

The ocular tilt reaction—a brainstem oculomotor routine

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Electrical stimulation of brainstem tegmentum in alert macaques elicits a stereotyped ocular movement routine characterized by vertical divergence and conjugate cycloverision. The movement pattern is similar to those seen in the clinical syndromes of see-saw nystagmus and skew deviation. The stimulated movement pattern is not dependent on initial eye position and cannot be produced when the animal is under barbiturate anesthesia. It is not overridden by saccadic inhibition stimulation and is present in cerebellectomized and labyrinthectomized monkeys.

Key words: ocular tilt reaction, nystagmus, see-saw, skew deviation, eye movements, cyclotorsional, vertical divergence.

An almost universal feature of ocular motility in the primate is the conjugacy of movements of the two eyes. Not only is this manifest under conditions of normal use, but also in movements artificially evoked by electrical stimulation of the brain. In several years' of experimental exploration of monkeys' brains, we have found the situations in which electrical stimulation yields disjunctive movements to be so separate that they can be clearly grouped under a very few individual headings: (1) when stimulation is confined to lower motoneurons of individual muscles, or to fibers projecting directly on to motoneuron pools of individual muscles; here

a movement will be truly dissociated in that either only one eye moves, or the movements of the two eyes are not interdependent; (2) when the pathway for the near reflex is stimulated: convergence, accommodation, and pupil constriction then occur conjointly; (3) when stimulation yields the ocular tilt reaction. The last set of circumstances produces a clear-cut, reproducible syndrome, and one with such striking resemblance to some clinically described abnormalities, that we have analyzed it in some detail to ascertain whether it might not reveal a specific component of the functional organization of the oculomotor apparatus.

Materials and methods

Healthy young male and female monkeys of several species (*Macaca irus*, *Macaca speciosa*, and *Cercocebus atys*) were implanted with headgear, which permitted periodic immobilization of their head, and with a screw-cap Lucite chamber over the vertex of the skull, which permitted introduction of electrodes. After thorough evaluation of

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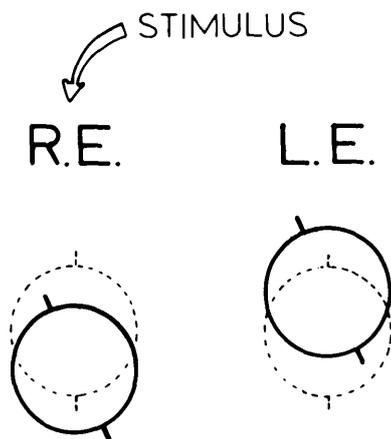


Fig. 1. Right ocular tilt reaction. Right eye moves down, left eye up, and both rotate to the right by an equal amount. This reaction occurs on stimulation of the brainstem on the right side in the region shown in Fig. 2.

normal oculomotor function, 0.9 per cent saline-filled micropipettes (impedance 1 to 3 M Ω) were advanced under stereotaxic control through the Lucite chamber into the brainstem. While the alert monkey carried out his normal eye movements in response to environmental stimuli, single units could be recorded and brainstem structures electrically stimulated. In the studies reported here, coordinates of the tip of the electrode were noted when the electrode was in a position where stimulation elicited eye movements of definite pattern, and one or more of the following were analyzed: (1) effect of varying parameters of stimulation, (2) effect of varying direction of gaze at onset of stimulation, and (3) effect of intravenous breivital (5 mg. per kilogram) on associated changes in response to stimulation.

Stimulation parameters were trains of 0.3 msec. pulses, usually at 440 Hz., from a Grass S-48 stimulator and SIU 5A stimulus isolation unit at amplitudes up to a maximum of 150 volts (50 to 150 μ A, depending on electrode resistance). In a few check experiments we used insulated sharpened tungsten needle electrodes. When these had similar impedance, as determined by the same method (voltage response to a 10^{-9} A. current pulse) they needed to deliver considerably less current (often only $1/10$) to produce the same response as a micropipette. This difference may be of interest to investigators who wish to compare results obtained with tungsten electrodes and micropipettes.

Eye movements were evaluated by direct observation, by television tape recording and subsequent single-frame analysis, and by horizontal and vertical direct current electro-oculograms

recorded via Beckman skin electrodes and Grass P-18 amplifiers, and displayed on a Mingograf 800 ink-jet paper recorder. Single units were recorded via a Grass P-15 amplifier and a Tektronix FM 122 amplifier and displayed on the Mingograf simultaneously with electro-oculograms. Selected parts of the data were recorded on magnetic tape (HP 3960). After about a dozen electrode tracks, the monkeys were deeply anesthetized and perfused with 10 per cent formalin or Karnovsky's fluid. Correlation of electrode tracks visible in the sectioned and stained brain with stereotaxic data allowed anatomic identification of stimulation and recording sites.

Parallel experiments were performed on several monkeys with lesions, including complete one-sided or both-sided ablation of the cerebellum or labyrinths.

Results

This report concerns a response pattern whose characteristic features are a vertical divergence of the two eyes coupled with a conjugate torsional movement in which both eyes move their 12 o'clock meridians equally in the direction of the eye that has infraducted (Fig. 1). For reasons that are developed in the Discussion section, we have assigned the name "ocular tilt reaction" to this complex movement.

During stimulation with a steady train of pulses, the eyes move faster than in smooth pursuit movements but slower than in saccadic movements to their end position, which is maintained as long as the stimulus train continues, after which the eyes return at a similar speed to their initial position. The latency is less than 20 msec. The basic vertical divergence-cycloverversion pattern may be coupled with a small horizontal convergence movement or a conjugate versional movement. With the latter, curved trajectories and apparently unequal horizontal and vertical movement of the two eyes may result. Horizontal convergence and version components are usually absent and the cyclotorsion is always equal in the two eyes, so we regard our findings as pointing to a movement routine consisting of a cycloverversion coupled to a vertical divergence. The vertical divergence is produced by equal opposite movements of the two eyes. When unequal vertical move-

ments occur this may be seen to be related to a superimposed vertical version movement simultaneously evoked at the particular stimulating site, or by the fact that one eye would have been carried beyond the limit of its movement.

The relative extents of cyclovergence and vertical divergence vary somewhat between animals and stimulation sites. A typical response may show a 20° cyclovergence, coupled with 8 to 10° vertical divergence between the visual axes of the two eyes.

Initial eye position. Within a central region of fixation, the magnitude of the evoked movement and distribution between the two eyes is entirely independent of initial eye position. When the eyes are vertically in a far eccentric position at the onset of stimulation, there is usually a smaller movement of the eye that has approached the limit of its field of movement.

Changes in parameters of stimulation. We have found 440 Hz. to be a most effective frequency of stimulation. In a location in which a good ocular tilt reaction could be elicited, lower frequencies give similar responses of lesser amplitude; near 100 Hz. there is only a faint residual eye movement. The components of the response (vertical divergence and cyclovergence) seem to change in an approximately parallel fashion with changes in voltage and frequency. A typical stimulus for a sustained ocular tilt reaction would be 5×10^{-6} A. at 440 Hz. with a tungsten electrode.

Interaction with vestibular responses and electrically evoked saccadic inhibition. While subjected to electrical stimulation producing the ocular tilt reaction, the monkey can be rotated around a vertical axis or the anteroposterior axis of the head. The resulting vestibulo-ocular reactions are identical with those seen in animals who were not stimulated.

When a second electrode is appropriately introduced and its stimulation yields the saccadic inhibition phenomenon,¹ the ocular tilt routine can be evoked though the monkey is unable to make saccadic movements in any direction.

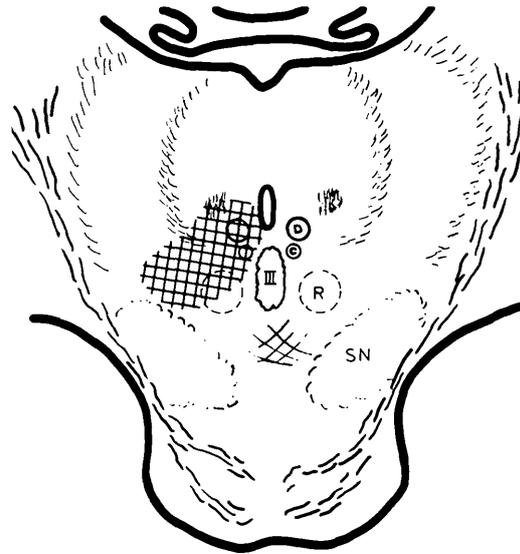


Fig. 2. Vertical section of brainstem of macaque about 8 mm. anterior to zero plane of Horsley-Clarke. Structures identified in the drawing include the Interstitial Nucleus of Cajal (C), Nucleus of Darkschewitsch (D), Third Nerve Nucleus (III), and Substantia Nigra (SN). A right ocular tilt reaction (Fig. 1) can be elicited by low-current electrical stimulation in the hatched area. This parasagittal ocular-tilt-generating zone extends through the tegmentum of the midbrain into the diencephalon.

Anesthesia. Anesthesia always eliminates the electrically evoked cyclovergence and vertical divergence. Residual conjugate movements which occasionally remain during anesthesia are usually also seen as a conjugate component of the total movement pattern before and after anesthesia.

Ablation of cerebellum or labyrinths. Monkeys with complete cerebellectomy, hemicerebellectomy, or labyrinthectomy do not differ from normal monkeys in so far as the ocular tilt reaction is concerned.

Location of stimulation electrodes when the ocular tilt reaction is induced. Anatomic sites from which the ocular tilt reaction can be evoked are midbrain regions lateral and dorsolateral to the III and IV nerve nuclei (Fig. 2), extend rostrally to include the nuclei of Cajal and Darkschewitsch, the walls of the third ventricle near the rostral end of the cerebral aqueduct and the habenular nuclei, and extend caudally to

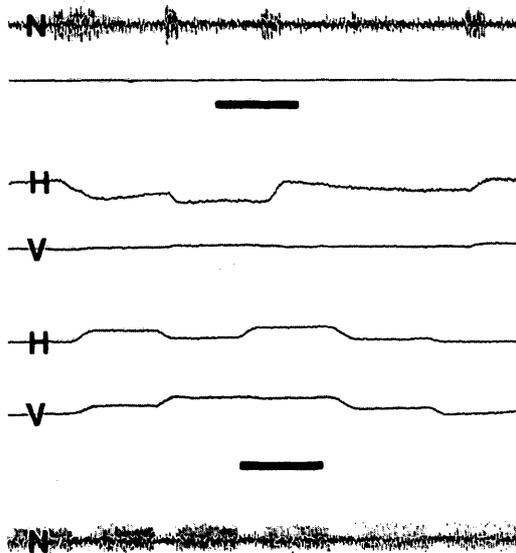


Fig. 3. Typical neuronal discharge patterns recorded in ocular tilt generating region (Fig. 2) in alert monkeys during spontaneous eye movements. A, unit which bursts for every saccade. B, unit which discharges tonically in intersaccadic intervals. In each figure: N = neuronal discharge; H = horizontal electro-oculogram (\uparrow = L \downarrow = R); V = vertical electro-oculogram (\uparrow = down \downarrow = up) time bar, 250 msec.

include the rostral parts of the floor of the fourth ventricle. Typically, stimulation produces ipsilateral infravergence and cyclovergence, i.e., down movement of the ipsilateral and up movement of the contralateral eye and conjugate cyclotorsional movement of both eyes, bringing their 12 o'clock positions toward the stimulated side. The direction of the ocular tilt reaction will be labeled according to the side toward which the 12 o'clock meridians of the eyes rotate. We have, on very rare occasions, seen ocular tilt reactions with contralateral infravergence and cyclovergence. These examples are too few to indicate whether they represent small areas with differing organization, or paths extending to or from the large areas described above.

Single unit activity. Since the alert monkey has come into use as an experimental preparation, a number of single-unit firing patterns closely related to ocular motor

activity have been identified in the brainstem and to some extent, characterized.²⁻³ Of those unit-response patterns recorded in the areas where the ocular tilt reaction may be evoked, none is unique to the area (with the possible exception of the tonic position-coded burst-for-every-saccade unit) and none is singularly absent. The most common pattern was the burst-for-every-saccade unit (Fig. 3, A) (eleven sites) and units which burst-for-saccades in particular directions (five sites). Tonic units which stopped during saccades (Fig. 3, B) were seen at four sites. On one occasion a type of very early directional burst-saccade unit, first described by Wurtz and Goldberg⁴ in the superior colliculus, was identified. While the area from which stimulation elicits ocular tilt reaction is generally not as rich in unit activity as the paramedian pontine reticular formation, the unit population does not differ markedly from that seen there.

Discussion

Is the ocular tilt reaction a single neural pattern? With stimulation of brain structures, accidental stimulation of parallel paths, creating artificial patterns of movement, is always a possibility. The arguments in support of the view that we are here dealing with a discrete neural pattern are quite decisive. The movements are distributed between the two eyes and independent of eye position. The wide range of effective stimulation sites precludes the possibility that current spread from an electrode tip always reaches just those muscles whose activity is required to elicit the movement. Analysis of muscle action shows that while the superior rectus of one eye and inferior rectus of the other would be major agonists of such movements, the cyclotorsional component of these muscles, were they stimulated exclusively, would not suffice to produce the observed cyclovergence, in particular since the observed cyclovergence is strongly independent of the initial eye position while the cyclotorsional components of these muscles is strongly

dependent on eye position. In addition, were inferior rectus and contralateral superior rectus the only muscles involved, horizontal conjugacy would not be retained. The effect of brevitall is important here. When the stimulating electrode is in a motoneuron pool or a cranial nerve root, there is little change in response to stimulation when the animal is anesthetized or goes to sleep. The same applies to a stimulation of the medial longitudinal fasciculus, which produces adduction of the ipsilateral eye even under anesthesia. The motor routine reported here is, however, abolished by anesthesia. It can be safely concluded, therefore, that ocular tilt represents excitation of a neural pattern which supplies the requisite excitation and inhibition, via one or more synapses, to motoneurons of many and perhaps all ocular muscles, where they are integrated with the remainder of the synaptic influences.

The strong torsional component of the motor routine directs attention to the situations when the primate oculomotor apparatus exhibits this feature. Cyclotorsion is often invoked in discussion of Listing's law. The question of torsion then comes up only when the eye position in a tertiary position is compared with an externally imposed measuring standard, such as a plumb-bob or a spirit-level. When Listing's law is viewed, however, as nothing more than an expression of the natural pattern of innervation, the need to invoke a special torsional component disappears. The cyclotorsion implied by Listing's law is only apparent, and does not need a cycloversive innervation. Indeed, the opposite is true. When the eyes do not show the orientation demanded by Listing's law, a special cycloversive innervation should be assumed. This is the case with appropriate vestibular or optokinetic stimuli.

It is accepted that there is a horizontal version mechanism (released by pontine stimulation and absent in horizontal gaze palsy) and a vertical mechanism (absent in Parinaud's syndrome). Does the observed ocular tilt reaction constitute a

manifestation of a basic cyclorotation-movement mechanism? The evidence is against such an assumption. Pure cyclovergence can be elicited by vestibular and optokinetic stimulation and there is then no vertical divergence.

If the observed ocular tilt reaction is not the basic cycloversional mechanism, could it be the basic vertical divergence mechanism? Horizontal convergence is a clearly identifiable neural configuration, which we can elicit by electrical stimulation always in association with accommodation and miosis. (The bilateral stimulation of the medial rectus motoneurons, or the direct influences on them by the medial longitudinal fasciculi, while technically inducing convergence, should be excepted in the present context.) Wearers of unequal spectacle corrections need vertical divergence much of the time to see singly, as do also, of course, patients with a whole range of neuromuscular disorders. Suffice it to say that, to the extent that vertical divergence can be exercised—and this may be several degrees—there does not appear to be the concomitant cyclovergence that the findings on evoked ocular tilt would demand.⁵

One feature which offsets the ocular tilt response from the mechanism of ordinary voluntary conjugate movements is illustrated by another finding. We have described¹ saccadic inhibition, i.e., the blocking of saccadic innervation by stimulation of specific brainstem regions in alert monkey. Such saccadic inhibition stimuli, on the other hand, fail to override stimulations evoking the ocular tilt reaction. This points to the likelihood that the pathways used to release the ocular tilt reaction are separate from those subserving saccades. Both need a rather carefully regulated distribution of excitatory and inhibitory innervation to many, if not all, the extraocular muscles, but these distributing networks cannot be identical.

One might consider a possible relationship between the monkey ocular tilt reaction and the head tilt pattern discovered

by Hess⁶ in the cat. The latter implicates the Interstitial Nucleus of Cajal, which is also a prominent, though not the sole, stimulation site in our experiments. Hess did not report vertical divergence in the cat, nor does it seem to be clearly conjoint with the cycloverision obtained by Hyde and Eason⁷ on stimulation of the cat Interstitial Nucleus of Cajal. If this is a species difference, it may have its origin in the fact that the rotation of the skull on the neck takes place around axes whose orientations with respect to gravity (as seen from the neck) are different in the higher primate than in the cat. The distinction between head turning (Wendereaktion),⁸ i.e., the rotation of the head around a vertical axis, and head tilting (Raddrehungsreaktion), i.e., the rotation of the head around an anterior-posterior axis, needs to be maintained. The interaction between head and eye turn is apparent in Bizzi's findings in the monkey⁹ and has also been reported by Hess⁶ and Hassler.⁸

Relationship between ocular tilt reaction and clinical neuro-ophthalmological syndromes. In the neuro-ophthalmological literature, there is a well-known syndrome, skew deviation, characterized by concomitant vertical divergence, usually of sudden onset in serious diencephalic, mesencephalic, or rhombencephalic affections. Ever since it was first described early last century by Hertwig and independently by Magendie,¹⁰ it has given rise to arguments as to the site of its release. We tend to think that the clinical skew deviation or Hertwig-Magendie phenomenon is identical with the ocular tilt reaction described in this report. Since the site of insult in the neurologic patients can almost never be determined unambiguously,¹¹⁻¹² and since we find an extensive region of stimulation sites in the monkey, anatomic arguments cannot at present be used to accept or reject conclusively the hypothesis that the clinical syndrome and experimental movement routine are identical. A major argument could be developed around the usual absence of an overt cycloverisional com-

ponent in the description of the clinical syndrome, but we feel that it need not be conclusive. Unless previous absolute determinations are available showing the eye in a state where cycloverision is absent, it cannot be immediately proved by any ocular tests that a pair of eyes is in a state of maintained non-zero cycloverision. (Tests of the subjective vertical may possibly help to resolve this point.) In our experimental animals, momentary comparison with and without stimuli makes the cycloverision easily discernible, but this is not possible in patient's with skew deviation.

Another clinical syndrome, see-saw nystagmus¹³⁻¹⁵ has the characteristic combination of vertical divergence and cycloverision that is seen in the ocular tilt reaction. It differs primarily in that direction alternates, giving a pendular nystagmus. This alternation may point to imbalance or lack of proper mutual inhibition between the two sides of the brainstem¹⁶ or may result from alternate reciprocal activation of the two sides. The ocular tilt reaction produced by unilateral stimulation is essentially like a half-cycle of see-saw nystagmus. Of interest would be an experimental lesion producing see-saw nystagmus. The area usually implicated, the diencephalon near the optic chiasm,¹⁵ is not one usually associated with oculomotor function, but may yet prove to be important in coordination of binocular movements.

REFERENCES

1. Westheimer, G., and Blair, S. M.: Saccadic inhibition induced by brainstem stimulation in the alert monkey, *INVEST. OPHTHALMOL.* 12: 77, 1973.
2. Westheimer, G., and Blair, S. M.: Mapping the visual sensory onto the visual motor system, *INVEST. OPHTHALMOL.* 11: 490, 1972.
3. Eckmiller, R., Blair, S. M., and Westheimer, G.: Oculomotor neuronal correlations shown by simultaneous unit recordings in alert monkeys, *Exp. Brain Res.* 21: 241, 1974.
4. Wurtz, R. H., and Goldberg, M. E.: Activity of superior colliculus in behaving monkeys. III. Cells discharging before eye movements, *J. Neurophysiol.* 35: 575, 1972.
5. Bielschowsky, A.: Die einseitigen und gegen-

- sinnigen (dissoziierten) Vertikalbewegungen der Augen, Albrecht v. Graefes Arch. **125**: 493, 1930.
6. Hess, W. R.: Charakter der im Zwischenhirn ausgelösten Bewegungseffekte, Pflüger's Arch. **244**: 767, 1941.
 7. Hyde, J. E., and Eason, R. S.: Characteristics of ocular movements induced by stimulation of the brainstem of cat, J. Neurophysiol. **22**: 666, 1959.
 8. Hassler, R.: Die zentralen Apparate der Wendebewegungen. I. Ipsiversive Wendungen durch Reizung einer direkten vestibulo-thalamischen Bahn in Hirnstamm der Katze, Arch. Psych. Zschr. Neurol. **194**: 456, 1956.
 9. Bizzi, E., Kalil, R. E., and Tagliasco, V.: Eye-head coordination in monkeys: evidence for centrally patterned organization, Science **173**: 452, 1971.
 10. Cogan, D. G.: Neurology of the Ocular Muscles. Ed. 2. Springfield, Ill., 1956, Charles C Thomas, Publisher, p. 134.
 11. Pötzl, O., and Sittig, O.: Klinische Befunde mit Hertwig-Magendiescher Augeneinstellung, Z. Ges. Neurol. Psychiat. **25**: 702, 1925.
 12. Smith, J. L., David, N. J., and Klintworth, G.: Skew deviation, Neurology **14**: 96, 1964.
 13. Maddox, E. E.: See-saw nystagmus with bitemporal hemianopia, Royal Soc. Med. **7**: 12, 1914.
 14. Daroff, R. B.: See-saw nystagmus, Neurology **15**: 847, 1965.
 15. Schmidt, D., and Kommerell, G.: Schaukelnystagmus (see-saw nystagmus) mit bitemporaler Hemianopie als Folge von Schädelhirntraumen, Albrecht v. Graefes Arch. Klin. Exp. Ophthalmol. **178**: 349, 1969.
 16. Kornhuber, H. H.: Physiologie und Klinik des vestibulären Systems, Arch. Klin. Exp. Ohren-, Nasen-, und Kehlkopfheilk. **194**: 150, 1969.