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Research Note

Gaze-related activity of brainstem omnipause neurons during combined eye-head gaze shifts in the alert cat

M. Paré and D. Guitton

Montreal Neurological Institute and Department of Neurology and Neurosurgery, McGill University, 3801 University, Montreal H3A 2B4, Canada

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Summary. Studies undertaken in head-restrained animals have long implicated the omnipause neurons (OPNs) in the initiation of saccadic eye movements. These inhibitory neurons discharge tonically but cease firing just before and during saccades in all directions. By recording from OPNs in alert behaving head-unrestrained cats, we have demonstrated that the activity of these cells is related to the displacement of the visual axis in space (gaze), which is the sum of the eye movement relative to the head and head movement relative to space. OPNs were found to exhibit a complete cessation of discharge for a period equivalent to the duration of the gaze shift, and *not* to the duration of either the rapid eye movement or the head movement components. In large gaze shifts, OPNs were silent even when the eye was immobile in the orbit, as long as the gaze shift was not completed. The results of this study show that OPNs are controlled by neural elements that take into account the actual position of the visual axis relative to its final desired position, irrespective of the trajectory of the eye in the orbit or of whether the head is moving or not.

Key words: Omnipause neurons – Saccade – Gaze control – Eye-head coordination – Alert cat

Introduction

Electrophysiological evidence has suggested that the firing pattern of omnipause neurons (OPNs) has a preponderant significance in saccadic eye movement generation (see Fuchs et al. 1985 for review). These neurons are located in the caudal pontine reticular formation, in an area of the raphe complex recently described as the nucleus raphe interpositus (Büttner-Ennever et al. 1988; Langer and Kaneko 1990). OPNs are tonically active when the animal is fixating (attentively or passively) or making smooth eye movements in response to vestibular or visual stimuli. Their neural activity is however abruptly stopped (pause) prior to and during all vestibular quick phases and omnidirectional saccades (Luschei and Fuchs 1972; Keller 1974; King et al. 1980; Evinger et al. 1982). Taking into account that OPNs send inhibitory projections to preoculomotor burst-neurons (Curthoys et al. 1984; Nakao et al. 1980; Furuya and Markham 1982; Nakao et al. 1988), their tonic activity is believed to ensure eye stability by preventing neural noise on burst cells from activating extraocular muscle motoneurons during non-saccadic eye movements and stationary positions of the eyes. Microstimulation studies have further supported this view by demonstrating that saccades are totally suppressed when the OPN area is electrically stimulated (Keller 1974; Evinger et al. 1982). Thus, the discharge pattern of OPNs is viewed to act as an on-off gate controlling the saccadic burst generator.

A trigger signal coming from higher command centers and inhibiting OPNs is presumably responsable for the initiation of saccadic eye movements (Robinson 1975; Keller 1977; Fuchs et al. 1985). It has been suggested that this trigger signal is provided by the superior colliculus (SC) (Keller 1981; Fuchs et al. 1985). However, OPNs receive excitatory monosynaptic and inhibitory polysynaptic inputs from the SC (Raybourn and Keller 1977; King et al. 1980; Kaneko and Fuchs 1982). A functional explanation for these complex inputs has been proposed by Munoz and Guitton (1989) who attributed two functions to the SC: (1) fixation control ensured by the direct excitatory input to OPNs, and (2) orientation control via a collicular projection to long-lead burst neurons which may inhibit OPNs. Worthy of note, the SC (at least in the cat) is now thought to be implicated in the control of gaze (Munoz and Guitton 1985, 1989; Munoz 1988). Gaze is defined here as the position of the eyes with respect to the stationary surroundings: eye-relative-to-head plus head-relative-to-space. Also relevant, OPNs may project to neural elements which participate in the control of eye-head coordination, e.g. reticulospinal neurons (Langer and Kaneko 1983; Strass-

Offprint requests to: D. Guitton, Montreal Neurological Institute (address see above)

man et al. 1987; Ohgaki et al. 1987). Together, these data may confer on OPNs a broader role in gaze control than the studies in head-restrained animals have hitherto indicated.

In the present study we have investigated the discharge characteristics of OPNs during combined eye-head gaze shifts in the head-unrestrained cat in order to determine their putative function in gaze control.

Material and methods

Experiments were performed on four adult cats trained to fixate and orient to a food target appearing unexpectedly from either side of a tangent opaque screen positioned in front of the animal, whose head was either held fixed or unrestrained (Guitton et al. 1984, 1990). The positions of gaze and head relative to space were monitored by the search-coil in magnetic-field technique. The calibration procedures have been reported elsewhere (Guitton et al. 1984). The cats were prepared in a single surgical session performed under Nembutal anaesthesia and aseptic conditions. A coil of wire was sutured to the sclera of one eye. A hole was trephined near the lambdoidal crest to provide access to the brainstem, via the cerebellum, through a stainless steel recording chamber tilted 25° back from the frontal plane. The chamber was constructed to hold a hydraulic micropositioner, and also served as a clamp for holding the cat's head. A bipolar stimulating electrode was implanted in the left abducens nerve as it exits from the brain stem. An attachment for a head coil, the connector for the eye coil wire, the stimulating electrode, and the chamber were cemented and held to the skull with anchoring stainless steel bolts and dental acrylic.

Recording began more than one week after the surgery. In order to determine precisely the site of recording, the location of the left abducens nucleus was determined by recording antidromic field potentials following single shock stimulations of the sixth nerve. OPNs were then identified by their distinctive neural activity and their location relative to the abducens nucleus. As confirmed afterwards by histology, the region explored in this study extended from the rostral margin of the abducens nucleus up to 1 mm anterior, 1.0 mm to 3.0 mm below the floor of the IV ventricle, and ± 0.6 mm lateral from the midline. The extracellular activity of single neurons was recorded using glass micropipettes (2.0- to 2.5-MΩ of impedance) and conventional recording techniques. Recorded data were stored in computer files and analyzed off-line. Movement velocity profiles were obtained from smoothed derivatives of position traces. The onset of a movement was defined as the moment when the velocity first reached a 10 deg/sec level, whereas the offset was taken as when the velocity fell again to this criterion. Using this criterion, cursors were manually positioned on movement traces. Our computer software then measured and stored all relevant parameters (e.g. duration, amplitude, peak velocity) of the movements and the duration between the last spike before a pause in the unit activity and the first one of the resuming activity.

Results

Of 65 OPNs identified in the head-restrained condition, 16 also were recorded for a sufficient time when the animal's head was unrestrained, and yielded the data described in the present report. Extensive quantification was possible for 8 out of the 16 cells. The omnidirectional property was assessed and confirmed for all the cells by testing their activity pattern in relation to several different directions of eye and gaze movements. No directionally sensitive neurons were encountered. In order to facilitate the comparison of data obtained in head-restrained and head-unrestrained conditions, only movements in the horizontal plane were considered in this analysis. The characteristic firing pattern of OPNs was clearly distinct from other reticular oculomotor units. The recording of a typical OPN (cell P1) is shown in Fig. 1A. The cell responded with a complete cessation of its relatively regular tonic activity during a saccadic eye movement made by a head-restrained animal. As has been previously reported (Luschei and Fuchs 1972; Keller 1974; Evinger et al. 1982), the duration of the pause was proportionnal to the duration of the saccade (Fig. 2A). A linear regression line (coefficient $r=0.92$) through 90 data points obtained from this representative neuron has a slope of 0.89 and a y-intercept of 15.2 ms. All units stopped firing before the onset of the saccade. For cell P1, the mean interval from the beginning of the pause to the onset of the saccade was 26.0 ± 12.9 ms ($N=90$). In addition, most units tended to resume discharging before the completion of the eye movement. For cell P1, the mean latency from the end of the pause to the end of the saccade was 26.3 ± 9.8 ms ($N=90$).

In the head-unrestrained condition, the cessation of OPN activity was associated with shifts of gaze, i.e. the displacements of the visual axis relative to space (Fig. 1B, C, D). In gaze shifts accomplished with a steplike sequence of small gaze displacements (Fig. 1B), the durations of the eye saccades and the gaze saccades were indistinguishable, and the pause in OPN firing could not be linked preferentially to either eye or gaze saccades. However, in large single-step gaze shifts, the ocular saccade duration was often shorter than the gaze shift duration. Most interestingly, in these cases the pause duration was closely time locked to the duration of the gaze displacement. Indeed, OPNs paused for the duration of the gaze shift even when the rapid eye saccade was already terminated and the eye was moving back in a compensatory direction (Fig. 1C). This relationship between gaze saccade duration and OPN silent period was more impressive for large eye-head coordinated movements in which a "plateau" phase appeared in the eye trace (Fig. 1D). These particular ocular phases define the period following the rapid eye movement during which the eye remains relatively immobile in the orbit while the visual axis is still moving through space because of the head motion. Noteworthy, these "plateau" phases occur when the eyes are still within the oculomotor range, and it has been argued that they are the result of a neural, rather than a mechanical saturation element in the brainstem oculomotor circuits (Guitton et al. 1984, 1990; Guitton and Volle 1987). The presence of a "plateau" in the eye trajectory during a gaze shift allows a clear discrimination between the duration of the eye saccade and the duration of the gaze displacement. In such gaze shifts, OPNs were found to resume discharging not when the eye had achieved a stationary position in the orbit but only when gaze was on target, or dynamic gaze error was null. This absence of activity from OPNs during the entire gaze shift, independently of eye trajectory, provides the best evidence for a gaze-related pause.

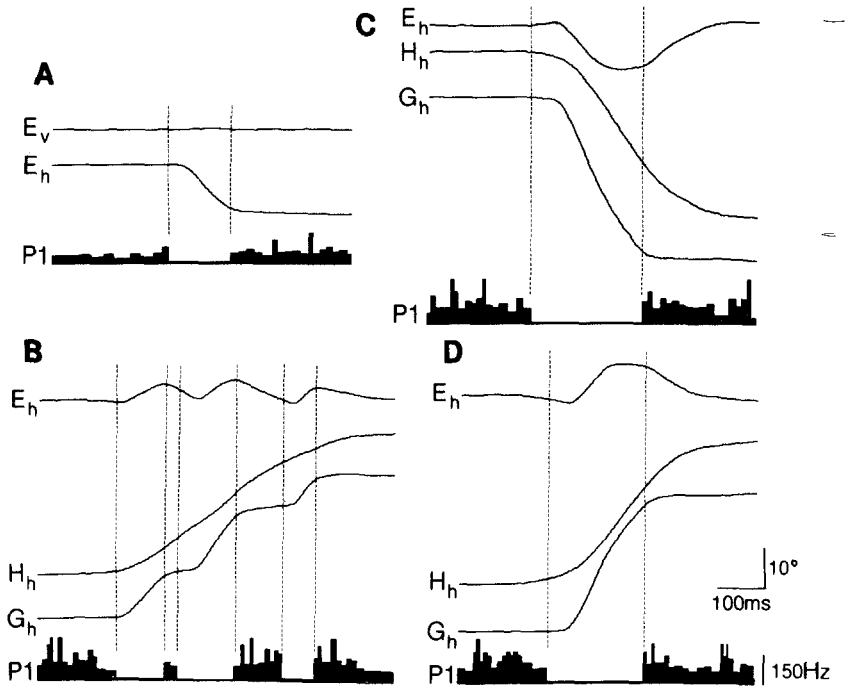

Fig. 1. A Discharge pattern of one representative OPN during a horizontal saccadic eye movement in the alert head-restrained cat. **B–D** Examples of the activity of the same OPN during combined eye-head gaze shifts in head-unrestrained condition. E_v: vertical eye position; E_h: horizontal eye position; H_h: horizontal head position; G_h: horizontal gaze position. Upward deflections are rightward movements. Lower traces show instantaneous firing rate of the neuron. Dotted lines indicate beginning and end of the cessation of activity

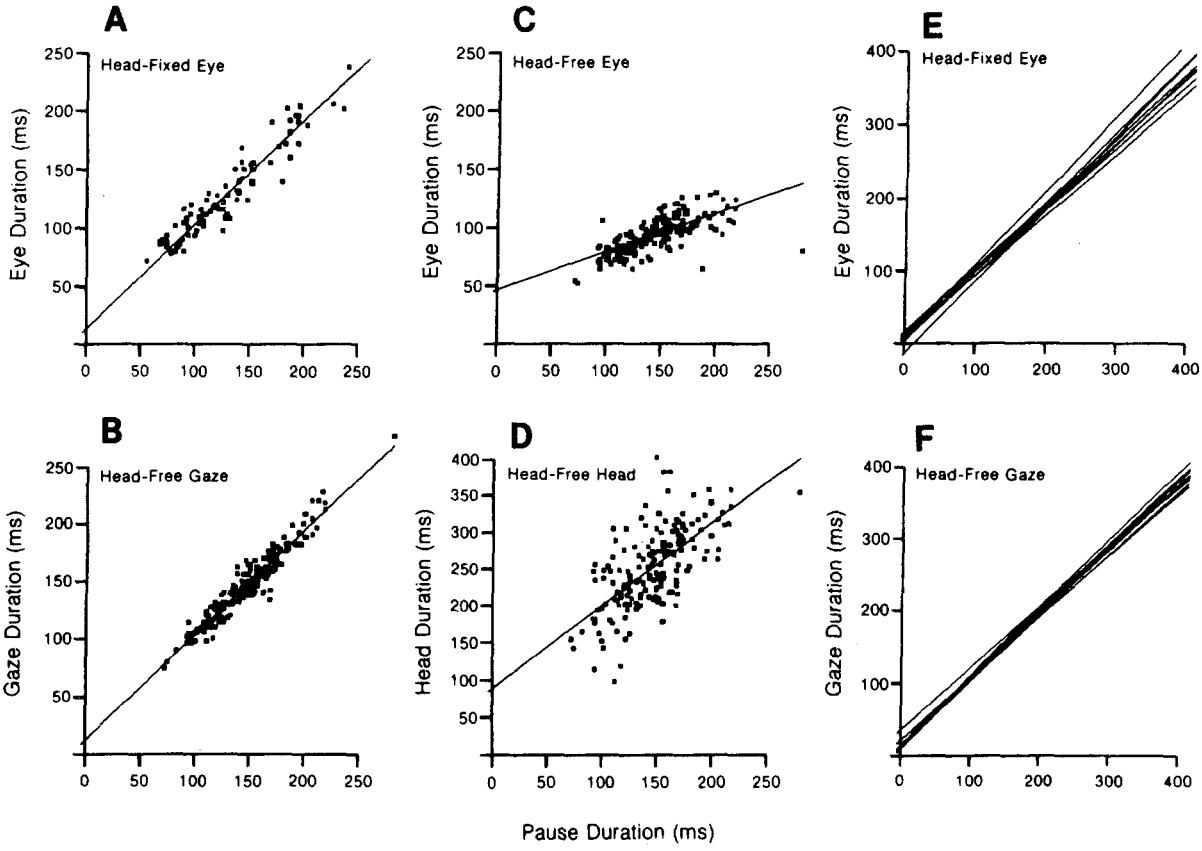

Fig. 2. A Relationship between the duration of the pause in activity of a representative unit (cell P1) and the duration of the eye saccade in head-fixed condition ($N=90$). **B.C.D.** Relationship between the duration of the pause in activity of the same neuron and the duration of the associated gaze, eye and head displacements in head-unrestrained (head-free) condition ($N=174$). The solid lines are the least-squares fit to the data points obtained by linear regression. The respective equations are the following: **A** $Y=0.89X+15.2$ ($r=0.92$); **B** $Y=0.91X+12.5$ ($r=0.92$); **C** $Y=0.33X+45.8$ ($r=0.47$); **D** $Y=1.10X+88.5$ ($r=0.43$). **E, F** Regression lines of gaze duration on pause duration in head-fixed and head-free conditions for 8 cells

Plots of the duration of the pause (for the representative cell P1) versus the duration of the concomitant gaze, eye and head movements reveal clearly that the OPN's pause is related to gaze (Fig. 1D and Fig. 2B, compared to Fig. 2C, D). On one hand, there is a linear relationship between the pause and the gaze durations (Fig. 2B). The linear regression line ($r=0.92$; $N=174$) has a slope of 0.91 and a y-intercept of 12.5 ms. On the other hand, the duration of the pause is very poorly correlated with the duration of either the fast component of the eye movement (Fig. 2C) or head movement (Fig. 2D). The regression coefficients are 0.47 ($N=174$) and 0.43 ($N=174$), respectively. Furthermore, the relation between the eye and pause duration is far from being a 1:1 relationship; the slope of the regression line is 0.33. Thus, the pause in activity of this OPN is preferentially related to the duration of the gaze shift. Interestingly, the relation observed between gaze and pause durations in the head-unrestrained cat is the same as the relation observed between eye and pause durations in the head restrained condition (Fig. 2A compared to Fig. 2B). This observation holds for all the cells analysed (Fig. 2E, F). Moreover, the timing of the gaze saccade trajectory and OPN discharge is also similar in head-restrained and head-unrestrained conditions. In the latter, the mean interval from the beginning of the pause to the onset of the gaze saccade (for the cell P1) was 25.4 ± 10.1 ms ($N=174$), and the mean interval from the end of the pause to the offset of the gaze displacement was 25.4 ± 7.5 ms ($N=174$).

Discussion

We have demonstrated that OPNs recorded in alert head-unrestrained cats have a gaze-related pause in activity during combined eye-head gaze shifts. It might be argued that our sample is not representative, that OPNs could be subdivided into two functionally and anatomically separate populations: one with its activity related to gaze saccades and another discharging in relation to rapid eye movements. The former would be connected to gaze-related elements and the latter to eye-related units. Anatomical studies (Langer and Kaneko 1983; Strassman et al. 1987; Ohgaki et al. 1987) have shown that OPNs in the area next to the abducens nucleus project to saccadic burst-neurons, which monosynaptically control oculomotoneurons. This area is exactly where we recorded our units. Thus we believe that all omnipause neurons in the cat possess the same type of discharge pattern, i.e. they pause during gaze shifts.

It remains to be determined how the gaze-related pause in activity of OPNs can be inserted into a conceptual framework. Classically, in the head-restrained animal, the inhibitory influence of OPNs has been considered to act as a gate that maintains the oculomotor burst generator in check until a saccade is to be initiated. In the head-unrestrained condition, this view is unsatisfactory: the pause in activity of OPNs frequently extends beyond the rapid part of the ocular saccade into a portion of the eye's trajectory where the eye velocity is zero. One explanation of this phenomenom is that, during these plateau phases, the burst generator is still active and the compensatory mode of the vestibuloocular reflex (VOR) is attenuating the saccadic signal. The situation appears to be more complex than this. Observations in the head-unrestrained cat suggest that the VOR does not necessarily add with the eye saccadic command during large combined eye-head gaze shifts (Roucoux et al. 1980; Fuller et al. 1983; Guitton et al. 1984). Moreover, it has been demonstrated that the VOR is completely suppresed during such gaze displacements in monkey (Tomlinson and Bahra 1986) and human (Laurutis and Robinson 1986; Pélisson and Prablanc 1986; Guitton and Volle 1987; Pélisson et al. 1988). Taking into account these observations, it has been proposed that combined eye-head movements are controlled by a gaze feedback-loop. Information about head motion is presumed to be constantly added to that about eye motion in order to provide an ongoing internal estimate of current gaze position. A comparison between current and desired gaze positions yields a gaze position error signal that drives both eye and head motor systems. Recent observations in our laboratory indicate that the latter signal is provided by efferent cells of the superior colliculus: the tecto-reticular and tecto-reticulo-spinal neurons (Munoz and Guitton 1985, 1989; Munoz 1988). On the basis of the known direct collicular projection onto OPNs (Raybourn and Keller 1977; King et al. 1980; Kaneko and Fuchs 1982), the presently observed OPN behaviour was predicted (Munoz and Guitton 1988, 1989; Guitton et al. 1990). To conclude, we propose that the term saccade be defined independently of the eye's trajectory in the orbit but rather be considered as the ocular response when gaze position error is not zero, i.e. during which OPNs are silent.

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