Rapid and coordinated processing of global motion images by local clusters of retinal ganglion cells

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Abstract: Even when the body is stationary, the whole retinal image is always in motion by fixational eye movements and saccades that move the eye between fixation points. Accumulating evidence indicates that the brain is equipped with specific mechanisms for compensating for the global motion induced by these eye movements. However, it is not yet fully understood how the retina processes global motion images during eye movements. Here we show that global motion images evoke novel coordinated firing in retinal ganglion cells (GCs). We simultaneously recorded the firing of GCs in the goldfish isolated retina using a multi-electrode array, and classified each GC based on the temporal profile of its receptive field (RF). A moving target that accompanied the global motion (simulating a saccade following a period of fixational eye movements) modulated the RF properties and evoked synchronized and correlated firing among local clusters of the specific GCs. Our findings provide a novel concept for retinal information processing during eye movements.

Keywords: vision, retinal processing, receptive field, correlated neuronal activity, electrophysiology

Introduction

Our visual perception is unified and continuous, although our eyes repeatedly shift position and alter fixation1)–3) even when the body is stationary. The whole image projected on the retina (the whole retinal image) not only moves rapidly during saccadic eye movements but also jitters even during steady gaze due to the nature of fixational eye movements.

Thus, the whole retinal image is never at rest but always in motion. This study explores ways in which retinal neuronal processing might help to achieve unified and continuous vision in the face of whole retinal image movement.

Eye movements affect visual computation in the brain. During a saccade, the visual system receives both retinal output and a corollary or copy of the command to move the eye (corollary discharges3)). Even in the early stages of the visual system (lateral geniculate nucleus;4),5) primary visual cortex (V1)6)–8), the activity is modulated by extra-retinal signals such as corollary discharges. During visual fixation, neurons in monkey V1 respond differently to self-generated motion (microsaccades) than to the equivalent motion in the visual field.9) Furthermore, neurons in cat V1 respond better, with sparse, temporally precise, and reliable spikes, when full-field natural images evoked by simulated eye movements are presented than when images are presented within the classical receptive field (RF).10)

In the retina, there are many morphological and physiological types of ganglion cells (GCs),11),12) each of which was initially assumed to process a specific local feature within its classical RF independently13),14) and in parallel.11) However, later studies
showed that peripheral motion stimulation outside the classical RF modulates the GC responses.\textsuperscript{15}–\textsuperscript{17} This response modulation was suggested to serve as the basis for shaping the responses of GCs during eye movements.\textsuperscript{17} This is important because eye movements produce image movement over the entire retina (global motion). Saccadic displacement of images in the peripheral retina inhibits certain GC responses.\textsuperscript{18} Global jitter motion induced by fixational eye movements also modulates the GC responses. Activation of polyaxonal wide-field amacrines (ACs) by global jitter motion suppresses firing of specific GCs, such as the local motion detector (fast OFF GC in salamander, ON brisk transient GC, and ON-OFF direction selective GC in rabbit,\textsuperscript{19} W3B GC in mouse\textsuperscript{20}) However, during natural eye movements saccades occur after a period of fixation and thus it is important to study the retinal output during saccadic global motion, after retinal processing has been modulated by global jitter motion. In addition, specific GCs show stimulus feature-dependent correlated activity,\textsuperscript{21}–\textsuperscript{23} which may contribute to efficient encoding of visual information.\textsuperscript{22,24} Thus, it is also important to investigate whether GCs respond independently or coordinately during global motion.

In the present study, we examined how retinal GCs respond to global motion images evoked by simulated fixational and saccadic eye movements, presented singly and in sequence. We simultaneously recorded the firing of many GCs in the goldfish isolated retina using a planar multi-electrode array; GCs were classified into six groups physiologically based on the temporal profile of the RF. We found that a moving target which accompanied the global motion (simulating a saccade following a period of fixational eye movements) evoked synchronized firing and temporally correlated firing among local clusters of the specific GCs. Thus, processing of global motion images during eye movements has already started in the retina, allowing the brain to receive temporally coordinated retinal signals, facilitating information processing in the visual system.

Materials and methods

Animals and preparation. Goldfish (Carassius auratus; 8–12 cm) was used for the experiments. Animals were kept in a room maintained at 23 °C on a 12 h light/dark cycle. All protocols complied with “A Manual for the Conduct of Animal Experiments in The University of Tokyo” and “Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences, The Physiological Society of Japan”.

Preparation. Animals were dark-adapted for more than 1 h before experiments. Under a dim red light, a goldfish was double-pithed and eyes were enucleated. The following procedure was performed under a stereomicroscope equipped with infrared (IR) image converter (C5100, Hamamatsu photonics) and IR illuminator (HVL-IRM, Sony). After the cornea and lens were ablated, the eye cup was treated with a mixture of hyaluronidase and collagenase (4 mg/mL each, Sigma-Aldrich Corp.) for a few min. A small cut was made at the dorsal part of the eye cup as a landmark and thus the ventral retina isolated from the pigment epithelium was properly oriented and positioned on the multi-electrode array.

Electrophysiology. The ventral retina was properly oriented and positioned on the multi-electrode array (60pMEA200/30iR-Ti, Multichannel Systems; MED Probe MED-P5305, Alpha MED Sciences) with the GC layer facing down. The retina was continuously superfused with a solution bubbled with 95% O\textsubscript{2}/5% CO\textsubscript{2} at the rate of 1 mL/min. The solution consisted of (in mM) 106 NaCl, 2.6 KCl, 28 NaHCO\textsubscript{3}, 2.5 CaCl\textsubscript{2}, 1 MgCl\textsubscript{2}, 1 Na-pyruvate, 10 D-glucose, 4 mg/L phenol red. Recorded spike discharges were band-pass filtered between 100–3,000 Hz, and sorted into single unit activities by principal component analysis (PCA) and the template-matching method with custom programs using MATLAB (Mathworks).\textsuperscript{25,26} We selected 1–3 single units with good signal-to-noise ratio for further analyses. To verify the accuracy of sorting, we performed auto-correlation analysis of the sorted spike train from each unit, and confirmed the presence of a silent interval (0 ± 2 ms) representing the refractory period of spikes.

Light stimulation. Light patterns were generated by Psychtoolbox\textsuperscript{27,28} on MATLAB. The light stimulus presented on a cathode-ray tube display (S501J, refresh rate 60 Hz, 1,280 × 1,024 pixels, Iiyama) was projected onto the retina through optics (CIE XYZ values of white, R: 0.28, G: 0.31, B: 0.41). We used a moving bar (1,600 in length × 1,200 µm in width or 1,600 × 1,600 µm on the retina, 9.56 cd/m\textsuperscript{2}, 65.6% contrast) and a large background frame (4,000 × 4,000 µm) which was either uniformly dark (0.11 cd/m\textsuperscript{2}) or a Gaussian-filtered (σ, 40 µm) random-dot pattern (51,325 dots/1,000\textsuperscript{2} pixels, 4 µm/pixel, mean intensity 6.67 cd/m\textsuperscript{2}, mean contrast 45.6%, Fig. 1A and B). Contrast was quantified by \(\text{luminance}_{\text{target}} - \text{luminance}_{\text{dark}}/\text{luminance}_{\text{max}}\).
where luminance_{dark} and luminance_{max} were 0.11 and 14.4 cd/m², respectively. Background contrast was calculated by \((\text{luminance}_{\text{background}} - \text{luminance}_{\text{dark}})/\text{luminance}_{\text{max}}\), where luminance_{background} was the mean intensity of the random-dot pattern.

We introduced two kinds of motion to simulate the \textit{in vivo} eye movements of goldfish: \textit{jitter} motion (≈ fixation eye movements) and \textit{rapid} motion (≈ saccade) (Fig. 1). Jitter motion was a horizontal-biased random walk (4 µm/50 ms, shift toward the same direction was repeated twice). Rapid motion was a horizontal (caudal-rostral) random walk, the velocity of which was usually set to 80 or 108 µm/16.7 ms (≈ 80 or 108°/s; one degree of visual angle, ≈60 µm on the goldfish retina). In the simulated eye movement condition (the S2 condition), a global random-dot background jittered (Phase 1, ≈4.0 s in duration), then the target accompanying the background moved rapidly (Phase 2, ≈0.4 s in duration), and finally it stopped at the center of the background frame and jittered (Phase 3) (Fig. 1C). In the experiment where motion preference of GCs was tested, following the global background jitter motion (Phase 1), the target accompanying the background was rapidly shifted in one of four cardinal directions (Phase 2).

**Estimation of the receptive field.** The spatiotemporal receptive field (RF) was estimated by the reverse correlation method (Fig. 2A and B). The retina was stimulated with a series of pseudorandom (M-sequence) checkerboard patterns. Each frame (pixel size: 50 × 50 or 30 × 30 µm) was updated at 30 Hz. The checkerboard frames that preceded each spike discharge by a time \(t (0–660 \text{ ms}, \Delta 33 \text{ ms})\) were averaged (STA, spike-triggered average). For the estimation of the spatial profile of RF, we selected one temporal frame with maximal intensity from a series of 20 temporal frames. The center of RF was defined as the position of a pixel with maximal intensity. We determined the “edge” of the correlated region of 8 directions from the RF center (0–315°, Δ45°, Fig. 2A, right) as the position of a pixel with the intensity six times higher than the SD of the intensity in uncorrelated image, which was obtained by the spike train and newly generated independent stimulus sequence. Eight edges were fitted by an ellipse based on the method of least squares (Fig. 2A, left). For the estimation of the temporal profile of RF, we calculated the mean intensity of 3 × 3 pixels in the RF central region for each frame. Then we obtained 20 values from a series of 20 frames as the temporal STA (Fig. 2B). The temporal ON STA was used for classification of GCs because the target was brighter than the background. In ON-OFF type GCs, the spike-triggered covariance analysis was performed to discriminate ON and OFF spikes. PCA of spike-triggered ensembles decomposed the spike-triggered stimulus vectors into two clusters (ON and OFF). Recalculation of STA for each cluster enabled us to characterize the spatiotemporal properties of RF of ON-OFF type GCs clearly.

For classification of GCs, we performed PCA for the population of ON STAs (Fig. 2C and D). The first and second eigenvalues explained more than 80% of the variance of the population. The first and second PCA axes represent mainly the time course and duration of the temporal STA, respectively (Fig. 2D).

**Spike train analysis.** Peri-stimulus time histograms (PSTHs) were calculated with a 10-ms bin width, and were smoothed with a Gaussian filter (\(\sigma, 10 \text{ ms}\)). The response latency was defined as the time-to-response peak in the PSTH after the leading edge of the target arrived at the RF edge. The peak firing rate was defined as a reciprocal of the peak
value of the PSTH. To quantify the extent of firing modulation by rapid motion, the response index was defined by \((\text{PSTH}_{\text{peak}} - \text{PSTH}_{\text{base}})/(\text{PSTH}_{\text{peak}} + \text{PSTH}_{\text{base}})\), where \(\text{PSTH}_{\text{peak}}\) and \(\text{PSTH}_{\text{base}}\) are the peak spike number during stimulation and the mean spike number for 1 s immediately before stimulation, respectively.

For cross-correlation analysis, the raw cross-correlogram (RCC) was calculated with a 2-ms bin width during Phase 2 (rapid motion). The noise correlation (the shift predictor-subtracted cross-correlogram) was calculated by subtracting the shift predictor correlogram (SC) from the RCC. To quantify the correlation strength, the correlation index \((CI)\) was calculated by \([P - M]/SD\) (\(P\), peak value; \(M\), mean; \(SD\), standard deviation; brackets, absolute value) of the noise correlation between \(\pm 300\) ms correlation delay. \(M\) and \(SD\) were calculated within a lag time of 50 ms (\(\pm 50\) ms of the peak time). We calculated 95% confidence limit for each SC, and the correlation was assumed to be significant if the CI exceeded the confidence limit.\(^{34}\) We confirmed that the CI calculated for the combined period of Phase 2 and Phase 3 yielded statistically the same results as that for the period of Phase 2 alone (\(p = 0.37\), paired \(t\)-test, 315 GC pairs).

**Statistics.** Error bars indicate the SD unless otherwise denoted. Multiple comparisons were performed by Tukey’s method or Paired \(t\)-test with Bonferroni correction. Asterisk (*) in Figures means: *, \(p < 0.05\); **, \(p < 0.01\); ***, \(p < 0.001\). We used logistic regression to evaluate the response function statistically. To estimate the distance constant \(\lambda\), each data set was fitted by a single exponential function. The validity of these fittings was evaluated by the method of least squares.
Results

GC classification based on the temporal profile of receptive field. Spike discharges were simultaneously recorded from multiple GCs in the goldfish isolated retina. Stationary flash illumination (1,600 × 1,600 µm, 2 s) on a uniformly dark background (4,000 × 4,000 µm), evoked ON or ON-OFF spikes from the majority of GCs (ON, 12.2%, OFF, 3.5%, ON-OFF, 84.2%, 256 GCs, 10 retinas), and we used these ON and ON-OFF GCs (248 cells) for further analysis. The RF profile of each GC was estimated by the reverse correlation method (Fig. 2A and B).32,33 We performed principal component analysis of the temporal profile of ON spike-triggered average (STA) and categorized 248 GCs into six groups, which were assigned to Fast-transient (Ft, 17.8%), Fast-sustained (Fs, 13.7%), Medium-transient (Mt, 11.3%), Medium-sustained (Ms, 12.5%), Slow-transient (St, 17.3%), and Slow-sustained (Ss, 27.4%) GCs, respectively (Figs. 2C and D, and 3 left).

In response to a stationary flash, the order of response latency for the GC groups was Fast < Medium < Slow, and the peak firing rate of the transient GC groups was higher than that of the sustained GC groups (Fig. 3 middle left). To a rapidly moving target (1,600 × 1,200 µm, 6.48 mm/s: 108°/s; Middle right) on the dark background, each GC responded with cell-group specific latency after the leading edge of the target arrived at the edge of its RF (Fig. 3 middle right, dotted black line, the timing of target arrival). RF size varied among the GC groups (Fig. 3 right,
119 cells, $p = 4.3 \times 10^{-12}$, one-way ANOVA). Notably, Ft GCs had smaller RFs than other GC groups (the major axis of RF (µm), Ft, 175.68; Fs, 231.08, $p_{F1.08} > 10^{-5}$; Mt, 203.3, $p = 0.03$; Ms, 215.64, $p = 3.58 \times 10^{-4}$; St, 230.06, $p = 2.1 \times 10^{-6}$; Ss, 262.91, $p = 6.58 \times 10^{-9}$, t-test with Bonferroni correction). The RF size variance within each GC group suggests that each GC group may contain heterogeneous GC subtypes.

**Global random-dot background modulates the response properties to the rapidly moving target.** We examined how GCs respond to the global motion images evoked by simulated fixational and saccadic eye movements (fixational eye movements, 1–4 s in duration, 2–3 Hz in jitter frequency; saccade, >67°/s to the horizontal (caudal-rostral) direction$^{29,30}$ Fig. 4). These global motion images were projected onto a frame comprising the majority of the ventral retina area (4,000 × 4,000 µm; see Materials and methods) under two conditions, each of which consisted of three Phases. In the S1 condition (no background condition), a dark background was presented in the frame (Phase 1, 94.8 s in duration), then the target (1,600 × 1,200 µm) was rapidly moved (108°/s) horizontally from the left frame edge (caudal side) toward the center (Phase 2, ~0.4 s), and finally the target stopped at the center and jittered (Phase 3) Fig. 4A **upper**). In the S2 condition (the simulated eye movement condition), a random-dot pattern jittered within the frame (the
random-dot background: Fig. 1A; Phase 1, ∼4.0 s), then the target accompanying the background moved rapidly from the left frame edge toward the center (Phase 2, the simulated saccade; ∼0.4 s), and finally it stopped at the center and jittered (Phase 3) (Figs. 1C and 4A lower).

In the S1 condition, a Ft GC responded with a short latency after the leading edge of the rapidly moving target arrived at its RF in Phase 2, (Fig. 4B–D, black; Note that this result reflects a linear RF property in the dark background condition as shown in Fig. 3 middle right, Moving bar). Remarkably in the S2 condition, the same Ft GC responded before the target arrived at its RF edge in Phase 2 (Fig. 4B–D, blue). The response was actually triggered by the moving target because Ft GCs did not respond to the rapid horizontal motion of the random-dot background without target (the total number of spikes in Phase 2, means ± SD, 9.3 ± 3.2 in the S2 condition, 1.9 ± 1.6 in the background motion condition, 14 Ft GCs, \( p = 1.01 \times 10^{-5} \), paired t-test).

The response modulation by global motion images in Phase 2 was GC group specific (Fig. 4E and F). In Ft, Mt, St, and most Ss GCs, the response latency (the time-to-response peak in the peri-stimulus time histogram, PSTH; see Materials and methods) after the leading edge of the target arrived at the RF edge in the S2 condition was significantly shorter than that in the S1 condition (Fig. 4F, 81 GCs, \( p = 4.91 \times 10^{-4} \), interaction in two-way repeated ANOVA). Remarkably, Ft GCs showed negative response latency (means ± SD [ms], 15 Ft GCs, 86.6 ± 12.5 in S1, −53.1 ± 17.5 in S2, \( p = 1.41 \times 10^{-12} \), Tukey’s method), indicating that Ft GCs respond before the target arrives at the edge of their RFs. In Ft, Ms, and most Ss GCs, the peak firing rate in the S2 condition was higher than that in the S1 condition (Fig. 4G, 28 Ft GCs, 35 Ss GCs, \( p < 0.001 \); 13 Ms GCs, \( p < 0.05 \), paired t-test with Bonferroni correction). These results suggest that specific GC groups respond with fast and vigorous (high frequency) firing to the target during simulated saccades.

A critical role of global jitter motion in the response modulation. In the S2 condition Ft GCs responded with negative latency to the rapidly moving target in Phase 2 (Fig. 4B–F). To elucidate the factor(s) responsible for this drastic modulation of Ft GC responses, the retina was stimulated with various light patterns. Firstly, the random-dot background in Phase 1 was immobilized (the static background) and then the target accompanying the background rapidly moved together (Note that the stimulus pattern in Phase 2 was identical to that in the S2 condition). Ft GCs responded with positive latency to the target (Fig. 5A). The response latency of Ft, Mt, St, and Ss GCs was the same as that in the S1 condition. Secondly, the size of the random-dot background in Phases 1–3 was changed while the target size was kept constant. Ft GCs responded with negative latency to the target when the background size was wider than \( 3.2 \times 3.2 \text{ mm} \) (> ∼50°) (Fig. 5B). These results suggest that global jitter motion in Phase 1 is necessary for the response modulation. Thirdly, the background contrast in the S2 condition was changed (see Materials and methods). Ft GCs responded with negative latency to the rapidly moving target when the background contrast was in the range between 5 and 60% (25 Ft GCs, 3 retinas, Fig. 5C). Other GC groups never responded with negative latency to the target in any contrast range (5 Fs, 8 Mt, 12 Ms, 16 St, 38 Ss GCs, 3 retinas, Fig. 5D).

Spatial spread of the response modulation. To evaluate the spatial spread where Ft GCs respond with negative latency to the rapidly moving target in the S2 condition (Fig. 4F), the target was stopped halfway across the central region (Fig. 6A, stop@2). In the S1 condition, each GC responded only when the target arrived at its RF (Fig. 6B upper, colored). However, in the S2 condition, Ft GC responded even when the target stopped well short of its RF, (Fig. 6B lower, colored, Ft#4 arrow), though Ss GC never responded to the target short of its RF (Fig. 6B lower, colored, Ss#3).

The response index \( ([\text{PSTH}_{\text{peak}} - \text{PSTH}_{\text{base}}]/[\text{PSTH}_{\text{peak}} + \text{PSTH}_{\text{base}}]) \), PSTH_{peak} peak spike number during stimulation; PSTH_{base}, mean spike number for 1 s immediately before stimulation) of each GC was plotted against the distance between the leading edge of the stopped target and its RF edge (Fig. 6C). In the S1 condition, no GC responded before the target arrived at its RF (Fig. 6C upper). In the S2 condition, only Ft GCs produced responses when the target stopped short of the RF edge (even as far as ∼400 μm short, Fig. 6C lower), i.e., ∼100 ms before the target arrival (the target velocity was ∼80°/s or 4.79 mm/s on the retina).31

Locally coordinated firing among specific GCs during global rapid motion. We examined whether GCs fire independently or coordinately during global rapid motion (Phase 2 in the S2 condition). To quantify the temporal relation of
firing between GCs, cross-correlation analysis was performed. We calculated noise correlation using the shift predictor-subtracted cross-correlogram (see Materials and methods) which denotes temporal correlation in the trial-to-trial variability of firing.35)

We examined the temporal relation of firing between Ft GC pairs in Phase 2. In the S1 condition, Ft GCs responded ~80 ms after the target arrived at the RF edge (Fig. 3, Moving bar; Figs. 4B–F and 7B upper), indicating that the timing of spike generation is determined by the location of the stimulus with respect to the RF for each individual Ft GC. The correlation of firing between Ft GCs was low (Fig. 7D top, 28 pairs, 8 Ft GCs). In the S2 condition, however, nearby Ft GCs responded synchronously to the rapidly moving target (Fig. 7B lower; Cluster 1 [Ft#1 and Ft#2], Cluster 2 [Ft#4, Ft#5, and Ft#6], and Cluster 3 [Ft#7 and Ft#8]). Timing of synchronization was different from one cluster to another, depending on its location. In the noise correlation, a significant peak at 0 correlation delay appeared in pairs of nearby Ft GCs (Figs. 7C left and D middle) but not in pairs of distant Ft GCs (Fig. 7C right). No synchronized activity was observed in pairs of other GCs (Fig. 7D bottom, 105 pairs, 15 GCs).

Next, we examined whether Ft GCs respond with correlated firing with cells of other GC groups in the S2 condition. In the noise correlation, a peak appeared at a positive correlation delay in nearby Ms-Ft and Ss-Ft GC pairs (Figs. 7E and F, arrows), indicating that Ms and Ss GCs fire with a precise latency after the firing of a nearby Ft GC. In contrast, no obvious peak appeared in the range of ±200 ms in distant Ms-Ft and Ss-Ft pairs (Fig. 7E and F, gray; ~600 μm apart). Thus, specific GCs respond in a locally “coordinated” manner in the S2 condition to form a “cluster” (Fig. 7G black line, local GC clusters with high noise correlation).
To examine the spatial profile of local GC clusters, the range of spike coordination was estimated by calculating the correlation index ($CI$) which denotes normalized correlation strength$^{34}$ (see Materials and methods). In Ft-Ft, Ms-Ft, and Ss-Ft GC pairs, the $CI$ was large in adjacent pairs but it decreased exponentially with distance between the paired GCs ($\lambda = \sim 450 \mu m$) (Fig. 7H upper). In Fs, Mt, and St GC pairs, however, the $CI$ was consistently small irrespective of the inter-cell distance (Fig. 7H lower). The distance between GCs with high $CI$ corresponded approximately to the spatial spread of the response modulation in Ft GCs ($\sim 460 \mu m$, see Fig. 6C lower). These results suggest that in each local GC cluster the synchronized firing evoked in Ft GCs before the target arrives is followed by the temporally coordinated firing in Ms and Ss GCs after the target arrives.

In the S2 condition, the $CI$ in nearby Ft-Ft, Ms-Ft, and Ss-Ft GC pairs was significantly larger than that in other GC pairs (Fig. 7I, 393 pairs, 8 retinas, $p_F 1.61 \times 10^{-6}$, interaction in two-way repeated measures ANOVA, Tukey’s method, $p_s < 1 \times 10^{-20}$). For stimuli other than the S2 condition, namely,
without background (the S1 condition; Fig. 4B–D black), with static background (Fig. 5A), and with narrow background (Fig. 5B), the CI between any GC pairs was small (Fig. 7I), indicating that each GC responded to the rapidly moving target independently in these conditions. Thus, the coordination among specific GCs is not either equipped intrinsically or driven by the rapidly moving target per se. These results indicate that the specific GCs in a local cluster may be temporally coordinated only when a saccade is preceded by fixational eye movements.

The stimulus features that evoke the response modulation in Ft GCs correspond to the characteristics of in vivo eye movements. During spontaneous eye movements in a natural environment, goldfish make horizontal (caudal-rostral) saccades faster than ~6°/s (~4.0 mm/s on the retina;29,30) electrical stimulation of the goldfish tectum evoked horizontal but not vertical saccade30). To elucidate whether the response modulation in Ft GCs is consistent with the characteristics of in vivo saccades, we first examined the preference to motion direction in Phase 2 (Fig. 8A). In the S1 condition, no obvious direction selectivity was observed (Fig. 8B upper; Fig. 8C black, 19 Ft GCs, firing rate, n.s.; response latency, n.s., one-way repeated ANOVA). However, in the S2 condition, horizontal rapid motion evoked higher frequency firing than vertical motion (Fig. 8B lower; Fig. 8C upper blue, 19 Ft GCs, firing rate, p = 1.08 × 10^-20, one-way repeated ANOVA). Horizontal, but not vertical, rapid motion evoked responses with negative latency (Fig. 8B lower; Fig. 8C lower blue, response latency, p = 5.27 × 10^-23, one-way repeated ANOVA). Furthermore, the noise correlation between specific GC pairs (Ft-Ft, Ms-Ft, and Ss-Ft GC pairs, see Fig. 7I) during horizontal motion was higher than that during vertical motion (Fig. 8D; Fig. 8E, red bars, CI in 28 Ft-Ft, Ms-Ft, and Ss-Ft GC pairs, p = 1.86 × 10^-5; gray bars, CI in 109 pairs from other GC groups, n.s., one-way repeated ANOVA, paired t-test with Bonferroni correction). Second, we examined the velocity tuning of the response latency to the horizontally moving target in Ft GCs. Ft GCs responded with positive latency to the target for velocities slower than ~60°/s, whereas these cells responded with negative latency for velocities faster than ~80°/s (Fig. 8F, blue shaded area; velocity of in vivo saccades29,30). It is evident that the preferred direction and the effective velocity for response modulation during global rapid motion (Phase 2 in the S2 condition) are consistent with the characteristics of in vivo goldfish saccades.

The present results show that global background jitter motion in Phase 1 of the S2 condition is a prerequisite for the observed response modulation and the temporally coordinated firing in Phase 2 (Figs. 4F, 5A and B). To investigate the time dependence of background jitter effects, we varied the duration of global jitter motion in Phase 1 to each of several values between 0.1 and 6 s (Fig. 8G–I). We found that global jitter motion longer than ~1 s was required for both aspects of the response modulation in local GC clusters in Phase 2: the generation of responses with negative latency in Ft GCs (Fig. 8G) and the establishment of high noise correlation between specific GCs (Fig. 8H; Fig. 8I, red bars, 79 Ft-Ft, Ms-Ft, and Ss-Ft GC pairs, p = 1.17 × 10^-6; gray bars, 116 pairs from other GC groups, n.s., one-way ANOVA, paired t-test with Bonferroni correction). These results are consistent with the characteristics of in vivo goldfish fixational eye movements29 (Fig. 8G, green shaded area; the range of in vivo fixation, cyan dotted line; the median duration 2.03 s29), suggesting a possible contribution of slow contrast adaptation mechanisms in the inner retina (time constant of 1–2 s, see Discussion; salamander;37,38) zebrasfish39).

Electrical and GABAergic synaptic transmission is required for coordinated firing during global rapid motion. The critical role of global jitter motion in response modulation suggests a possible involvement of wide-range lateral interactions in the retina. Diverse gap junctions are found between various retinal neurons40,41) and electrical transmission through gap junctions serves various lateral interactions.40,42–46) In the retina, gap junctions are in a position to mediate the global response modulation we observed because they electrically couple Mbi bipolar cells (BCs), which are ON-type presynaptic neurons to ON and ON-OFF GCs. Note that the wide-range lateral, but not the local, modulation at the Mbi BC terminal is affected by mefloquine (MFQ, a specific blocker of connexin 36/5017,41) To investigate whether electrical transmission is required for global response modulation in Phase 2, MFQ (10 µM) was bath-applied to the retina (Fig. 9A–D). We found that in the presence of MFQ Ft GCs responded to the moving target with positive latency in the S2 condition comparable to that in the S1 condition (Fig. 9A lower, orange trace) and that the synchronized firing in adjacent Ft GC pairs disappeared (Fig. 9B upper, orange trace) reversibly (Fig. 9A lower, blue trace). We also found that gap junctions contributed to the shortening of
the response latency in Mt, St, and Ss GCs (Fig. 9C, 76 GCs, main effect of cell type, \( p = 1.54 \times 10^{-6} \), main effect of MFQ, \( p = 7.81 \times 10^{-23} \), interaction, \( p = 0.001 \), two-way repeated measures ANOVA, paired \( t \)-test with Bonferroni correction) and the establishment of the noise correlation in Ft-Ft, Ms-Ft and Ss-Ft GC pairs (Fig. 9B and D, 103 GC pairs, \( p = 7.24 \times 10^{-43} \), one-way repeated measures ANOVA, paired \( t \)-test with Bonferroni correction).

It has been shown that GABAergic ACs modulate lateral interaction in the retina. 12) We examined whether GABAergic transmission also contributes to the response modulation. In the S2 condition, bath-applied GABA antagonist (picrotoxin, 100 µM) changed the response latency from negative to positive and reduced the noise correlation in Ft GC pairs (Fig. 9E–G). These results suggest that lateral interactions mediated by electrical and GABAergic synaptic transmission are required for the response modulation of specific GCs during simulated eye movements.
Discussion

We find that global motion images during simulated fixational and saccadic eye movements are processed in a coordinated manner by local clusters of specific GCs in the goldfish retina. Global rapid motion following a period of global jitter motion evokes fast, high-frequency, and temporally correlated firing in local clusters of specific GCs (Ft, Ms, and Ss GCs). The parameters of the simulated motion (duration of global jitter motion, and preferred direction and effective velocity of global rapid motion) that evokes the response modulation are consistent with the characteristics of in vivo goldfish eye movements.\(^{20,30}\) The wide-range lateral interaction, possibly mediated by electrical and GABAergic synaptic transmission, contributes to the response modulation. These results demonstrate that the retinal processing during global motion induced by eye movements is different from that resulting from local motion or presentation of static images. There are many ways in which this unique processing may help the retina to inform the brain about the retinal image as it moves during fixational and saccadic eye movements, and previously-described retinal circuitry may provide some of the neuronal basis for the processing.

Response modulation induced by global motion images far beyond the classical RF.

Global modulation mediated by GABAergic amacrine cells. Retinal GCs have spatially-tuned (center/ surround antagonistic) RFs.\(^{13,14}\) Accumulating evidence indicates that the response properties of GCs are also affected by wide-field dynamic stimulation outside the classical RF.\(^{16,19,39}\) Responses to motion stimulation in the RF of cat Y-type GCs and the analogous rabbit brisk-transient GCs are modulated by global stimulation of the far-surround region of the classical RF.\(^{48,49}\) Specific GCs of the rabbit retina receive inhibitory inputs during the global shift in the peripheral retina, resulting in saccadic suppression.\(^{18}\) Several studies report that the peripheral modulation is mediated by wide-field amacrine cells (ACs).\(^{16,18,19,49}\)

We found that the response modulation of Ft GCs occurred only when the size of the jittered background was larger than \(\sim 3 \times 3 \text{ mm (} > \sim 50^{\circ};\) Figs. 5B and 7I). In the fish retina, several ACs have

![Fig. 9. Effects of a gap junction blocker and a GABA antagonist on the response modulation. (A) Effects of a gap junction blocker, mefloquine (MFQ, 10 µM). Firing of a Ft GC before (black, control), during (orange, MFQ), and after (blue, Washout) application of MFQ. Gray, yellow, and dotted gray lines indicate the Phase 2 onset, the period of Phase 2, and the timing of the target arrival at the RF edge, respectively. (B) The noise correlation calculated from Ft#2-Ft#1 (upper) and Ss-Ft#1 (lower) pairs in the control (black) and MFQ (yellow) conditions. (C) Response latency in the control (colored) and MFQ (black) conditions (76 GCs, 4 retinas). Black and gray bar, mean ± SD. (D) Effects of MFQ on the CIs calculated from Ft-Ft, Ms-Ft, and Ss-Ft GC pairs (124 pairs). Red, mean ± SD. (E, F) Effects of a GABA antagonist, picrotoxin, (PTX, 100 µM). Blue, control. Red, PTX. Firing in Phase 2 (E) and the noise correlation of the Ft GC pair (F). (G) Effects of PTX on the response latency (left, 10 Ft GCs, 3 retinas) and the correlation index (CI) (right, 13 Ft pairs, 3 retinas). *, p < 0.05. ***, p < 0.001. Paired t-test with Bonferroni correction.](image-url)
wide dendritic fields and wide RFs (a few mm in diameter) (goldfish;[50]–[52] Japanese dace53)). GABAergic synapses, deriving primarily from ACs, comprise a majority of the inhibitory synapses in the inner plexiform layer (goldfish53). It has been shown that local and lateral inhibition at the BC terminal is mediated by different types of GABAergic ACs.[41,55] In particular, lateral inhibition is activated by the AC which receives input from a wide area through the electrically coupled Mb1 BC network in the goldfish retina43) (see also below). We found that response modulation disappeared in the presence of a GABA antagonist (Fig. 9E–G) as well as gap junction blocker (Fig. 9A–D). It seems likely that global networks mediated by wide-field and/or electrically coupled GABAergic ACs43,52) and by electrically coupled Mb1 BCs contribute to the response modulation. In addition, it has been shown that contrast adaptation gradually depresses the synaptic transmission from BC to AC,[39,56,57] If AC-mediated inhibition is reduced during long (> ~1 s) global jitter motion (Phase 1, Fig. 8G–I) by synaptic depression, such disinhibition may sensitize the response properties of BCs and, in turn, that of GCs.

**Global modulation mediated by gap junctions.** It has been shown that retinal gap junctions40,41) contribute to the neural noise reduction that is mediated by signal transmission far beyond each classical RF.[31,42,45,46] In the goldfish retina, it is possible that global jitter motion (Phase 1 in the S2 condition) reduces the neural noise and synchronizes the membrane fluctuations in electrically coupled Mb1 BCs.[43,44] The synchronized excitatory inputs from electrically coupled BCs to GCs would contribute to the fast and high-frequency firing and the correlated activity in Ft GCs (Note that high noise correlation between neurons may reflect the correlated presynaptic inputs58)).

The delayed correlation between Ms-Ft GC pairs and between Ss-Ft GC pairs may also be explained by electrical coupling. The spatial spread of excitation in an electrically coupled neuronal network may contribute to sequentially correlated activity. It has been shown that moving bar stimulation evokes delayed firing in coupled GCs (Hb9 retinas in mouse)55) and delayed correlation between GCs.[46,58] It seems likely that the electrically coupled Mb1 BCs mediate the spread of signals and contribute to the delayed and correlated inputs to GCs (Fig. 7E and F). Second, Slow-type GCs receive slow synaptic input from BCs with slow kinetics of glutamate release.[60,61] This explanation is consistent with the observation that the response latency in Ss GCs was much longer than that in Ft GCs to a stationary flash on the dark background (Fig. 3 middle left, Flash).

**Functional relevance.** Fast and synchronous firing during saccade. We found that the response latency to the rapidly moving target in the simulated eye movement condition (the S2 condition) is shorter than that in either the dark (the S1 condition), the static, or the narrow background condition in specific GCs (Figs. 4F, 5A and B). During visual motion processing, compensation of the neuronal temporal delay between the retina and the brain is a serious problem that must be solved to estimate the object location in the visual space.[62] Thus, retinal encoding with short latency would be a useful mechanism to transmit information about a visual scene rapidly.[63]

The responses of several GC types, such as fast-OFF GCs in the salamander retina, anticipate the arrival of a moving stimulus in their RFs.[62,64] Population activity of fast-OFF GCs can extrapolate the trajectory of a moving object (such as a prey motion seen in the natural scene), and could be utilized in the brain for prediction of the future position.[64] The mechanisms of motion anticipation are assumed to be dendritic computation and feedforward inhibition from ACs during moving stimulation.57 In contrast, the response modulation of Ft GCs in our study was not evoked by local object motion (the S1 condition) but by eye movement-like global motion, and are better explained by a retina-wide network mediated by electrical coupling and GABAergic ACs (Fig. 9). It is likely that the retinal anticipatory signal for motion trajectory reported in previous studies62,64) serves to compute the local object motion during visual fixation, whereas the coordinated GC signals described in our study may send visual representation during and immediately after saccades. Our finding that Ft GCs fire synchronously before the target arrives at their RFs (Figs. 4F and 6B, C) suggests that the brain may promptly receive the information about the future visual scene from the Ft GCs that fire during saccades.

**Coordinated firing during global rapid motion.** A saccade is fast in velocity and brief in duration. If retino-recipient neurons function by an integrate-and-fire mechanism, these neurons would not be activated efficiently during saccades. However, synchronous firing of Ft GCs (Fig. 7C) may allow retino-recipient neurons to improve their efficiency of integration and to respond with enhanced activities.
In addition, this enhanced activity would facilitate the processing of the delayed input from Ms and Ss GCs in postsynaptic neurons. Furthermore, the correlated firing of GCs with temporal difference (Fig. 7E and F) may be suitable for calculation of motion information: the Reichardt motion detector uses the temporal difference of firing between two cells.69 Thus, the coordinated firing with precise delay established in the retina would present useful visual information to the brain. In the goldfish visual system, the optic tectum has a topographical map,36 and the midbrain (mesencephalic reticular) and the optic tectum have reciprocal circuits that regulate eye movements.67 The lateral preglomerular nucleus also receives retinal signals and relays these signals to the dorsal telencephalic area (pallium of the cerebrum homologue68). These areas are possible candidates for projection areas of specific GCs which are modulated during eye movements. Our results demonstrate that specific GCs perform a characteristic coding of global motion images. Such ongoing processing during eye movements in the retina may contribute to visual computation in the brain.

**Modulated retinal signals sent to the brain during saccades.** We show that Ft, Ms, and Ss GCs respond to the rapidly moving target with unique firing rate (Fig. 4G) and noise correlation during saccadic global motion (Fig. 7C–F). A possible functional meaning of this finding may be to send “reafferent” signals to the brain during saccades (Note that “reafference” is the retinal signal generated not by local motion in the environment but by global motion induced by saccades3,69). High firing rate (Fig. 4G) and the correlation structure in GC firing (Fig. 7C–F) could provide powerful information for the brain to interpret images during eye movements. Even when activities of cortical neurons in some visual areas of the brain are suppressed just before and during saccades,3 specific retinal GCs could send reaferent signals related to the saccades without interruption.

Peripheral modulation is assumed to serve as the basis for information processing during saccades.17,18 In the present study, we confirm that the peripheral stimulation corresponding to the eye movements evokes a conspicuous retinal output (Figs. 4 and 8). In natural vision, the whole retina is stimulated by a visually-rich environment,30 and firing properties of GCs are appropriately modulated. Our results show that the response modulation of specific GCs during simulated eye movements is a part of the mechanism by which the visual system continues to interpret retinal images correctly as the eye is constantly moving during fixational and saccadic eye movements.

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