Effects of Vergence on Human Ocular Following Responses (OFR)

Anand C. Joshi
Matthew J. Thurtell
Mark F. Walker
Alessandro Serra
R. John Leigh

Departments of Biomedical Engineering and Neurology, Daroff-Dell’Osso Laboratory, Veterans Affairs Medical Center and University Hospitals, Case Western Reserve University, Cleveland, OH;

Keywords: Visual tracking, saccades, gaze shifts; optokinetic; pursuit; first-order motion

Running title: Ocular Following and Vergence

Address correspondence to R. John Leigh, M.D., Department of Neurology, 11100 Euclid Avenue, Cleveland Ohio 44106-5040. Phone: 216-844-3190; Fax: 216-231-3461; Email: rjl4@case.edu
Abstract

The human ocular following response (OFR) is a pre-attentive, short-latency visual field-holding mechanism, which is enhanced if the moving stimulus is applied in the wake of a saccade. Since most natural gaze shifts incorporate both saccadic and vergence components, we asked whether the OFR was also enhanced during vergence. Ten subjects viewed vertically moving sine-wave gratings on a video monitor at 45 cm that had a temporal frequency of 16.7 Hz, contrast of 32%, and spatial frequency of 0.17, 0.27 or 0.44 cycles/°. In Fixation/OFR experiments, subjects fixed upon a white central dot on the video monitor, which disappeared at the beginning of each trial, just as the sinusoidal grating started moving up or down. We measured the change in eye position in the 70 – 150 ms, open-loop interval following stimulus onset. Group mean downward responses were larger (0.14°) and made at shorter latency (85 ms) than upward responses (0.10° and 96 ms). The direction of eye drifts during control trials, when gratings remained stationary, was unrelated to the prior response. During vergence/OFR experiments, subjects switched their fixation point between the white dot at 45 cm and a red spot at 15 cm, cued by disappearance of one target and appearance of the other. When horizontal vergence velocity exceeded 15 °/s, motion of sinusoidal gratings commenced and elicited the vertical OFR. Subjects showed significantly (p < 0.001) larger OFR when the moving stimulus was presented during convergence (group mean increase of 46%) or divergence (group mean increase of 36%) compared with following fixation. Since gaze shifts between near and far are common during natural activities, we postulate that the increase of OFR during vergence movements reflects enhancement of early cortical motion processing, which serves to stabilize the visual field as the eyes approach their new fixation point.
Introduction

The human fovea corresponds to the area of retina with greatest visual acuity for objects with high spatial frequencies, such as conventional text. Thus, the foveal line of sight of each eye must be pointed at a feature of interest in the visual environment to see it best (Carpenter 1991). Many elements of the visual world lie in different directions and at different distances (depths). Consequently, most natural shifts of the binocular point of fixation are achieved using a combination of saccades and vergence movements (Collewijn et al. 1995). During locomotion, shifts of the binocular point of fixation between a hand-held object and the distant visual environment may occur frequently, such as when a hunter moves his point of visual fixation from a near, hand-held weapon to a distant prey. During such gaze shifts, the visual background is moving due to the optic flow caused by locomotion. Thus, it appears that some short-latency mechanism is required to hold the eye steady at its new point of fixation, whether at near or far.

The human ocular following response (OFR) is a pre-attentive, short-latency visual tracking mechanism, which seems suited to act as a visual field-holding response (Miles 1998; Sheliga et al. 2005; Sheliga et al. 2008). Thus, the OFR is enhanced by as much as 100% in the wake of a saccade, when ocular drifts occur and could constitute a threat to clear vision, if not promptly terminated (Gellman et al. 1990). The OFR has been extensively studied in response to horizontal stimulus motion (Sheliga et al. 2005; Sheliga et al. 2008), but during fixation of a near object in the lower visual field, the background optic flow induced by locomotion is predominantly downward. Thus, the first goal of this study was to examine the vertical OFR in a group of ten normal human subjects, define their range of responses and relate them to other forms of visual tracking during locomotion, such as optokinetic responses. A second goal was to determine if the vertical OFR would be enhanced as subjects shifted their point of fixation between targets lying at different depths in the horizontal plane. We found that the vertical OFR was enhanced during ongoing smooth vergence eye movements compared with
responses when there was no need to shift the point of visual fixation. Preliminary results have appeared as an abstract (Joshi et al. 2008).

Subjects and Methods

We studied 10 healthy human subjects (8 male; median age 38, range 27-61 years); five were naive to the goals of the study. None were taking any medicine with effects on the central nervous system. All gave informed written consent in accordance with the Declaration of Helsinki and our Human Subjects Institutional Review Board. Binocular eye movements were measured using the magnetic search coil technique (Robinson 1963); the standard deviation (SD) of the noise of our system was $\pm 0.016^\circ$.

Visual Stimuli

Subjects sat in a dark room with their head stabilized by supports attached to a chair with a distance of 45 cm from the corneal vertex to a Viewsonic G225fB computer monitor; any small head movements that occurred were detected using a search coil attached to their forehead. Visual images presented on the computer monitor were viewed binocularly and consisted of one-dimensional horizontal sine-wave grating patterns shifted at a temporal frequency of 16.7 Hz, which has been shown to evoke optimal responses (Gellman et al. 1990). These stimuli had a contrast of 32%, and a spatial frequency ($F_s$) of 0.17, 0.27 or 0.44 cycles/$^\circ$, so that corresponding speeds were 100, 62.5, and 37.5$^\circ$/s. Each image extended 400 mm horizontally (1600 pixels, subtending 50$^\circ$) and 300 mm vertically (1200 pixels, subtending 37.5$^\circ$); mean luminance was 42.6 cd/m$^2$, and frame rate was 100 Hz (Sheliga et al. 2005). The initial phase of a given grating was randomized from trial to trial at intervals of 1/6-wavelength. Prior to each OFR-fixation trial, subjects viewed a white central spot (diameter, 0.25$^\circ$) centered on stationary gratings on the computer monitor. For experiments in which OFR was tested during vergence movements, subjects viewed a “near stimulus”, consisting of a red laser spot (diameter 0.4$^\circ$), which was projected onto a transparent sheet of plastic at a viewing distance of 15 cm. Before testing, a 9 point calibration procedure was run as subjects fixed upon a small white dot that moved from the center to 4 horizontal and 4 vertical eccentric positions on the computer monitor.
Subjects who were not emmetropes wore their spectacles during testing, and we were able to make an adjustment for the rotational magnification due to their refractive correction during this 9-point calibration procedure. Three test paradigms, each with a control, were applied; these are summarized in Figure 1. In addition, four further control experiments were conducted to take account of differences in visual stimuli during each of the test paradigms.

**Fixation/OFR experiments:** Subjects were instructed to fix upon a white spot centered on a grating pattern on the video monitor, which was presented for a random period of 200-300 ms, before it disappeared, just as the sinusoidal grating started moving up or down (Figure 1A). The motion lasted for 200 ms, at which point the screen became a uniform gray (luminance, 42.6 cd/m²), marking the end of the trial. After an inter-trial interval of 1500 ms a new grating pattern together with a fixation point appeared, commencing a new trial. During 20% of trials, the sinusoidal grating remained stationary during the trial, instead of moving up or down (Fixation/OFR control trials – Figure 1B).

**Divergence/OFR experiments:** Subjects were instructed to fix upon the near red stimulus, with the monitor screen set at an iso-luminance gray; after a randomized period of 2.5-3 s, the near red stimulus was turned off and the white spot and gratings appeared on the monitor, which was the cue to diverge. The OFR stimulus (and offset of the white spot) was triggered when divergence velocity exceeded a threshold of 15°/s (Figure 1C). In practice, the time period from when divergence velocity exceeded this threshold until the onset of vertical motion of the sinusoidal grating was about 30 ms. During 20% of trials, the sinusoidal grating remained stationary during the divergence movement (Divergence/OFR control trials – Figure 1D).

**Convergence/OFR experiments:** Subjects were instructed to fix upon the white spot centered on stationary gratings on the computer monitor; after a randomized period of 2.5-3 s, the white spot was turned off and the near red spot appeared, which was the cue to converge. The OFR stimulus was triggered (and the red spot was turned off) when convergence velocity exceeded a threshold of 15°/s; the actual onset of vertical motion of the sinusoidal grating occurred about 30 ms later (Figure 1E).
During 20% of trials, the sinusoidal grating remained stationary during the convergence movement (Convergence/OFR control trials – Figure 1F).

Each Fixation/OFR and Vergence/OFR session lasted for 150 seconds, comprising 6 different stimulus conditions (3 spatial frequencies and 2 directions of motion). Stimulus conditions, including control trials, were randomized in order and timing of presentation. Subjects completed at least three sessions for each of the three test paradigms, with rest breaks in between (total test time: about 20 minutes).

Control Experiments: Four sets of control experiments were conducted on four subjects. Control Experiments 1 and 2 induced a "gap" between offset of the fixation target and onset of grating motion; Control Experiments 3 and 4 had "no-gap" between the offset of the fixation target and onset of grating motion. Thus, for Control Experiment 1, the fixation target was turned off and vertical grating motion started after a controlled delay, which was the average time that each subject took to reach the convergence threshold (15°/s) during Convergence/OFR experiments. For Control Experiment 2, the fixation target was turned off and vertical grating motion started after a controlled delay, which was the average time that each subject took to reach the divergence velocity threshold (15°/s) during Divergence/OFR experiments. For Control Experiment 3, subjects fixated on the white spot, with no gratings pattern, on the monitor for 2.5-3 s, and the moving grating stimulus was presented for the last 200-300 ms, (similar to stimulus presentation during the Divergence/OFR experiments). For Control Experiment 4, subjects fixated on the white spot, centered on stationary gratings pattern, on the monitor for 2.5-3 s, and the moving grating stimulus was presented for the last 200-300 ms, (similar to stimulus presentation during the Convergence/OFR experiments). Responses from each of these control experiments were compared with responses from the standard Fixation/OFR experiment.

Data Analysis

Horizontal and vertical eye position data were obtained from coil signals following analog low-pass filtering (0-150 Hz) and digitization at 500 Hz with 16-bit precision. For Fixation/OFR trials, we measured the change in eye position (OFR amplitude) in the interval 70 – 150 ms following stimulus
onset. We also estimated the latency of OFR, by fitting a linear regression within the subset of data between 0 and 70 ms and within the subset of data between 90 and 150 ms after stimulus onset, and measuring time at the intersection point of these lines (Carl and Gellman 1987). The minimum latency of onset was ~80 ms (see Results), so that the measured OFR amplitude corresponded to the initial open-loop response. Each response was extracted and filtered as previously described (Sheliga et al. 2005). Trials contaminated with saccadic intrusions (identified interactively when horizontal or vertical eye velocity exceeded a threshold of 15 °/s during the OFR) were deleted. The control trials exhibited consistency across the 3 spatial frequencies and were not dependent on the direction of the stimulus, and were so averaged for each individual paradigm and subject. After discarding trials contaminated with saccades or blinks, the median number (range) of trials per subject for all conditions during Fixation/OFR was 219 (179-257) of which 44 (29-52) trials were control experiments. During Divergence/OFR the median number (range) of trials per subject was 94 (52-181) of which 24 (15-36) were control experiments. During Convergence/OFR the median number (range) of trials per subject was 70 (55-163) of which 17 (12-33) were control experiments.

For data from experiments in which OFR occurred during a vergence movement, it was also necessary to take into account any vertical eye movements associated with the vergence movement and any associated small vertical saccades. In practice, each subject showed a small vertical eye movement in association with the shift of the fixation point between far and near, even if the targets were carefully aligned. Such vertical movements were idiosyncratic, but stereotyped, for each subject. Based on prior approaches to this problem (Gellman et al. 1990; Zee et al. 1992), we analyzed our data in the following way. First, we averaged vertical eye movement components of the responses from the control trials, which consisted of convergence or divergence responses made against a stationary visual background. We then subtracted these mean vertical components of control convergence or divergence responses from corresponding OFR responses made with convergence or divergence movements for each subject. We also used a simple model to compare responses during Fixation/OFR and Vergence/OFR for each subject at each spatial frequency, applying the techniques of parameter
Results

OFR following fixation of a stationary target

Figure 2 displays mean, representative upward responses from Subject 7 and downward responses from Subject 5 for each of the three spatial frequencies for the three paradigms (black traces). Vertical dashed lines indicate the times at which eye position was sampled (70 ms and 150 ms) to calculate the amplitude of the OFR.

Figure 3 is a boxplot summarizing mean amplitude values of OFR from all 10 subjects. Group mean OFR ± standard error of mean (SEM) of upward responses was 0.10 ± 0.01° and of downward responses was 0.14 ± 0.02°, similar to values previously reported (Gellman et al. 1990). Substantial inter-subject variability was evident, but a paired t-test showed that downward mean responses were significantly greater in amplitude than upward mean responses (p <0.001). Using a pair-wise multiple comparison procedure (3-way ANOVA, Holm-Sidak method), we found that the Fixation/OFR response magnitude showed dependence on the spatial frequency of the stimulus (p<0.001). The group mean ± SEM response amplitude for each spatial frequency were: Fs of 0.17 cycles/°: mean amplitude = 0.16 ± 0.02°; Fs of 0.27 cycles/°: mean amplitude = 0.12 ± 0.02°; Fs of 0.44 cycles/°: mean amplitude = 0.08± 0.02°. Thus, despite the inter-subject variability, there was an inverse relationship between OFR amplitude and the spatial frequency of our stimuli; this is evident in Figure 3.

We found that the latency (mean ± SD) to onset of downward OFR (85 ms ± 15) was significantly shorter (p<0.001) than that of upward OFR (96 ms ± 17). Using a 3-way ANOVA, we found that latency showed dependence on the spatial frequency (p = 0.005), being significantly shorter (84 ± 14 ms) for the lowest spatial frequency (Fs of 0.17 cycles/°, p< 0.023). However, latency was not statistically different between the two higher spatial frequencies (91 ± 18 ms for 0.27 cycles/° and 95 ± 17 ms for 0.44 cycles/°).

We investigated whether eye drifts occurring during each Fixation/OFR control trial was
influenced by the moving stimulus of the prior trial. We found that eye drifts during control trials were small, idiosyncratic and stereotyped for each subject, and uncorrelated with the direction of grating motion in the preceding trial ($r = -0.05$).

**Comparison of OFR with predictable visual tracking**

Since different subjects showed a broad range of OFR values (Figure 3), we asked whether this variability was related to smooth ocular following of predictable target motion (Kawano 1999; Leigh and Zee 2006). Accordingly, we compared OFR and “optokinetic responses” (OKR) to a 0.27 cycles/º grating that moved sinusoidally through several cycles at frequencies between 0.1 – 2.5 Hz. Note that this visual stimulus was predictable, not open-loop, and that subjects attempted to track an individual grating (“look” optokinetic responses). Inspection of Bode plots of OKR (Figure 4, top) indicated that the gain (eye velocity/target velocity) declined sharply for frequencies above 1 Hz, and so we conducted a paired comparison of OKR gain at 1.0 Hz and mean OFR amplitude in response to the 0.27 cycles/º stimulus. The OKR gain and mean OFR amplitudes were separately normalized by assigning a value of 1.0 for the response of the individual with the best tracking and scaling values for other subjects proportionally. Figure 4 (bottom) shows that there was no correlation between OFR and OKR for up or down movements for our group of 10 subjects. Thus, these two tracking behaviors appear to differ, as previously suggested (Gellman et al. 1990).

**OFR during vergence movements**

Figure 5A displays mean (total number of trials =133) upward and downward OFR during divergence movements from Subject 2; note that the downward response to the 0.44 cycles/º stimulus is small and does not move the eye below zero vertical position. Figure 5B shows the mean (n=33) vertical eye movement occurring during divergence when the visual background was stationary (divergence control trials). Note that the upward drift in Figure 5B persists throughout the 200 ms epoch. Such vertical eye drifts associated with the vergence response occurred even after careful attempts to align the near and
far targets and, when they persisted beyond 70 ms after the onset of grating motion, we assumed that they would be superimposed on the OFR. Such an effect could be corrected as shown in Figure 5C, which shows the results of subtracting the waveform in panel B from the OFR responses in panel A, and offsetting the curves to zero at 70 ms. We confirmed that the direction of eye drifts occurring during vergence control trials, when gratings were stationary, was not correlated ($r = 0.04$) with the stimulus direction in the prior trial. Furthermore, we carried out a paired comparison of mean change of vertical eye position during the period 0-60 ms after the onset of grating motion for upward versus downward stimuli for each subject at each spatial frequency and found no significant difference for either convergence ($p=0.052$) or divergence ($p=0.13$).

Figure 2 compares representative upward and downward Fixation/OFR raw responses (in black) versus Divergence/OFR responses (in red) and Convergence/OFR responses (in blue), from two subjects, S5 (downward responses) and S7 (upward responses), for each of the three spatial frequencies. The responses made during vergence/OFR are greater than responses during Fixation/OFR. Of the group of subjects, three were unable to reliably generate divergence responses and two were unable to generate convergence during our test conditions. The remaining subjects, as for Fixation/OFR, showed substantial variability of the amplitude of responses between individuals. Group mean ± SEM was $0.19^\circ \pm 0.02^\circ$ for Divergence/OFR, and $0.22^\circ \pm 0.02^\circ$ for Convergence/OFR. A paired t-test of Convergence/OFR versus Divergence/OFR responses for each subject, stimulus direction and spatial frequency showed no significant differences ($p=0.06$). Paired t-tests showed no significant differences between the amplitude of upward and downward responses during either divergence ($p=0.62$) or convergence ($p=0.24$) movements. Thus, group mean ± SEM OFR amplitude for upward/divergence was $0.18\pm0.02^\circ$ and for downward/divergence was $0.19\pm0.02^\circ$; group mean OFR amplitude for upward/convergence was $0.21\pm0.02^\circ$ and for downward/convergence was $0.24\pm0.02^\circ$. Using a pair-wise multiple comparison procedure, we found that the Divergence/OFR response magnitude showed no dependence on the spatial frequency of the stimulus ($p = 0.623$). For Convergence/OFR responses, the magnitude showed a significant ($p=0.002$) dependence on the spatial
frequency of the stimulus, except between the higher two frequencies. Thus, for Fs of 0.17 cycles/º, mean ± SE amplitude was 0.30±0.03º; for Fs of 0.27 cycles/º, mean amplitude was 0.19±0.02º; and for Fs of 0.44 cycles/º, mean amplitude was 0.18±0.03º.

Using a paired t-test, we found no significant difference between the latency of upward (mean ± SD: 83 ± 15 ms) versus downward (82 ±9 ms) responses during Divergence/OFR (p = 0.697). However, during Convergence/OFR, we observed significantly greater (p = 0.01) latency for upward (89 ± 14 ms) versus downward (80 ± 11 ms) responses. The latency was not dependent upon the spatial frequency for either Divergence/OFR or Convergence/OFR. There was no significant difference in latency between Convergence/OFR versus Divergence/OFR.

Comparison of Fixation/OFR and Vergence/OFR

Figure 6 displays a paired comparison of the amplitude of responses for each subject at each spatial frequency for OFR following fixation (abscissa scale) versus OFR either during divergence (A and C) or convergence (B and D) (ordinate scale). Subjects showed significantly larger OFR during convergence (absolute group mean increase of 46%) or divergence (absolute group mean increase of 36%) compared with following fixation.

Note that the Vergence/OFR data in Figure 6 have been calculated using the drift correction exemplified in Figure 5. Since some convergence responses showed a persistent drift even after this correction, we carried out a further analysis after eliminating such responses. To select responses to eliminate, we used a criterion of change in eye position exceeding two standard deviations for the corresponding vergence control during the period 0-60 ms following stimulus onset. Using this reduced data set (mean number of trial per subject =46), paired comparison of mean amplitudes still demonstrated a significantly greater response (p< 0.001) for Convergence/OFR versus Fixation/OFR.

We also considered a second way in which persistent vertical drifts associated with vergence responses could influence OFR: they could subtract from retinal image slip due to grating motion. Prior studies have suggested that retinal image slip due to saccades have less than 30% effect on OFR
(Gellman et al. 1990), but vertical slip due to vergence movements is more prolonged and might
directly affect OFR. Thus, to estimate the magnitude by which retinal image slip due to the vertical
component of vergence may have affected OFR, we applied a simple model in which retinal image
velocity was due to both vertical eye drifts and the motion of the visual stimulus (Figure 7). Note that
our goal was to address two issues: (1) whether vertical eye drifts influenced the stimulus for OFR; (2)
whether there was an increase of internal gain (G) during Vergence/OFR. First, we calculated optimal
values of the internal parameters, gain G, and time constant T, for the mean Fixation/OFR response of
individual subjects at one spatial frequency (see Appendix for details). We took into account any small
drifts that occurred during control trials when the gratings were stationary. Thus, EVcontrol is mean eye
drift during Fixation/OFR control trials, and EVOFR is the model’s output. The value of the Delay was
set as measured for that subject and stimulus. The model gave a good fit, defined here as a residual
sum-of-squares error of < 20% and R² values > 0.9, for > 80% of subjects upward or downward mean
Fixation/OFR responses at each frequency; a representative example is shown in Figure 7B. We then
asked whether the model with the parameter values estimated for Fixation/OFR could also simulate
mean Divergence/OFR or Convergence/OFR responses to the same visual stimulus; in all cases it
failed. Finally, we re-estimated parameter values as the model was applied to simulate Vergence/OFR
responses, taking account of the effects of vertical eye drifts upon retinal image slip; thus, in addition
to G and T, we estimated the optimal value of K (see pathway in gray in Figure 7A, in which the
summing junction represents the retina). For Vergence/OFR trials, the model was less successful in
obtaining a good fit, especially for Convergence/OFR, when vertical drifts were more commonly
affected by saccades. Nonetheless, we were able to identify 18 trials (21% of total) when the model
gave a good fit for Vergence/OFR responses; an example is shown in Figure 7C. Paired comparisons
of Vergence/OFR versus Fixation/OFR made with the Wilcoxon rank-sum test (Figure 7D) showed a
statistically significant increase (p = 0.004) of G from a median of 0.10 to 0.17 but no significant
change in T (median of 0.03s for both conditions). The median value of K was 0.13, indicating a
relatively small effect of vertical eye drifts on retinal image slip, and being smaller than the estimate of
0.3 for the effects of image motion due to saccades on the OFR (Gellman et al. 1990).

When we compared the latency of Vergence/OFR versus Fixation/OFR, using a paired t-test, we found that for downward responses, there was no significant difference between the latency for Fixation/OFR (mean ± SD: 82 ± 14 ms), Divergence/OFR (82 ± 9 ms), or Convergence/OFR (80 ± 11 ms). For upward responses, Fixation/OFR latency (94 ± 13 ms) was significantly greater (p<0.05) than Divergence/OFR (83 ± 15 ms) but not Convergence/OFR (89 ± 14 ms).

Results of Control Experiments

A pair-wise multiple comparison procedure (ANOVA) showed no significant difference (p = 0.98) for each of the four control experiments versus responses during the standard Fixation/OFR experiment. Thus, the increased amplitude of OFR that occurred during vergence movements could not be ascribed to differences in stimulus presentation during Fixation/OFR versus Convergence/OFR or Divergence/OFR experiments.

Discussion

We set out to determine whether the magnitude of the vertical OFR in normal humans is increased if it is generated as subjects shift their point of fixation between near and far visual targets. First, we established the range of the vertical OFR in ten normal human subjects following visual fixation of a stationary target (Fixation/OFR), and found responses similar to those previously reported (Gellman et al. 1990). We then compared each subject’s Fixation/OFR responses with those occurring if the stimulus was presented during the course of a vergence eye movement, and found that these Vergence/OFR responses were consistently increased in amplitude. The Discussion addresses four issues raised by our results. First, what are the characteristics of the vertical OFR? Second, what relationship does OFR bear to other smooth ocular tracking responses? Third, what factors could account for the increase of OFR that occurs if it is made during a vergence movement? Finally, how could the OFR contribute to gaze stabilization during combined vergence-saccade gaze shifts?
Properties of Vertical OFR following fixation

There was substantial variability of OFR between different subjects (Figure 3), similar to a prior report (Gellman et al. 1990). Nonetheless, subjects tended to show the same overall pattern (e.g., Figure 2), with downward responses being larger, and made at shorter latencies, than upward responses. This is the opposite of the asymmetry of latency reported for vertical saccades (Zhou and King 2002), which may reflect a shorter response time for shifts of attention to targets presented in the upper visual field. Since the OFR is pre-attentive, the up-down asymmetry might, therefore, be due to different mechanisms. The largest responses were also evoked with the stimulus with the lowest spatial frequency (0.17 cycles/°). These consistent properties of the vertical OFR are discussed further in the final section.

We wondered whether the variability of responses for each subject was influenced by anticipatory drifts based on prior experience. Such a possibility has been suggested during studies of the initial, pre-saccadic component of smooth-pursuit (Barnes and Collins 2008), which might be related to the OFR. Accordingly, we compared vertical eye movements during control trials, during which the grating stimulus was stationary, with stimulus direction during the prior OFR. We found no correlation between the direction of eye drifts occurring during control trials, which were idiosyncratic and stereotyped for each subject, and the prior trial. This result supports the view that, at least under our experimental conditions, the OFR is not noticeably influenced by anticipatory or memory-driven eye drifts.

Relationship between OFR and other forms of visual tracking

It has been suggested that OFR may act as a visual field-holding reflex that is most influential in the wake of a gaze shift (Gellman et al. 1990). During locomotion, which induces an optic flow of images on the retina, other visual tracking systems act to stabilize gaze, such as smooth pursuit and optokinetic responses. (Vestibular mechanisms make an important contribution for high-frequency
Although the OFR appears to have unique properties (Gellman et al. 1990; Sheliga et al. 2005), we took the opportunity to compare our subjects’ OFR with other visual tracking responses. Accordingly, we tested each subject’s responses to the 0.27 cycles/° visual stimulus when it was moved sinusoidally through frequencies ranging from 0.1 – 2.5 Hz. The ability of individual subjects to track this predictable “optokinetic” stimulus, during which they were instructed to follow an individual grating (“look” optokinetic behavior, without induced circularvection) bore no relationship with their OFR responses (Figure 4). Thus, it appears that OFR and tracking responses to our sinusoidal stimulus motion are due to different tracking mechanisms. However, it remains possible that OFR is related to other forms of visual tracking. Recent studies demonstrated that the amplitude of the OFR was maximized when the moving gratings occupied 50% of a screen subtending 45° horizontally and 30° vertically; responses decreased with larger stimuli that possibly favored local inhibitory surround over central excitatory mechanisms (Sheliga et al. 2008; Miles et al. 1986). Thus, a large-field visual display may not be the optimal stimulus to evoke the OFR, whereas it is for optokinetic responses.

Other studies have indicated that the smooth-tracking response to onset of motion of a small visual stimulus has two main components: an initial response that is variable and does not match target velocity, and a second component following the first saccade that more accurately tracks the target (Wilmer and Nakayama 2007; Priebe et al. 2001; Barnes 2008). Although the latency to onset of OFR is smaller than for smooth pursuit, it would seem of interest to determine whether OFR has other differences from the initial component of smooth-pursuit tracking. Differences of OFR from optokinetic and smooth-pursuit responses would support the view that OFR is driven by a low-level system that senses first-order motion energy (Sheliga et al. 2005).

**Mechanisms by which OFR is increased during vergence**

Our subjects showed consistent increases in the magnitude of the OFR made during vergence movements compared with following steady fixation. The OFR is known to be enhanced in the wake of a saccade (Gellman et al. 1990), but most natural shifts of the point of fixation are between targets
located at different distances and in different directions. Our study differed from that of Gellman and colleagues (1990) in that we tested the OFR in the direction orthogonal to the (vergence) eye movements; also our stimuli lay in different depth planes. Furthermore, Gellman and colleagues were only able to study post-saccadic enhancement up to 600 ms, yet vergence movements last longer.

One question we addressed was how much our measurements during Vergence/OFR were affected by vertical eye drifts that accompanied horizontal vergence movements, even if the near and far targets were carefully aligned. Our initial approach was to subtract vertical drifts occurring during vergence control trials, when no movement of the visual grating stimulus occurred (Figure 5). However, since some vertical drifts persisted throughout the OFR, we needed to take into account not only the superimposed eye drift itself, but also its potential effect on retinal image slip during the period of grating motion. For this additional analysis, we used a simple model of the OFR, which did not seek to represent details of the underlying neural mechanism (Yamamoto et al. 1997), but which did take account of retinal image slip due to vertical eye drifts (Figure 7). This analysis of a subset of our data indicated that vertical eye drifts had only a small impact on retinal image motion. Estimation of optimal parameter values demonstrated a substantial increase of the internal gain of the OFR when responses occurred during vergence, compared with OFR following fixation (Figure 7D). Such an enhancement is consistent with the notion that OFR is a visual field-holding reflex, which is called into action after each gaze shift, and it is also consistent with prior studies showing increased responsiveness of one eye movement response when combined with another (Lisberger 1998; Das et al. 1999; Kumar et al. 2005). In preliminary, unpublished studies, we have found no increase in OFR if stimuli are presented during sinusoidal vergence versus the OFR following fixation. Thus, it may be that the sudden shift of the point of fixation and center of visual attention are the cue to increase the OFR.

Possible function of human OFR

One may ask what visual role these small, variable eye movements serve during natural
behavior. One possibility is that they contribute to gaze stabilization during head perturbations. However, when the vestibular sense is lost, visually mediated eye movements fail to provide a clear stable view of the world (J.C. 1952). Another possible purpose, for which they evolved, might be to compensate for eye drifts immediately following gaze shifts (Gellman et al. 1990). Following saccades, transient eye drifts – glissades – may impair vision. During combined saccade-vergence movements, larger eye drifts are more likely, and so it seems possible that OFR may help to stabilize the field of view after such gaze shifts. In accord with this view, the OFR is increased in the wake of both saccades and saccade-vergence movements, although their amplitude may not be adequate to compensate for some eye drifts occurring during such gaze shifts (e.g., Figure 5).

Although the amplitude of the OFR shows inter-subject variability, up-down asymmetries and its dependence on contrast and spatial frequency are consistent properties across subjects, leading to the suggestion that the OFR reflects the activity of low-level motion detectors (Sheliga et al. 2005). Given the small, variable size of responses, it remains possible that the OFR does not actually contribute to clear vision but rather represents the initial processing of motion signals that later lead to eye movements that can help to stabilize gaze. If this were correct, the OFR could be regarded as a probe of early cortical motion processing (Kodaka et al. 2007), even though the responses have little protective effect (“survival value”) for vision during gaze shifts. As an experimental probe, the OFR holds potential value for studying a range of clinical disorders affecting either the afferent (Rucker et al. 2006) or efferent components of visual tracking mechanisms.

Acknowledgments:

We are grateful to Dr. Boris Sheliga for conceptual advice and technical assistance during the initial development of this research. We also thank Drs. Frederick Miles, Graham Barnes, Arun Kumar, Louis Dell’Osso, Robert Kirsch, and Dominic Durand for advice, and the subjects for volunteering their service. Supported by NIH grant EY06717, Department of Veterans Affairs, and Evenor Armington Fund. The work reported in this paper constitutes research performed by A. C. Joshi as part
of the requirements for his Doctoral Dissertation.
APPENDIX A

The simple model shown in Figure 7A was coded in SIMULINK (The Mathworks Inc., Natick, MA). Parameter estimation techniques provide a rigorous mathematical procedure to simultaneously estimate the value of several parameters with precision, and have been previously applied to studies of eye movements (Huebner et al. 1992; Seidman et al. 1995; Das et al. 1999; Kumar et al. 2006). In our analysis, we took advantage of the seamless integration of SIMULINK with MATLAB (The Mathworks Inc., Natick, MA) to execute the model at each iterative step of the parameter estimation procedure. Parameter estimation was performed using the "lsqcurvefit" function of the MATLAB Optimization Toolbox (Coleman et al. 1999), which uses the method of conjugate gradients to minimize the objective function ($\Phi$):

$$\Phi(B) = \sum_{i=1}^{n} [y_i - f_i(B)]^2$$

where $y_i$ are the measured data values, $f_i(B)$ are the calculated model output values, and $B$ is the optimal parameter vector. The goal of the optimization algorithm is to minimize this objective function. The difference ($y_i - f_i$) is called the residual at time point $t_i$.

We selected individual cases for simulation, consisting of one subject’s mean response, upward or downward, to one stimulus spatial frequency. Initially Fixation/OFR responses were selected for simulation and parameter estimation. Subsets of the recorded vertical eye position data from the mean response and the control trial were selected, corresponding to the epoch 0-150 ms after stimulus onset. The stimulus to the model was a velocity step of 200 ms duration, corresponding to the speed of the actual stimulus (see Methods). Velocity input signals were used for model simulation and these were integrated to provide positional displays that were compared with subjects’ data. The value of the Delay was set to the measured value for that subject and stimulus. Initially, the model simulation was run with parameters set to initial guess values, consistent with published values of smooth-tracking models (Robinson et al. 1986). We did not incorporate the pathway by which EVcontrol influenced retinal image slip (gray pathway in Figure 7A) for Fixation/OFR because control eye drifts were very...
small; we confirmed this impression in some simulations using the gray pathway: there was no
detectable effect. After the first simulation (pre-estimation), we applied constraints on the range of
parameter values, so that $G$ could range 0-5 and $T$ could range 0.03-0.2 s. Then the formal parameter
estimation process was started, from different initial guess values (to avoid convergence on local
minima) using the recursive least-squares algorithm (lsqcurvefit), until the objective function was
minimized and was not changing. Then the residual sum-of-squares (RSS) and $R^2$ (coefficient of
determination) were obtained, along with optimal values for $G$ and $T$. Only simulations with RSS <
20% and $R^2$ values > 0.9 were considered good fits, and were included in our analysis. A
representative comparison of a subject’s mean Fixation/OFR response and the model’s simulation of it
following parameter estimation is shown in Figure 7B.

We then tested whether the model, with the parameter values estimated for Fixation/OFR,
could also simulate mean Divergence/OFR or Convergence/OFR responses to the same visual
stimulus. The value of Delay was set to that measured for the corresponding Vergence/OFR trial. In all
cases, the model failed to simulate the recorded data. Finally, parameters were reset to initial guess
values and the effects of vertical eye drifts upon retinal image slip (differentiated $EV_{control}$ signal)
were studied by estimating the optimal value of $K$ (see pathway in gray in Figure 7A); $K$ was allowed
to vary in the range 0-1.0. Parameter estimation then was re-run. Whereas >80% of cases of
Fixation/OFR satisfied goodness-of-fit criteria, only 35% of Divergence/OFR and 7% of
Convergence/OFR did so (due to large, vertical eye drifts, which were especially common during
convergence). A representative comparison of a subject’s Divergence/OFR mean response and the
model’s simulation with a good fit is shown in Figure 7C. Paired comparisons for $G$ are shown in
Figure 7D; there is a significant increase when OFR is performed during vergence. No significant
changes in the values of $T$ or $K$ occurred.
Figure Legends

Figure 1. Schematic summary of visual stimuli. Upward or downward motion of three sinusoidal gratings were applied under each experimental condition. During Fixation/OFR trials (A), the subject was instructed to fix upon a white spot at the center of the gratings on the video monitor. After 200-300 ms, the white spot was turned off and the sinusoidal grating started to move up or down. After 200 ms, the screen was switched to uniform gray (trial end). During Fixation / OFR control trials (B), the gratings did not move when the white spot was turned off. During Divergence/OFR trials (C), the subject started by fixing upon a near red stimulus; after a randomized period of 2.5-3 s, the near red stimulus was turned off and the white spot and gratings appeared on the monitor, which was the cue to diverge, and when divergence velocity exceeded 15º/s, the white spot was turned off and the grating began to move. During Divergence/OFR control trials (D), the gratings did not move when the white spot was turned off. During Convergence/OFR trials (E), the subject started by fixing upon the white spot on the monitor. After a randomized period of 2.5-3 s, the white spot was turned off and the near red spot appeared; this was the cue to converge, and when convergence velocity exceeded a threshold of 15º/s, the red light was turned off and the gratings started to move. During Convergence/OFR control trials (F), the gratings did not move when the red light was turned off.

Figure 2. Summary of representative mean responses from subjects S5 (downward responses) and S7 (upward responses), corrected for offset by setting eye position for each curve to zero at 70 ms, for each stimulus condition and spatial frequency. Vertical dashed lines indicate times at which eye position was sampled (70 ms and 150 ms) to calculate OFR amplitude. Fixation/OFR responses (black) are greatest in response to the 0.17 cycles/º stimulus (the lowest spatial frequency) and smallest for the 0.44 cycles/º stimulus; for each spatial frequency. Divergence/OFR responses are shown in red and Convergence/OFR responses in blue; both are generally greater than responses to Fixation/OFR. In this and following figures, positive values indicate upward eye movements.
Figure 3. Box-plot summary of mean Fixation/OFR amplitudes for all ten subjects; percentile values for each data set are labeled at left (50% is the median). Note that response magnitude is inversely related to the spatial frequency of the stimulus, and that responses are generally greater for downward than upward stimuli.

Figure 4. Comparison of Fixation/OFR with sinusoidal tracking of the 0.27 cycles/º stimulus ("optokinetic responses"). Panel A is a Bode plot of subjects’ optokinetic responses; note the sharp decline in gain for stimulus frequencies above 1 Hz (vertical gray line). The bottom two plots compare normalized amplitude of upward (B) or downward (C) optokinetic responses versus normalized OFR for each subject (see text for details). There was no correlation between optokinetic responses and OFR.

Figure 5. Representative example of how control responses were used to take account of vertical eye drifts during vergence responses. OFR amplitude was measured from the difference between eye position at 70 ms and 150 ms, indicated by the gray vertical dashed lines. (A) Mean Divergence/OFR data from Subject 3 for each of the stimulus spatial frequencies are shown; note the upward bias, especially evident for the downward 0.44 cycles/º stimulus. (B) Mean responses to Divergence control stimuli, with upward eye drift. (C) Divergence/OFR responses after correction for drift (by subtracting the curve in B from each of the raw curves in A) and offset (by setting eye position for each curve to zero at 70 ms).

Figure 6. Paired comparison of mean amplitudes of responses during Fixation/OFR (abscissa scale) versus either Divergence/OFR or OFR/convergences (ordinate scale). In each case, OFR amplitude was greater when it was accompanied by a vergence eye movement. Note that seven subjects could diverge during Divergence/OFR and eight subjects could converge during Convergence/OFR testing (see text). Significance levels shown are from paired comparisons using the Wilcoxon rank-sum test.
Figure 7. Summary of an application of a simple model (A) to compare Fixation/OFR responses with Vergence/OFR responses. Grating Vel is the velocity-step stimulus that sums at the retina (summing junction) with the velocity of vertical drifts of the eyes (EVcontrol – estimated from control trials); s is the Laplace complex frequency. The difference is retinal error velocity (REVel) that, after a Delay (mean value measured for each stimulus), is the input to a first-order lag element of gain G and time constant T. EVOFRvel is the model’s velocity command to move the eyes, which sums with vertical eye drifts, and is integrated to give EVsum, which was compared with the subject’s measured OFR.

First, optimal values of internal parameters, gain G, and time constant T, were calculated for the mean Fixation/OFR response for individual subjects at one spatial frequency (see text and Appendix 1). Since mean eye drift (EVcontrol) during Fixation/OFR control trials was small, K was set to zero for this part of the estimation. Panel B shows a representative mean response (Subject 4, upward 0.27 cycles/° stimulus) and the model’s simulation after optimal parameter values were estimated (summarized in box, along with residual sum-of-squares error (RSS) and R² value). Panel C shows the subject’s mean Divergence/OFR response to the upward 0.27 cycles/° stimulus, and the model’s simulation of it after optimal parameter values were estimated; in this case the value of K (gray pathway) was estimated to determine the effect of mean eye drift. Note how G and T increase from Fixation/OFR to Divergence/OFR, but K is zero. A paired comparison of the values of gain G estimated for Fixation/OFR versus Vergence/OFR is shown in D; the Wilcoxon rank-sum test showed a significant difference, as indicated (see text).
References


9. Huebner WP, Leigh RJ, Seidman SH, Thomas CW, Billian C, DiScenna AO, Dell'Osso LF (1992) Experimental tests of a superposition hypothesis to explain the relationship between the
vestibuloocular reflex and smooth pursuit during horizontal combined eye-head tracking in humans. J Neurophysiol 68:1775-1792


Figure 7

A

\[ EV_{\text{control}} \]

Grating Vel → REVel → Delay → \( G/sT+1 \) → EV_{OFRvel} → \( \frac{1}{s} \) → EV_{sum}

B

OFR/fixation

\[ G = 0.051 \]
\[ T = 0.053s \]
\[ \text{Delay} = 0.060s \]
\[ K = 0.0 \]
\[ \text{RSS} = 1.1\% \]
\[ R^2 = 0.98 \]

C

OFR/divergence

\[ G = 0.134 \]
\[ T = 0.054s \]
\[ \text{Delay} = 0.065s \]
\[ K = 0.0 \]
\[ \text{RSS} = 8.7\% \]
\[ R^2 = 0.96 \]

D

Gain (G)

\( p=0.004 \)