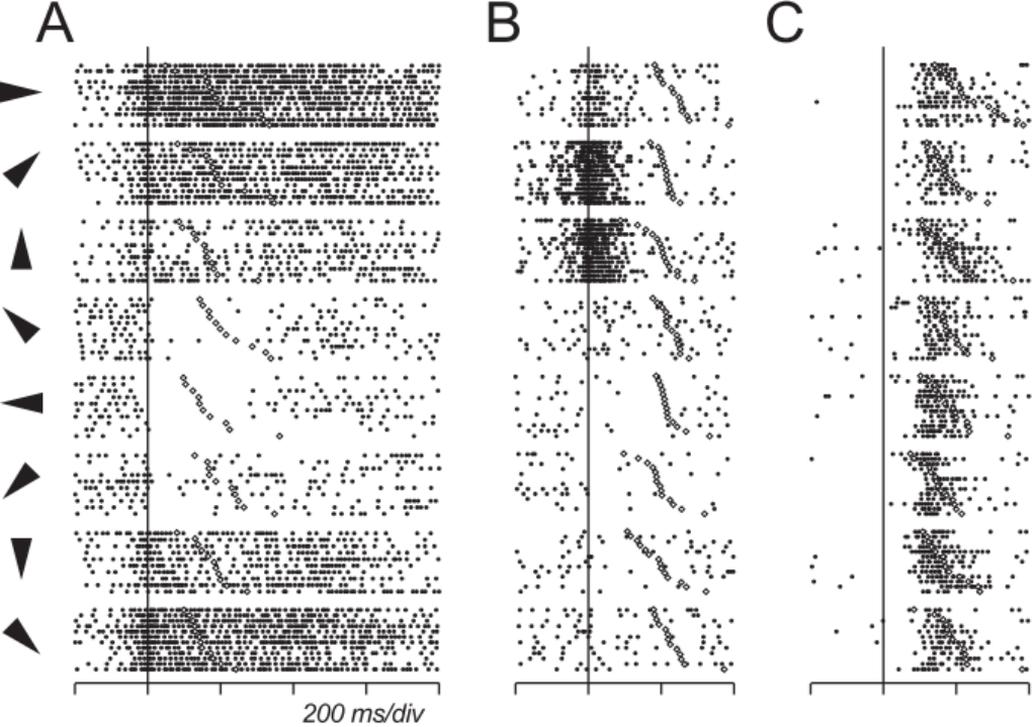
Figure 3, Tanaka

A

Position

Saccade

N=31

N=41

contra

ipsi

contra

ipsi

80 spikes/s

100 spikes/s

B

Position

Saccade

Cumulative frequency (%)

Deviation from cardinal axes (deg)
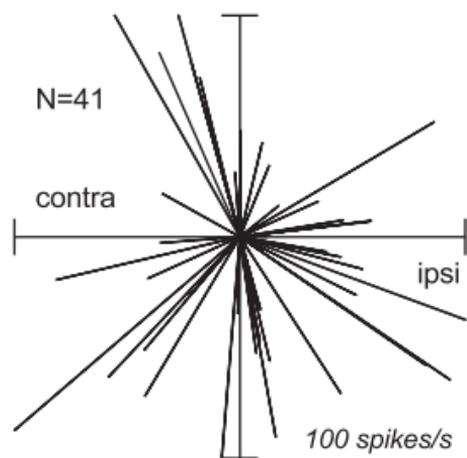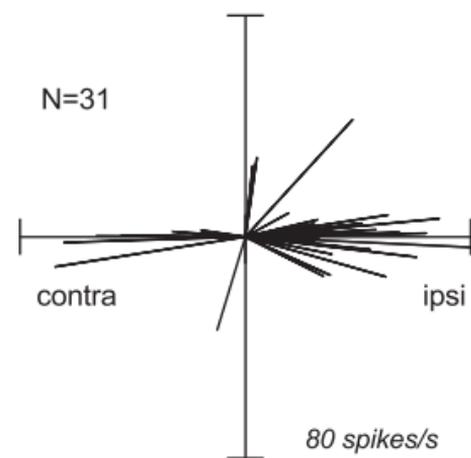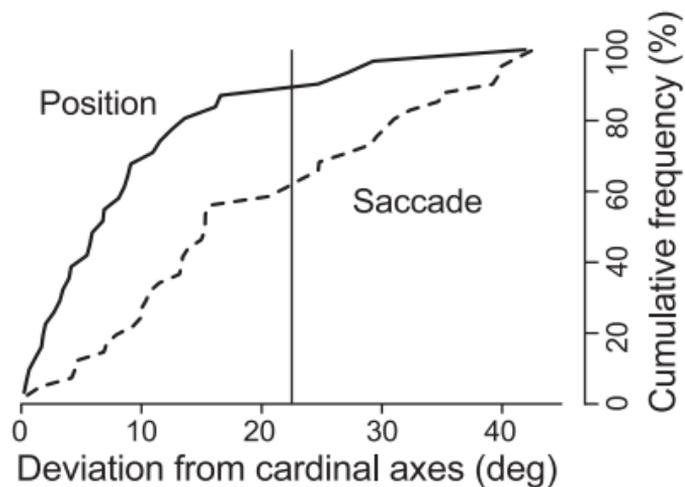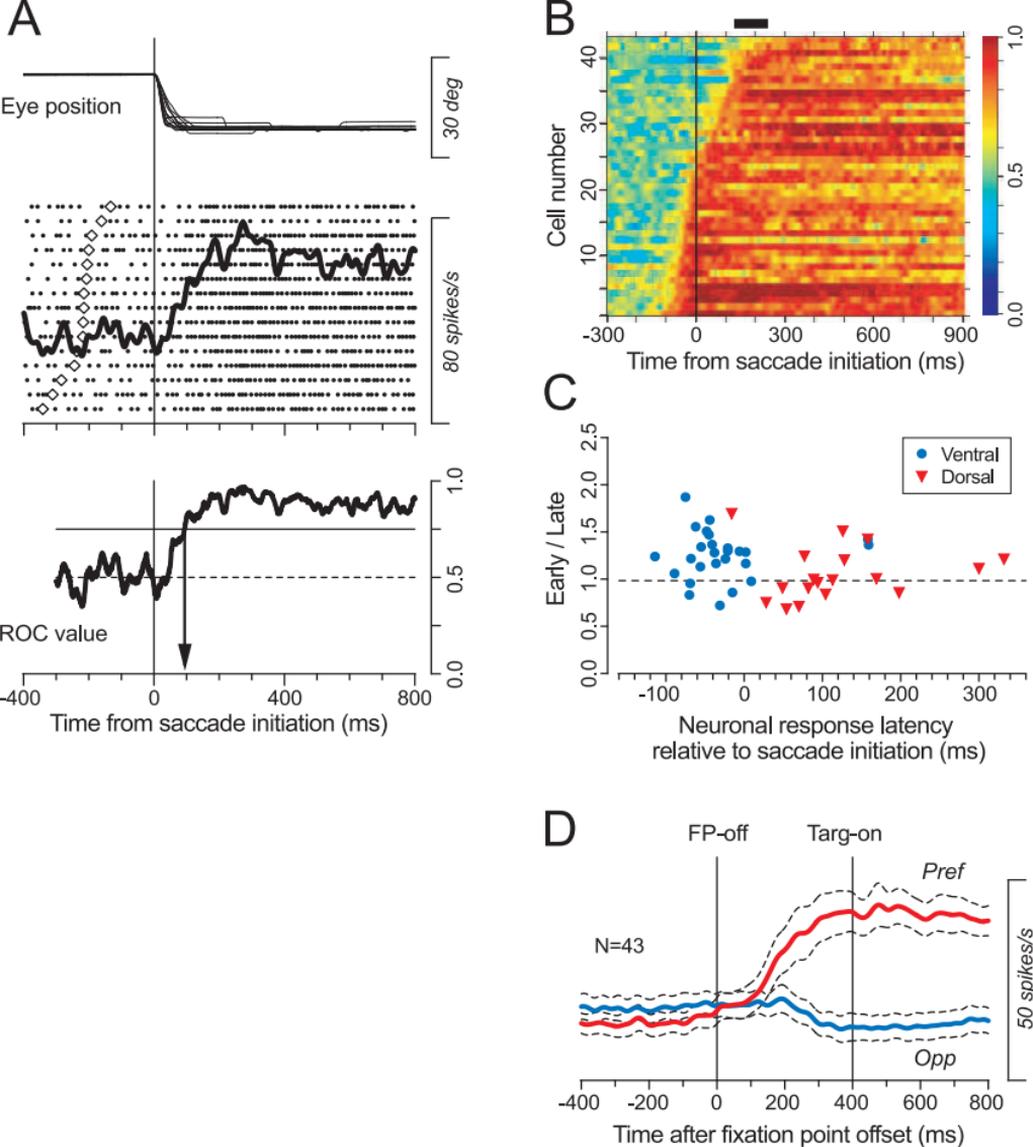
Figure 4, Tanaka

Figure 5, Tanaka

Figure 6, Tanaka

A

Eye position

Toward +20° −10° 0° +10° +20°

Away −20° −20° −10° 0° +10°

40 deg

100 spikes/s

400 ms/div

B

Firing rate (spikes/s)

Toward

Away

Eye position (deg)

C Hysteresis

Toward (spikes/s)

Away (spikes/s)

D Sensitivity

Toward (spikes/s/deg)

Away (spikes/s/deg)

N=18

Figure 7, Tanaka

A

Eye
position

B

C

D

N=15

30 deg

60 spikes/s

200 ms/div

Firing rate (spikes/s)

Eye position (deg)

Toward (spikes/s)

Away (spikes/s)

Figure 8, Tanaka