Modulation of Gaze-Evoked Blinks Depends Primarily on Extraretinal Factors

Shawn S. Williamson
Ari Z. Zivotofsky
Michele A. Basso

1Department of Physiology
2Department of Ophthalmology and Visual Sciences
University of Wisconsin - Madison
Madison, Wisconsin 53706 USA

3Gonda Brain Science Program
Bar Ilan University
Ramat Gan, Israel

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To whom correspondence should be addressed:
Michele A. Basso, Ph.D.
Department of Physiology
University of Wisconsin - Madison
1300 University Avenue, Room 291 MSC
Madison, Wisconsin 53706 USA
email michele@physiology.wisc.edu
voice 608.262.7110
fax 608.265.5512

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ABSTRACT

Gaze-evoked blinks are contractions of the orbicularis oculi (OO) - the lid closing muscle - occurring during rapid movements of the head and eyes and result from a common drive to the gaze and blink motor systems. However, blinks occurring during shifts of gaze are often suppressed when the gaze shift is made to an important visual stimulus, suggesting that the visual system can modulate the occurrence of these blinks. In head-stabilized, human subjects, we tested the hypothesis that the presence of a visual stimulus was sufficient, but not necessary, to modulate OOemg activity during saccadic eye movements. Rapid, reorienting movements of the eyes (saccades) were made to visual targets that remained illuminated (visually-guided trials) or were briefly flashed (memory-guided trials) at different amplitudes along the horizontal meridian. We measured OOemg activity and found that the magnitude and probability of OOemg activity occurrence was reduced when a saccade was made to the memory of the spatial location as well as to the actual visual stimulus. The reduced OOemg activity occurred only when the location of the target was previously cued. OOemg activity occurred reliably with spontaneous saccades that were made to locations with no explicit visual stimulus, generally, back to the fixation location. Thus, the modulation of gaze-evoked OOemg activity does not depend upon the presence of visual information per se, but rather, results from an extraretinal signal.
INTRODUCTION

In humans, rapid, reorienting movements of the eyes and head - gaze shifts - are frequently accompanied by contraction of the orbicularis oculi (OO), the lid-closing muscle. These contractions have been referred to as gaze-evoked blinks (Evinger et al. 1994). Generally, gaze-evoked blinks occur with changes in gaze larger than about 20º in amplitude. This phenomenon does not appear to be a result of a reflex evoked from stimulation of the cornea by wind during the large gaze shift, but rather, appears to be a command signal that is shared between the lid, eye and neck motoneurons (Evinger et al. 1994).

Why blinks are associated with shifts of gaze is unknown. One hypothesis proposed, is that the mechanisms for saccadic suppression and blinking are shared (Volkmann et al. 1980). In this scheme, the corollary discharge responsible for the decreased visual sensitivity that occurs during saccades, also drives contraction of OO motoneurons. The common drive ensures that a blink occurs during a saccade. This motor hypothesis has two advantages. First, it can explain why, despite the frequency of blinking (20/min; Leigh and Zee 1999), resulting in large changes in the image on the retina, the visual world remains stable. Second, corneal lubrication can occur when any disruptive effects on visual processing that would result from blinking, are minimized. Whereas this scheme assumes that blinks have a negative role from the visual system perspective, others have suggested that blinking during saccades has a useful role for the visual system. Spurious visual information such as retinal blur that might occur during saccades is minimized if a blink occurs along with a saccade (Watanabe et al. 1980).
Whether both or neither of these schemes is correct, is unknown. What is clear is that there is a linkage between the visual, saccadic and blink systems.

Previous experiments have demonstrated that the linkage of saccadic gaze shifts and blinking is not obligatory. For example, when humans make saccadic eye movements to a continuously visible target in a single plane, gaze-evoked blinks are smaller than those made during similar amplitude, re-centering saccades (Evinger, et al., 1994). What is responsible for this modulation is unknown. As a first step toward understanding this, we consider here whether the visual stimulus is responsible for the reduction in gaze-evoked blinking or whether some other, extraretinal factor, produces the suppression. We tested the hypothesis that visual information is sufficient but not necessary to produce the suppression of gaze-evoked OOemg activity during certain saccades. To do this, we compared gaze-evoked OOemg activity during head-stabilized saccadic eye movements made to visible and previously visible target locations. We found that the occurrence of gaze-evoked OOemg activity was dramatically reduced within the context of saccade tasks regardless of whether a visual target was present. These results support the hypothesis that the visual stimulus per se, is not solely responsible for the reduction in OOemg activity during saccades.
METHODS

**Subjects.** Six male and two female subjects (ages: 29-40) participated in the experiments. All had uncorrected, normal vision. One subject (MAB) knew the goals of the experiment; the other 7 were naïve. Similar results were observed in all subjects so the data were pooled across subjects. Each subject participated in at least one recording session lasting 30-40 minutes and they sat in a 4’ magnetic field frame with their head supported on a chin rest to minimize movements of the head. We used the scleral search coil technique to monitor eye movements (CNC Engineering: Robinson, 1963; Fuchs and Robinson, 1966; Collewijn, 1999). We measured orbicularis oculi electromyographic activity (OOemg) by differential recording across a pair of silver ball electrodes (~1.5mm diameter) that were gently taped to the upper lid. The placement was such that the electrodes did not impede normal movements of the lid (Evinger, et al., 1994). A small (~3mm) gold-plate electrode was placed on the center of the forehead as a ground.

Eye movements and lid OOemg were measured from the left eye. No attempt to determine ocular dominance was made. All experiments were conducted with informed consent and according to standards set by the Guidelines for Use of Human Subjects. All procedures were approved by the Institutional Review Board at the National Eye Institute, NIH, where the data were collected.

**Behavioral Tasks.** Visual stimuli were rear projected on a tangent screen located 57cm from the subject, using an LCD (*Infocus*) projector operating at 60Hz. The visual stimuli subtended a visual angle of 0.5°. Stimulus presentation and data acquisition were controlled using a QNX based real time experimental control system (REX; Hays et al., 1982).
There were two saccade tasks (Fig. 1), a visually-guided, delayed saccade task (Fig. 1A) and a memory-guided, delayed-saccade task (Hikosaka and Wurtz, 1985; Fig. 1B). In both tasks, a spot was illuminated at the center of the screen or at 20 or 30° in the periphery. Subjects fixated this spot for a random delay between 500-1500ms. Then, a second spot was illuminated at varying amplitudes (20, 30, 40 and 60°) from the fixation spot along the horizontal meridian. In the memory task, this spot was illuminated only briefly (200ms, Fig. 1B), whereas in the visually-guided task, the spot remained illuminated for 800-1200ms (Fig. 1A). Removal of the fixation point was the cue to make a saccade to the location of the target.

Lid movements that occur with vertical saccades (lid saccades) are associated with changes in the activity of the levator palpebrae muscle and not the orbicularis oculi (Evinger et al., 1991). In some cases, large vertical saccades (>40°) can be accompanied by OOemg activity despite the fact that contraction of the OO would counteract the lid saccade at least for upward saccades (Evinger et al., 1991). To eliminate these possibilities we presented targets only along the horizontal meridian. Placing the fixation point either at the center or at a peripheral location allowed us to present large amplitude saccade targets. For the 20° and 30° targets, the fixation point was located at 0°. For the 40 and 60° targets, the fixation point was located at 20 and 30° respectively.

Interleaved with delayed-saccade tasks, was the gap saccade task (Saslow 1967). These saccades are also visually-guided, so for the analysis we included these with the visual-guided delayed trials. In the gap task (Fig. 1C), the fixation stimulus appeared for a random delay (500-1500) and then was removed. After a delay of 200ms, during which the subject was required to remain fixating in the dark, a peripheral target was
illuminated. The appearance of the peripheral target was the cue for the subject to make a saccade to the location of the visual stimulus. The removal of the fixation point serves to disengage visual attention allowing more rapid processing of subsequent, incoming visual stimuli (Fischer and Weber 1993) although other hypotheses have been proposed (Paré and Munoz 1996). All saccade conditions were randomly interleaved and the color of the fixation point identified the trial type.

Generally, after subjects completed the saccade to the cued target location, they made a saccade back to the location of the center of the tangent screen or to the fixation location. We termed this saccade, the ‘refixational saccade’ (Fig. 1). This saccade was not cued but was made in anticipation of the upcoming trial.

Subjects were required to maintain an accuracy of 5º square around the fixation point and 12.5º square around the target. This was monitored using an electronic window. If subjects failed to maintain this level of accuracy, the trial was aborted. A time out period was imposed (1500ms) after which a new trial commenced. Subjects received instructions to maintain eye position on the target and to make eye movements, without head movements, to track the target as accurately as possible.

**Data Acquisition and Analysis.** Voltage signals proportional to horizontal and vertical components of eye position were filtered (8 pole Bessel -3dB 180Hz), digitized at 16-bit resolution and sampled at 2kHz. The signals from the OOemg electrodes were filtered (300Hz-5kHz) and amplified (100x). These data were digitized at 16-bit resolution and sampled at 2kHz.

All analog data were saved for off-line analysis using an interactive computer program designed to display and measure eye position, velocity and OOemg activity.
Measurements of the data were made on eye position traces and saccadic eye movements were identified using velocity and acceleration criteria (10-25º/sec and 500-800º/sec²). Each trial was inspected by the experimenter to ensure the accuracy of the algorithm. If saccades were missed, the criterion was adjusted to catch all saccades. OOemg data analysis was performed in Matlab using a custom designed program. For each trial, the OOemg trace was rectified and then displayed. An algorithm computed the baseline OOemg activity and determined the point on the OOemg trace that exceeded two standard deviations of the baseline. This point determined the onset of a blink. The algorithm then defined the region of the OOemg where the amplitude was maintained at the level of 2SD above baseline to define the duration of the blink. The end of the blink was defined as the point on the OOemg trace where the activity dropped below 2SD from baseline. The area under the curve defined by the beginning and end of the blink, was computed to determine the OOemg magnitude. The occurrence of OOemg activity was computed for all saccades within a trial. This was performed for each trial of each saccade task. The experimenter verified the beginning and end of OOemg activity. Statistical analyses were performed in Matlab, Excel or Sigma Stat. Parametric descriptive, and inferential statistics, such as ANOVA and t-tests were performed. If the distributions failed normality tests, the non-parametric equivalents such as the Kruskal-Wallis or the Mann-Whitney Rank Sum and Dunn’s Test were used.
RESULTS

When subjects made saccades to a visible target, the OOemg was very small (Fig. 2A, visually-guided saccade). However, when a similar, refixational, saccade was made back to the center of the screen, the OOemg was large (Fig. 2A, refixational saccade). Indeed, the refixational saccadic eye movement in this example was slightly (~2°) smaller than the initial, targeting saccade but the OOemg activity was more than twice the magnitude of that occurring during the initial saccade. In a second subject, the effect was so profound, that this person rarely showed OOemg activity for the initial targeting saccade (Fig. 2B) but showed robust OOemg activity for the return saccade.

Figs. 2C and D compare OOemg activity during visually-guided and memory-guided saccades. During the visually-guided saccade, the initial targeting saccade was unaccompanied by OOemg activity whereas the return saccade was associated with a robust drive to the OO motoneurons (Fig. 2C). This occurred despite the fact that the initial saccade was larger than the return saccade. In memory-guided saccade trials (Fig. 2D), a similar pattern was observed. The initial saccade to the location of the now invisible target was not associated with OOemg activity, whereas, the return saccade, was associated with robust OOemg activity.

Across our sample of 8 subjects, this pattern was very consistent. We normalized the magnitude of the OOemg activity in all conditions by the OOemg magnitude measured during targeting, visually-guided saccades (Fig. 2E). Thus, the visual - to target condition magnitude is 1. The magnitude of the OOemg measured during the memory-guided trials was statistically indistinguishable from that measured
during the visually-guided trials (p>0.05) for all subjects. Similarly, the OOemg activity associated with the refixational saccade in both trial types, was different from the OOemg measured during the targeting saccades (p<0.05). One way ANOVA (Kruskal-Wallis) and Dunn’s pairwise comparison tests, revealed significant differences (p<0.05) in OOemg magnitude between the visual - to target and refixational conditions as well as the memory - to target and refixational conditions. There were no significant differences between visual - to target and memory - to target or between the refixational saccade conditions. These results support the hypothesis that the presence of a visual stimulus is not necessary to reduce the OOemg activity during a saccade. Therefore, the modulation must arise from an extraretinal source.

Thus far, we have examined the modulation of OOemg magnitude. Previous work has shown that in head-unrestrained subjects, the probability of OOemg activity associated with a gaze shift is modulated by the amplitude of the head movement (Evinger et al., 1994). To determine whether OOemg activity was modulated during head-stabilized saccadic eye movements, we asked subjects to perform a delayed-saccade task while varying the amplitude of the required saccade. There were 2 notable results. First, as the amplitude of the saccadic eye movement increased, the probability of measuring OOemg activity during the saccade also increased as was described for head-free gaze shifts. Second, and similar to the OOemg magnitude data just presented, the probability of OOemg activity occurring along with a saccade was low when the saccade was made to the target. However, when the return saccade was made, the probability of OOemg activity was dramatically increased. This was evident across all amplitudes of saccades.
Across our 8 subjects we computed the mean probability of OOemg occurrence during the saccade to the target location in the visually-guided and the memory-guided tasks (Fig. 3A). We then plotted these probabilities against the saccade amplitude. As the saccade amplitude increased, the probability of measuring OOemg activity increased. We performed an ANOVA comparing the probability of measuring OOemg activity across target eccentricity (4 levels, 20° 30° 40° and 60°). We found an effect of target eccentricity indicating that the differences in the probability of OOemg occurrence we measured with varying saccade amplitudes were statistically significant, ANOVA f(3,1617) = 1220.00, p < 0.001. The mean probability of OOemg occurrence for the visually-guided condition was 2.9% (Fig. 3A Δ), whereas the mean for the memory-guided was 3.4% (Fig 3A ○). Thus, there was a small, but significant (p<0.001), difference in the probability of OOemg occurrence depending upon whether the visual target was present as the saccade amplitude increased. However, this difference was small and did not exceed the difference in OOemg probability measured during saccades made to the target location, compared to those made back to the fixation location, in either the visually-guided (2.9% versus 74%) or the memory-guided saccade task (3.4% versus 67%). Thus, it appears that the presence of the visual stimulus can exert a small amount of inhibition on the occurrence of OOemg activity during saccades, but does not override the effects of targeting a spatial location regardless of the presence of the visual stimulus. Thus, the presence of a visual stimulus is sufficient, but not necessary, to reduce OOemg activity concomitant with a saccade.

Interestingly, the difference in OOemg probability occurring during saccades made to the visible target location and those made to the invisible target location was
evident even in the execution of the return saccade (cf, 74% versus 67%). This difference was also significant (p<0.001) and suggests that there is more modulating OOemg occurrence than simply the presence or absence of a visual stimulus. Because of the difference between OOemg occurrence during memory-guided saccades and refixational saccades, this indicates that the modulatory influence may reflect a factor related to the attention to spatial location rather than a simple non-visual phenomenon. In the case of the refixational saccade, attention is not required since accuracy is not demanded. Future experiments will test this hypothesis.

Finally, for the refixational saccades, a similar trend was evident (Fig. 3B). As the saccade amplitude increased, the probability of measuring OOemg activity also increased. However, the trend appeared primarily, as a reduced variability (note the decrease in scatter; solid line is the mean). This difference was not because the refixational saccades were smaller than targeting saccades, though they tended to be so. The mean amplitude of the saccades made to the target was 50°, whereas the mean amplitude of the saccades made in the refixational condition was 39°. However, the difference in the saccade amplitudes across the bins was not significantly different (ANOVA; f(3,19) = 1.00, p = 0.461). This result also suggests that there is more modulating the occurrence of OOemg activity during saccades than either visual stimuli or saccade amplitude.
DISCUSSION

In this report we describe experiments in which we measure the magnitude and probability of occurrence of OOemg activity with saccadic eye movements. We manipulated the type of saccade task in which the subjects were engaged to test whether the visual stimulus per se, was responsible for OOemg reduction during certain saccades. First, we found that OOemg activity frequently occurred with saccadic eye movements independent of head movements. Second, we found that OOemg activity was not obligately linked to saccade generation since OOemg activity was different depending upon the amplitude of the saccade. Finally, we found that the suppression of OOemg activity that often occurs when visually-guided saccades are made, did not depend solely upon the presence of the visual stimulus. This result supports the hypothesis that the suppression results primarily from an extraretinal source.

Blinks are associated with large, head-free gaze shifts. Here we demonstrated that the same relationship holds for head-stabilized, saccadic eye movements. We had subjects make saccadic eye movements ranging in amplitude from 20° to 60°. The results from the large amplitude saccades show that OOemg activity co-occurs with saccadic movements and that the probability of OOemg activity varies with the size of the saccade. Larger saccades are associated with higher probability of OOemg activity. Therefore, the relationship between the occurrence of OOemg activity and saccade amplitude is the same for saccadic eye movements and saccadic gaze movements. These results, combined with previous reports (Evinger et al. 1994), show that the linkage
between blinks and gaze shifts occurs before the decomposition of signals into head or eye commands.

Observations such as these also demonstrate that the linkage between blinks and saccades is not obligatory (Evinger et al. 1994). If the gaze-evoked blink was obligately linked to saccades, the occurrence of OOemg activity should be independent of the amplitude of the saccades. Moreover, since we found that OOemg modulation occurred regardless of the presence or absence of the visual stimulus, this suggests that there are other factors involved. By interleaving memory-guided and visually-guided saccades we tested the hypothesis that the reduction of the gaze-evoked OOemg activity during certain saccades did not result from the presence of the visual stimulus per se. Because only in the visually-guided saccade task is the visual stimulus still present, the probability of measuring OOemg activity in the memory-guided saccade task should be as high as that measured for the refixational saccade, where no visual stimuli are present. We found that the distribution of OOemg probabilities measured in the visually-guided and memory-guided task were statistically indistinguishable, consistent with an extraretinal factor, mediating the modulation of OO motoneurons during saccade tasks.

The gaze-evoked blink is thought to originate from a drive that is common to the eye, neck and lid motoneurons (Evinger et al. 1994; Rottach et al. 1998). The superior colliculus (SC), a brainstem region critically involved in the generation of saccadic gaze shifts (Sparks 2004), may be the site of overlap. Indeed, a role of the SC in reflex blinking (OOemg activity evoked by trigeminal activation) has been demonstrated (Basso et al. 1996). However, if the command to initiate a saccadic gaze shift is also responsible for a drive to the OO motoneurons causing a blink to occur, why does the probability of
OOemg activity increase as the saccade amplitude is increased? In other words, why are small saccades less likely to be accompanied by a blink if the origin of the drive is the same?

We propose that the extraretinal signal described here - perhaps in the form of an attentional signal - may reconcile this. This signal may provide a constant drive, either directly or indirectly, to inhibit the omnipause neurons (OPNs; Baloh et al., 1982; Langer and Kaneko, 1984; Horn et al., 1994), the brainstem neurons considered to gate saccadic eye movements (Keller, 1974; Fuchs et al., 1985). Small saccades would drive a population of OPNs to pause, but it would take a larger or longer OPN pause to also release OOemg activity. The generation of larger saccades would release more inhibition on the OPNs or release it for a longer time, allowing a blink to occur along with the saccade. This hypothesis is dependent upon the premise that evoking blinks along with saccades requires a larger or longer cessation of OPN activity than that required for a saccade, and that larger saccades are associated with great pauses in OPNs.

There is support for this. The distribution of activity within the SC is invariant for saccades of different amplitudes, however a faster decline in the activity of SC neurons is associated with smaller saccades (Anderson et al. 1998; Keller 2004; Sparks et al. 1976). This causes the OPNs to resume their discharge faster, perhaps precluding the occurrence of concomitant OOemg activity. Moreover, there is some suggestion that the rostral SC has a stronger, excitatory input to the OPNs (Paré and Guitton 1994) making a pause in OPNs less likely when the rostral SC is active. The latter idea, that a larger (eg., recruitment of more OPNs or longer duration) pause in OPNs is required to produce a blink along with a saccade, is supported by the observation that the velocity of
abnormally slow saccades can be normalized if a voluntary blink is initiated at the time of the saccade (Leigh et al. 1983; Zee et al. 1983).

Finally, we propose that exploring the linkage between blinking and saccadic eye movements in clinical populations will help determine where the linkage is and where the extraretinal modulation is. For example, a hallmark symptom of Parkinson’s disease is a loss of habituation and a hyperexcitable blink reflex (Dengler et al. 1982; Kimura 1973). It is possible that these patients may also have disturbances in gaze-evoked blinks. If the loss of blink suppression during gaze shifts occurs in these patients, it would implicate the basal ganglia as an important component of the interaction between extraretinal factors and motor control.
FIGURE LEGENDS

**Figure 1.** Saccadic eye movement tasks. The temporal arrangement of the tasks is shown on the left and the spatial arrangement of the tasks is shown on the right. The black lines are schematic representations of eye position and are labeled Eye. By convention, up is right and down is left. The boxes in the right panel represent the tangent screen the subjects viewed and the black circles represent the visual stimuli. The smaller black boxes represent the location of the eye during the different periods of the task. FP = fixation point.

**Figure 2.** Visually and memory-guided saccadic eye movements and OOemg activity. Position of the eye against time is plotted. A. In this example one large saccade is made to a visual target (visually-guided saccade) located in the periphery and then a second large saccade is made back to the approximate center of the screen (refixational saccade). B. An example in another subject. The arrangement is the same as in A. C. A single trial from the visually-guided saccade task and D shows the same arrangement for a single memory-guided saccade trial in the same subject. In each of these four panels the dotted line indicates the 0 position. E. Normalized OOemg magnitude measured during four conditions is plotted. Visual - to target is the OOemg magnitude measured during visually-guided saccades made to the location of the target. Refixational\textsubscript{v} is OOemg measured during the saccade back to the fixation location in visually-guided trials. Memory - to target is the OOemg measured during saccades made to the target location in the memory-guided trials and refixational\textsubscript{m} is OOemg measured during the saccade
back to the fixation location in the memory trials. The data from all 8 subjects are included in this plot. The ‘T’ bars are 1 SD.

**Figure 3.** OOemg probability is modulated by sensory conditions. The probability of OOemg activity is plotted as a function of the amplitude of a saccadic eye movements sorted into 5 bins.  A. Data are taken from visually - guided (Δ) and from memory-guided trials (○). B. The arrangement is the same as in A except the data are taken from the refixational saccades. The data from 8 subjects contributed to these plots. The bins were determined by first computing the mean saccade amplitude in the visually-guided saccade trials. The SD was computed and this value determined the bin width (~7º). The saccade amplitudes were sorted into 5 bins for each condition. The occurrence of OOemg with a saccade was determined and the probability of each occurrence was computed for each bin for each subject. There are 16 points (Δ) per bin (2 per subject) in the visually - guided trials since we combined the data from the overlap and gap tasks. There are 8 points (○) per bin (1 per subject) for the memory trials. Each point is the mean of multiple trials. Zeros in these plots indicate either the subject did not have measurable OOemg during these saccades or they did not have saccades of the amplitude within the range of the bin. The solid line in both panels is the mean.
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A. Visually-Guided Delayed Saccade

FP

Target

"targeting saccade"

Eye

"refixational saccade"

B. Memory-Guided Delayed Saccade

FP

Target

Eye

C. Gap Saccade

FP

Target

Eye

Figure 1
Williamson, et al.,
Figure 2
Williamson et al.,
Figure 3
Williamson, et al.,

A  saccades to the target

B  refixational saccades

memory trials
visual trials

saccade amplitude bin number