Induced extraocular muscle afferent signals: from pigeons to people

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Abstract

While the muscles which move the eyes, the extraocular muscles (EOM), are well endowed with proprioceptors, afferent signals from these receptors are usually assumed to play little or no role in the control of eye movement. In a series of experiments, a suction contact lens was used to impose movements on one eye, thus inducing afferent signals. Single unit activity was recorded centrally (to examine the interactions between EOM afferent signals and visual or vestibular signals), or the movements of the other eye were measured (to investigate their effects on the output of the oculomotor system). In a model preparation, the decerebrate pigeon, EOM afferent signals modified single unit activity in the medial vestibular nucleus, and the third and sixth motor nuclei, during sinusoidal vestibular stimulation. When one eye was moved to mimic the VOR, movement faster than required for compensation for a given head velocity reduced the gain of single unit vestibular responses. In awake, alert, pigeons the overall output of the VOR, as evidenced by movements of the other eye, was modified. In humans, when one eye was impeded, the saccades and smooth pursuit executed by the other eye were altered. Taken together, these results suggest that EOM afferent signals play a functional role in the shaping of eye movement.

Introduction

One of the challenges any organism faces is, given sensory information about the “state of affairs” in the external world, how to shape effective action to improve that “state of affairs” from the organism’s point of view. For motor systems, this reduces to the need to monitor and evaluate responsive motor acts. It is no surprise that most motor systems incorporate various mechanisms for providing feedback about the state of the effectors bringing about movements. One might expect the oculomotor system to be no exception

in this regard. Indeed, the muscles which move the eyes in the orbits, the extraocular muscles (EOM), are well endowed with intramuscular receptors of various types (Cooper et al. 1955; Eberhorn et al. 2005). However, the role of proprioception in the oculomotor system has long been controversial (Donaldson 2000). The sources of EOM proprioceptive signals, the utility and even the necessity for such signals, have all been questioned and debated over a long period.

A number of new developments have prompted a re-evaluation of these issues. Firstly, views of orbital mechanics and control have changed markedly in recent years. The active muscle pulley hypothesis and the notion of separate mechanical and functional roles for, and control of, the global and orbital layers of the EOM (Demer et al. 2000; Ugolini et al. 2006), have led to new suggestions concerning the role of proprioceptive signals from a class of receptor (the palisade ending, Richmond et al. 1984) unique to the EOM and novel structures for modulating the afferent signals arising from them (Buttner-Ennever et al. 2002). Secondly, the demonstration that EOM proprioceptive signals provide somatosensory cortex with an eye position signal (Wang et al. 2007) has raised important functional questions such as the timescale over which EOM afferent signals influence processing. In this review, data from experiments designed to investigate the role of EOM afferent signals in both a model animal preparation (the decerebrate pigeon) and in human subjects will be examined.

Methods

In order to investigate the role of EOM afferent signals, it is necessary to manipulate them. One approach is to remove them either surgically (by cutting the afferent pathway; eg Fiorentini et al, 1985, 1986; Buisseret, 1995; Ventre-Dominey et al, 1996) or to block

them (eg Steinbach, 1981, Wang et al, 2007). However, these approaches rely on knowing where afferent fibres run, and the pathway being accessible; both may be problematic. In order to induce signals, stretch of individual or groups of EOMs (eg Cooper et al, 1953; Donaldson and Dixon, 1980; Buisseret and Maffei, 1977; Dancause et al, 2007) and single muscle vibration have been used (Allin et al. 1996). Such techniques might provide a highly non-physiological input to central control structures via the afferent pathway. An alternative is to move the whole globe, producing an overall pattern of lengthening and shortening the EOM analogous to that occurring during eye movement (Ashton et al. 1984a; Donaldson and Knox 1990; Gauthier et al. 1994). A further advantage of this technique is that stimuli may be described parametrically, with reference to the direction, speed and amplitude of the imposed movement.

An opaque suction contact lens was used to impose movements on one eye in a range of species in single unit recording studies (trout, Ashton et al, 1989; toad, Ashton et al, 1984; cat, Ashton et al, 1984). This was done while imparting other stimuli such as vestibular or visual stimuli. A particularly extensive series of experiments was conducted in the pigeon. Pigeons have excellent vision, and a good repertoire of oculomotor behaviour (Nye 1969; Hodos et al. 1985). The pigeon was also used because both visual and vestibular processing could be explored in a decerebrate, paralysed preparation, free of the complicating effects of general anaesthesia.

Both unparalysed decerebrates and alert animals were also used in behavioural experiments, the results of which revealed that altering the movements of one eye could lead to detectable changes of the movements of the other eye. Therefore in a series of human experiments, a similar lens system (using a fenestrated scleral lens) was used to

impede movements of one eye while subjects responded to visual targets with the other eye. Once local anaesthetic was instilled into the right eye, the lens was placed on that eye, and gentle suction applied. The lens carried a stalk which fitted into a fixed holder. By observation it was clear that while the eye continued to move slightly against the lens, its movements were reduced relative to the fellow eye. Lenses were kept in place for short periods of up to five minutes. In these circumstances they were well tolerated.

Single unit results

The primary afferent pathway in the pigeon follows the familiar vertebrate pattern, with primary afferent cell bodies in the ophthalmic division of trigeminal ganglion (Hayman et al. 1995) from which Fahy and Donaldson (1998) recorded their responses to passive eye movement. Single units exhibited both amplitude and velocity sensitivity, and responded to only one direction of eye movement. Sinusoidal oscillation in the horizontal plane was combined with passive eye movement of one eye; the eye was moved rapidly to an eccentric position, held eccentrically for a short period, and then returned to the central position (Donaldson and Knox 1990). It was clear from unit activity recorded in the medial vestibular nucleus, and the IIIrd and VIth nuclei, as well as the surrounding reticular formation, that EOM afferent signals conveyed information related to the size, direction and speed of eye movement (Donaldson and Knox 1990; Donaldson and Knox 1991). Further, the effects did not build up over a number of trials, but were evident within at least a few tens of milliseconds of the eye being moved. They were thus consistent with the online control of vestibularly generated eye movement in the short term, as well as with longer term, parametric, changes in eye movement control.

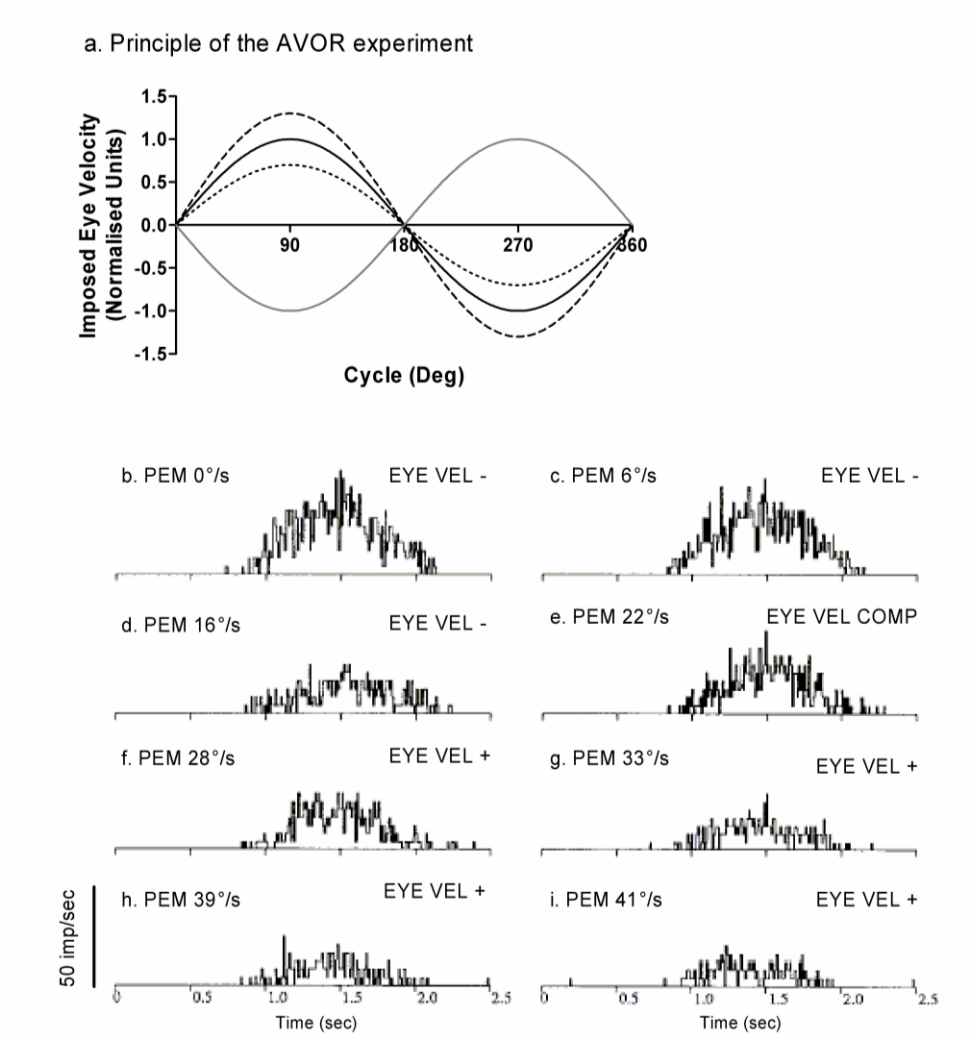

Figure 1. a. Principle of the "artificial VOR" experiment. Grey solid line: head velocity; black solid line: compensatory eye velocity; dashed line: eye velocity greater than that required for compensation for head velocity; broken line: eye velocity less head velocity. b-i. Peristimulus time histograms illustrating the response of a single unit recorded in the medial vestibular nucleus of the decerebrate pigeon during sinusoidal oscillation in the horizontal plane (±8°at 0.4Hz). In c-i the vestibular stimulus is combined with the passive eye movement of one eye at various velocities as shown. Each panel also shows whether the imposed eye velocity was less (c,d; EYE VEL-) or greater than (f-I; EYE VEL+) the compensatory velocity (e). (Modified with permission from Donaldson and Knox, 1993)

As useful as these experiments were, they failed to take account of the functional context. During sinusoidal vestibular stimulation the objective of the oculomotor system is

to counter-rotate the eye, with approximately the same peak speed as the head. This suggested a different experiment, which we called the “artificial VOR” (AVOR) experiment (Figure 1a). We sought to mimic the slow phase of the VOR by imposing a sinusoidal eye movement on one eye 180° out of phase with the head. At an appropriate velocity (in this case 22°/s) the imposed eye movement was compensatory. But we could also introduce functionally specific errors by moving the eye either faster or slower than required for compensation. Note that in our earlier experiments the velocity of the imposed eye movements had been much higher (of the order of 120°/s), although still within the oculomotor range of the pigeon. However, the vestibular responses of single units were sensitive to low velocity errors when induced in this functionally relevant manner (Figure 1b to i). This sensitivity had an important functional implication. Assuming that the response when the eye velocity was compensatory was the “normal” response, then when the eye was moved more slowly than required for compensation the single unit gain increased; when it was moved more quickly than required, the gain decreased. When the range of eye velocities was held constant, and head velocity was varied over a range, unit firing was also altered (Donaldson and Knox 1993). This suggests that a comparison is being made between the desired eye velocity or position, and the actual eye velocity and/or position with the resultant error signal altering unit firing.

Behavioural results on the VOR

It is possible that these single unit results do not reflect what is going on in the VOR pathway as a whole. And they were recorded from a reduced (ie a decerebrate), paralysed, preparation. However, we found that in an unparalysed, though still decerebrate preparation, during the VOR, EOM afferent signals altered the

electromyogram recorded from the muscles (Knox and Donaldson 1991). We were able to improve on this by repeating the AVOR experiment in awake, alert pigeons (Donaldson and Knox 2000). The eye movements of head-restrained adult pigeons were recorded from one eye using a chronically implanted scleral search coil, during sinusoidal oscillation in the horizontal plane, while the movements of the other (locally anaesthetised) eye were controlled with a suction contact lens. We observed essentially the same pattern of results as before: when one eye was moved more quickly than required for compensation the gain of the VOR, as measured from the movements of the other eye, was reduced compared to that observed when the eye velocity was compensatory. When the eye was moved more slowly than required, the gain increased. In pilot VOR experiments in human subjects, we found that although the effects did not reach statistical significance, a similar monotonic decline in VOR gain was observed, as the peak speed of imposed eye movement was increased (Knox and Donaldson 1993).

Experiments on human oculomotor control

The pigeon and human VOR results suggested that by imposing movements on, or interfering with, the movements of one eye, it might be possible to observe effects by measuring the movements of the other eye. We therefore decided to use suction contact lenses on human subjects in order to investigate saccades and smooth pursuit. We were encouraged by the results of Gauthier at al (1994) who demonstrated that passive deviation of one eye in humans for relatively short periods could alter eye alignment in the absence of binocular vision.

Subjects sat facing a stimulus monitor, with their heads stabilised using a chin rest and cheek pads; the movements of the left eye were recorded using infrared oculography. A

lens was used to impede the movements of the right eye. In the first experiment, each trial began with a randomised fixation time; a stationary saccade target then appeared (duration 200ms) at either 5° or 10° to the left or right (Knox et al. 2000). In a second experiment the stimulus was a step-ramp smooth pursuit stimulus (step amplitude 5°, target speed 14°/s; Weir and Knox 2001).

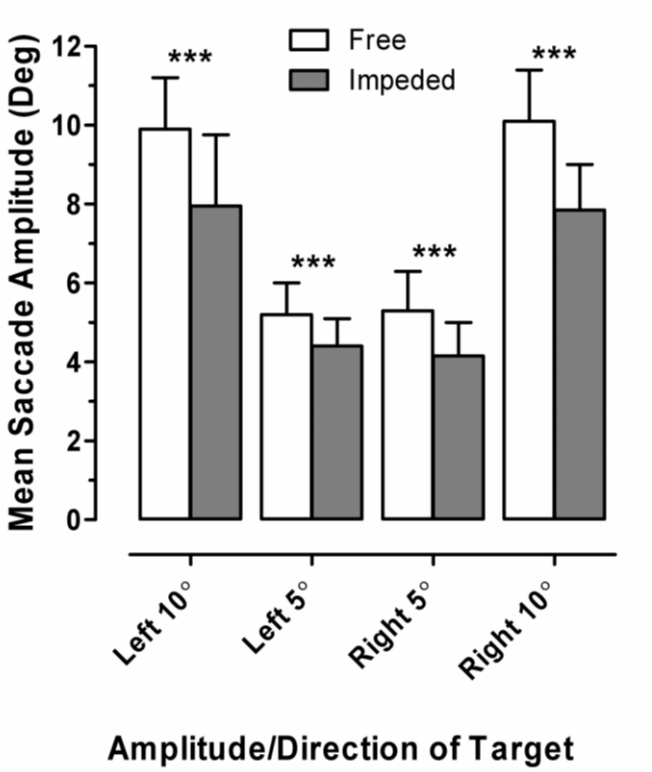

Figure 2. Pooled mean (±SD) saccade amplitude of the left eye before (open bars “Free”) and while (grey bars “Impeded”) the right eye was impeded. Data averaged for three human subjects. All column pairs are statistically significantly different (t-test, $p<0.001$).

When the left eye was impeded, the amplitude of saccades executed by the right eye was reduced by 19% averaged across subjects and target positions (Figure 2). However, the peak velocity and duration of saccades were appropriate for the reduced amplitude. Although the lens was in place for only a few minutes at most (up to approximately five

minutes), when it was removed the saccade amplitude returned toward the control values, but remained slightly reduced by approximately 5%. We also examined average saccade amplitude for each target position, for each trial in order, over the three subjects who participated (Figure 3). This analysis revealed that from the start of the run saccade

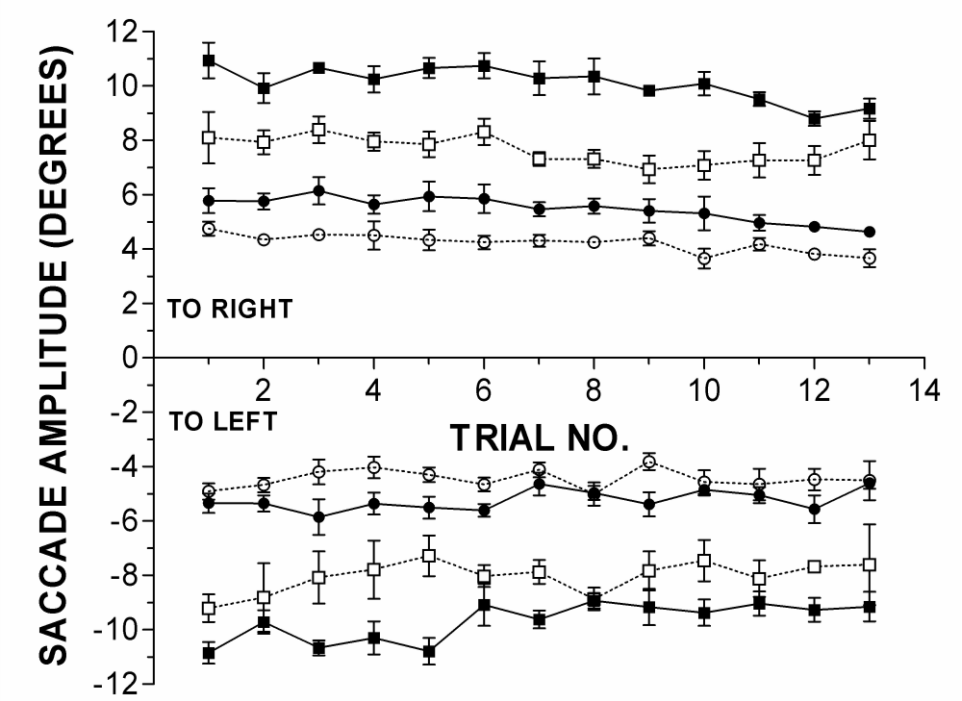

Figure 3 Effect of impeding one eye on the saccades amplitude of the other eye. Trial-by-trial pooled (±SEM) mean of left eye saccade amplitude before (open symbols) and while (filled symbols) the right eye was impeded. Squares: data from right and left 10° trials; circles: from right and left 5° trials. Data averaged across three subjects. (Modified with permission from Knox et al, 2000)

amplitude was reduced. This is not the same as claiming it was reduced as soon as the lens was in place. It took several tens of seconds to place the lens on the eye, place the stalk into the holder and initiate the run. During this period, while we sought to keep the subject's vision to a minimum, it is possible that an adaptive effect could have built up. All we can say is that, as Figure 3 shows, the saccade amplitude was reduced from the first trial in the run. The amplitude effect was relatively consistent throughout the run of trials,

neither building up, nor adapting out. As the target presentation time was 200ms, there was no target present when the reduced amplitude saccades landed. This meant there was no retinal error signal which might have caused adaptive increases in saccade amplitude. It would be interesting to repeat the experiment with a longer target presentation time in order to establish whether such adaptive effects occur.

The smooth pursuit results were generally similar. When one eye was impeded, the initial eye acceleration of the other eye was reduced by approximately 20%, as was the eye velocity 100ms after pursuit was initiated ie at the end of the open-loop period. When eye velocity was averaged over four 20ms epochs, with the first epoch beginning at the time of pursuit initiation, the velocity reductions compared to the control (non-impeded) values were evident from early in the pursuit response, and were statistically significant from the third epoch (ie 40-60ms into the response). Again, the velocity reduction effects were present from the first trial, and were unchanged for as long as the other eye was impeded.

These results remain to be confirmed and need to be extended. We have no means of demonstrating independently that the effects which we observed were the result of stimulating intramuscular proprioceptive signals. However, given the existence of various intramuscular receptors in humans, the most parsimonious explanation would be that it is afferent signals from these receptors that mediate the effects on saccades and pursuit. These signals have rapid access to the oculomotor control circuitry. Our results are consistent with both short term feedback control and rapid and longer term parametric adaptation. Where might such feedback signals interact with the central oculomotor control circuitry? Given that the saccades, although smaller when one eye was impeded,

still clearly exhibited the normal main sequence relationships, a site beyond the brainstem is implied. Given also that both saccades and smooth pursuit were modified in similar ways (ie we observed gain reductions) a structure involved in both pathways is probably involved. The cerebellum is important for both saccades and pursuit, is involved in gain control, and plays a role in adaptive responses. It would therefore seem to be a likely candidate.

Summary

It has long been generally accepted that the EOMs are endowed with intramuscular receptors of various types. Further, we and others have shown that the signals arising from these receptors, or their effects, can be recorded from a wide range of locations in the central nervous system involved in visuomotor processing. Recently intriguing results have reopened old questions a raised new ones. One recent report has reopened the issue of whether the EOM exhibit stretch reflexes (Dancause et al. 2007) while another has indicated that eye position signals in the primate primary somatosensory cortex appear to be proprioceptive in origin (Wang et al. 2007). Along with the experiments reviewed here, these suggest that the role of EOM afferent signals in visuomotor control remains a conundrum worthy of investigation.

Acknowledgements

All of the experiments I have described were collaborative efforts, and I am grateful to all of those colleagues who have been involved in them. However, particular thanks is due to Iain Donaldson who introduced me to these issues almost twenty years ago, and who for ten of those twenty years was a patient and skilful mentor.

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