EXTRAOCULAR MUSCLE AFFERENTS TO THE CEREBELLUM OF THE CAT

By A. F. FUCHS and H. H. KORNHUBER

From the Department of Clinical Neurophysiology, University of Freiburg and the Department of Neurology, University of Ulm, Germany

SUMMARY

1. Afferents from the extraocular muscles to the cerebellum of the cat were investigated by evoked potential techniques using muscle stretch as a stimulus.

2. Short (about 4 msec) latency responses occurred in the vermian folia anterior (Larsell's lobule V b, c) and posterior (lobules VI and VII) to the primary fissure under light Nembutal anaesthesia.

3. The location of the cerebellar eye muscle responses coincides with the visual and auditory projections as well as homologous projections from cortical Areas 8 (the frontal eye fields) and 17 in the monkey. It also overlaps the oculomotor area of the cerebellum as revealed by electrical stimulation.

4. Facts 2 and 3 above, together with the selective disturbance of saccadic eye movements in humans with cerebellar atrophy, suggest a cerebellum mediated proprioceptive feed-back loop for the control of saccadic eye movements.

INTRODUCTION

Although no encapsulated spindle organs exist in the extraocular muscles of the cat, Cooper & Fillenz (1955) have shown that low threshold stretch receptors are present in the inferior oblique. These authors conclude that the receptor fibres start in the mixed oculomotor nerve in the orbit and eventually reach the mesencephalic nucleus of the Vth nerve (Fillenz, 1955). Wilkenson (1930) has seen occasional fibres in the cat orbit which leave the ophthalmic branch of nerve V to run in the IVth nerve to the superior oblique where they terminate in 'numerous little end loops, end nets, or reticula'. Bach-y-Rita & Murata (1964) examined the stretch receptors in the cat lateral rectus and demonstrated that some of the proprioceptive impulses reach the brain stem over the VIth nerve. Once they arrive there, however, the further path and function of the impulses

is unknown. Fillenz (1955) was even unable to record any responses from the oculomotor nuclei.

It has long been known from stimulation and ablation studies (Hampson, Harrison & Woolsey, 1952; Dow & Manni, 1964; Cohen, Goto, Shanzer & Weiss, 1965) that the cerebellum is concerned with eye movements. Recently, in patients with cerebellar atrophy, one of us (Kornhuber, 1968) has found a selective disturbance of saccadic eye movements characterized by an inability to execute large saccades and occasional increase in saccadic duration. Furthermore, Fillenz (1955) was able to record afferent responses from the cat extraocular muscles among the fibres of the brachium conjunctivum. Since, in addition, the cerebellum is well endowed with proprioceptive inputs for its role in the motor control of the limbs, a cerebellar projection from the extrinsic eye muscles can also be expected.

In this study, cerebellar evoked potentials were obtained from the vermian portions of Larsell's lobules V, VI and VII in response to a stretch of the extraocular muscles. The short latency of the responses evoked from the folia adjacent to the primary fissure indicates that the cerebellum would be capable of influencing the rapid saccadic eye movement.

METHODS

Animal preparation. The series of sixteen adult cats (2–3 kg) used in this study can be divided into three groups. In the first four cats, under a mixture of Nembutal and chloralose anaesthesia, a thread was attached to the sclera at the left lateral rectus insertion and the eye was adducted to stimulate the muscle receptors. The effect of tactile afferents was precluded by carefully removing the bony orbit and peeling back and cutting away the conjunctiva up to the muscle insertions. Control experiments eliminated both auditory and visual inputs. A 'step' of displacement applied to the eye (e.g. 1·4 mm in 10 msec) resulted in average velocities of 800 deg/sec. This velocity lies between the maximum values reached in normal human and monkey saccades (Fuchs, 1967) and therefore probably causes no pain responses or visual afferents from an unphysiological bending of the optic nerve. There remained, however, the possibility that the cerebellar response was due to an activation of the muscles of mastication (particularly the pterygoids) which in the open cat orbit originate in the vicinity of the eye muscles (Fillenz, 1955). Therefore, these muscles were carefully removed in the subsequent cats.

In the second group, six cats were anaesthetized with a preliminary injection of Nembutal (30 mg/kg I.P.). This initial dose could be supplemented during the experiment through a femoral vein catheter either by additional Nembutal or by chloralose (usually 30 mg/kg). A tracheotomy was performed and a cannula inserted. The orbit was approached laterally through the removal of the anterior part of the temporal muscle. The masseter muscle and most of the mandible were then removed to reveal the deep attachment of the pterygoid muscles. Located just lateral to the medial pterygoid was the second branch of the Vth nerve which was sectioned before removing the underlying muscle. After this dissection, movement of the jaw caused no movement of the still intact sheath surrounding the orbital contents. Most of the bony orbit was then removed and the conjunctiva up to the muscle insertions was cut away. A nylon thread was tied to the insertion of each of the four rectus

muscles and often to the inferior oblique, and they were cut away from the globe. The rest of the orbital contents were carefully peeled off the globe but not cut away, and the freed eyeball was removed by sectioning the optic nerve.

The scalp over the cerebellum was cut in the mid-line and the brain was exposed by rongeuring away the overlying bone. As will be seen later, the area of short latency responses was located on the vermis approximately beneath the confluence of the sagittal and transverse venous sinuses. The left transverse sinus was cut and a large portion of it removed in order to reveal the left paramedian and lateral lobules. Bleeding was minimized by the prompt application of bone wax. The connexion between the sagittal and right transverse sinuses was left intact in most experiments. This technique was generally successful since although we noticed cyclical variations in cerebellar responses due to changes in levels of anaesthesia we did not observe a steady deterioration of the preparation. The reflected skin was then gathered up and sutured to a ring suspended above the cerebellum to form a pouch. Just before recording, the dura was removed and the cerebellar pouch was filled with mineral oil.

The entire exposed vermian cortex from the rostral part of lobule IX to the rostral folia of lobule V was explored. Because of the bony tentorium, the responses in lobule V were only pursued to the rostral limit of the short latency area (see Results). All of the exposed lateral lobules together with both paramedian lobules were also explored.

The remaining six cats were specifically used to investigate a possible projection to the nodulus. Under a light Nembutal anaesthesia which was maintained throughout the experiment, the cats were prepared either for whole eyeball or single muscle stimulation. The head was tilted to allow a vertical electrode pass to miss the sinuses, and hence only a small skull hole which never compromised the cerebellar circulation was ever necessary.

Stimulation and recording. One or more of the extraocular muscles were stretched approximately along their lines of action by an electronically controlled mechano-stimulator (Burchard, Kapp & Kornhuber, 1967). Briefly, the muscle is pulled by a plunger which is mounted on a loudspeaker coil. The plunger position is continuously monitored by a photocell and fed back to control the coil current. In this way, rapid, constant amplitude displacements (2 mm in 10 msec) free of auditory stimulation can be obtained. Before application of the rapid displacement, the muscles were prestretched approximately to their rest lengths. Except for the threads to the muscles, the stimulator and the cat were mechanically isolated.

Surface evoked potentials were recorded by conventional silver ball electrodes. Depth recordings were made by mechanically sharpened silver wire electrodes with an over-all diameter of 300 μ. The electrodes were advanced from the cortical surface in 2 mm steps and in 1 mm steps in the neighbourhood of the nodulus. The gross location of all electrode tracks were verified post-operatively on the 10 % Formalin-fixed brain. All signals were amplified by a Tektronix Type 2A61 differential amplifier and were led to a CAT 400B where at least ten and as many as sixty responses were summated.

RESULTS

Surface recordings

In both the first group of cats in which the whole eyeball was moved and the second group in which only the muscles were pulled, evoked potentials could be recorded from the cerebellum. Under light Nembutal anaesthesia, a short latency response (minimum 4 msec) was obtained from the vermian folia of Larsell's lobules Vb and c, VI and VIIA. Averages of sixty responses showed no significant difference in the response latencies

or amplitudes obtained from the anterior and posterior lobes or between lobules. A typical short latency response is seen in Fig. 1. The initial slow wave was always surface positive reaching amplitudes of 20–40 μV within 20–30 msec. The form of the surface negative second wave was variable. In this study, only the first 125 msec of the response were considered.
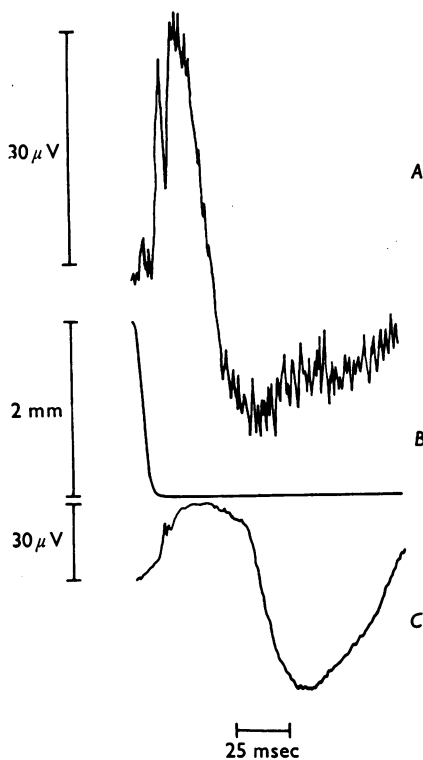

Fig. 1. Averaged short latency responses evoked from the cerebellar surface (lobule VII A) in response to stretching a single extraocular muscle. *A*: under light Nembutal anaesthesia, *B*: the stretch applied to the left lateral rectus muscle and *C*: under a combination of Nembutal and chloralose. Each trace is the average of ten responses.

When the cat's level of anaesthesia was very light, single unit spikes from Purkinje cells were superimposed on the slow wave. These occurred with such temporal regularity that they were easily identified even after the CAT averaging. The first spike in Fig. 1*A* occurs after a latency of 5 msec showing a very rapid activation of the Purkinje cells. A deeper level of anaesthesia silences the individual single unit activity and results in the smoothed curve of Fig. 1*C*. Here the latency to the slow wave response is clearly less than 5 msec.

Smaller (about 15 μV), short latency responses could also be recorded from lobule VII B under light Nembutal anaesthesia. Increasing the depth of barbiturate anaesthesia first abolished the responses in VII B and then simultaneously all the responses in V, VI and VII A. No responses were obtained from V a, VIII and IX and the paramedian or lateral lobules.
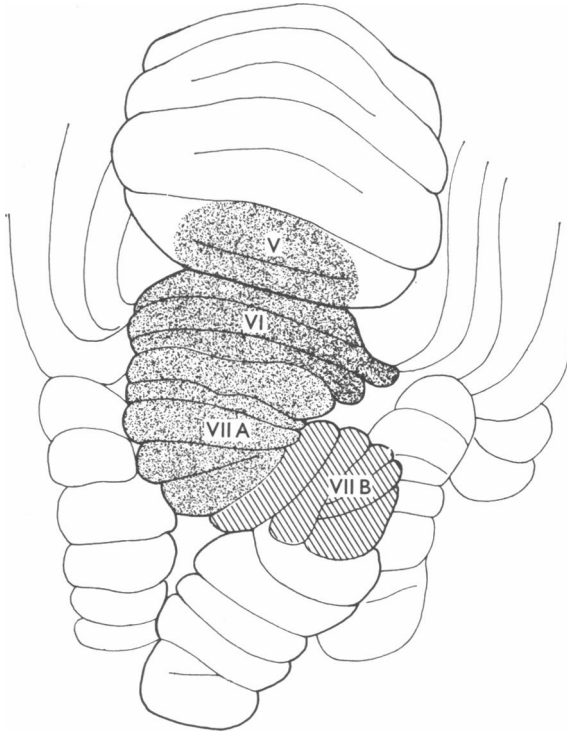

Fig. 2. Topographical distribution of evoked potentials elicited from the cerebellar surface upon stretch of the extraocular muscles. The dotted zone indicates the stronger, short latency projection area whereas the open shading (VII B) locates a weaker projection region from which smaller, more anaesthetic-sensitive responses are obtained.

Figure 2 summarizes the cerebellar regions from which evoked potentials are recorded upon natural stimulation of the extraocular muscles. The main short latency projection goes with apparently equal strength to lobules VI and VII A of the posterior lobe and folia V b and c of the anterior lobe. The projection to lobule VII B is weaker.

Further observations can best be itemized as follows:

1. Although the threshold varied with the level of anaesthesia, stretching a single muscle by as little as 0·4 mm could elicit a response.

2. Individual eye muscles did not have unique projection areas on the cerebellum. All projections were superimposed and displayed the same

characteristics shown in Fig. 2. All mechanical stimuli were suprathreshold and since all of the deep orbital connective tissue was intact some muscle interaction might have been possible. Therefore, the possibility of separate projections cannot be absolutely ruled out.

3. The simultaneous stretch of an antagonist (e.g. the lateral rectus) did not affect the response of its agonist (the medial rectus). Usually, the more muscles that were simultaneously stretched the more reliable but not the larger was the response.

4. Projections to the ipsilateral and contralateral vermian cortex were equal as judged by the amplitude of their evoked potentials.

Control experiments eliminated the possibility that the evoked potentials were the result of auditory, visual or exteroceptive tactile afferents. Finally, the cerebellar response due to pulling a single muscle disappeared upon cutting its nerve supply.

It should be mentioned that the level of anaesthesia was critical in obtaining good reliable evoked potentials. Best results were obtained when the cat was maintained under light Nembutal anaesthesia.

Depth recordings

No response was obtained from fourteen points that were post-operatively verified as having been located in the nodulus. The results of a typical depth track are shown in Fig. 3. Immediately upon penetration of the cortical surface, the positive potential reverses sign. This initial negative wave (occasionally one also sees other sign reversals or a null potential point) characterizes the response until the electrode enters the nodulus where the wave disappears (Fig. 3). Hence, under the same conditions that cause a short latency response in lobule VIIA, no evoked potentials are detected in the nodulus (lobule X). Evoked potentials were recorded from the hidden folia lying in the depths of lobules V, VI and VII indicating that the extraocular muscle projection is quite extensive.

If the electrode track is continued into the brain-stem below the nodulus, a very large (80 μV) short latency (3–4 msec) response is obtained. Therefore, not only the cerebellum but also the brain-stem receives a strong projection from the extraocular muscles.

DISCUSSION

From this study, it is clear that at least some of the eye muscle afferents reach both the anterior (Vb, c) and posterior (VI and VIIA) lobes of the cerebellum. Furthermore, the projection sites coincide, in part, with known oculomotor, visual and auditory projection areas in the cat and homologous afferent projections from cerebral areas 8 and 17 in the

monkey. In the decerebrate cat, Hampson *et al.* (1952) found conjugate ipsilateral eye movements when stimulating the tuber vermis and lobus simplex. When stimulating cervically transected cats, Cohen *et al.* (1965) found ipsilateral horizontal eye movements from the mid line vermis of lobule VII and mostly upward movements from the mid line of lobules VI and V. In chloralosan treated cats, Snider & Stowell (1944) described
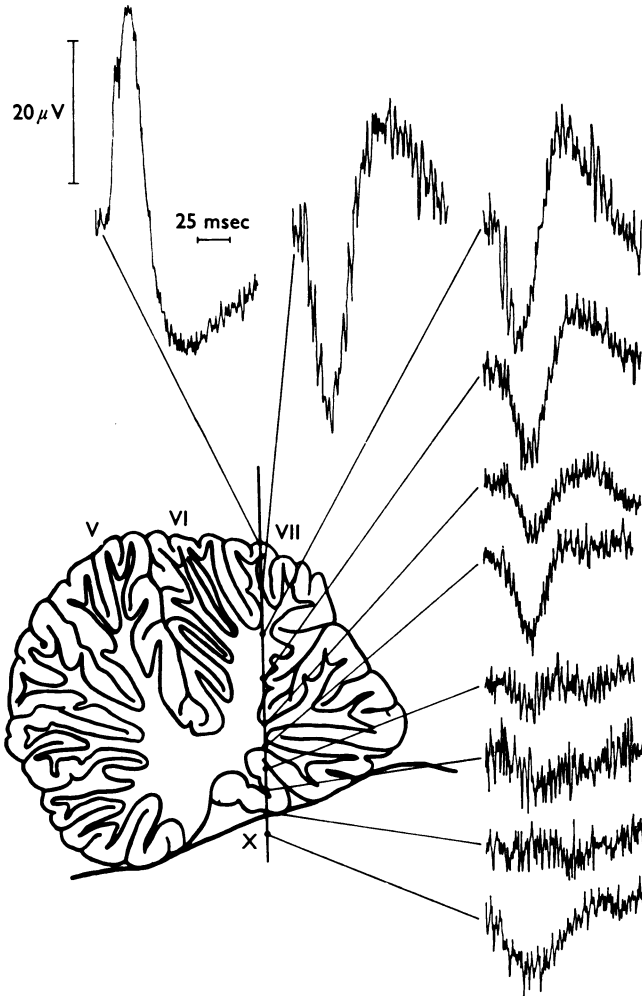

Fig. 3. Mid-sagittal section of the cerebellum showing the averaged evoked potentials elicited upon stretch of the extraocular muscles during a typical depth recording track. The sign of the surface potential reverses upon penetration of the cortex, but the potential is present throughout the entire depth of lobule VII. Note, however, the absence of any potential at the three points in the nodulus (X). Each trace is the average of ten responses.

two cerebellar areas, one corresponding to lobules Vc, VI and VIIA and the second to VIIB which were maximally sensitive to photic stimuli. These findings were confirmed on curarized unanaesthetized cats by Fadiga & Pupilli (1964). Both of the latter groups also found a cerebellar auditory response in the same general location as the visual projection. Finally, by stimulating the cerebral cortex of the anaesthetized monkey, Snider & Eldred (1952) found a projection from Areas 8 (the frontal eye field) and 17 to the folium vermis and the lobulus simplex-folium vermis complex respectively. Hence, we find the short latency extraocular muscle projection impinging on an area which already has all the inputs necessary to direct the eyes to visual or auditory targets. How the cerebellum co-ordinates these inputs and the role the cerebellum plays in regulating eye movements are not known.

Most of the experiments on the control of eye movements have been done on man. Robinson (1965) has shown that smooth pursuit movements are subserved by a continuous control system regulated by a visual feed-back loop. Saccades, on the other hand, have long been considered to be pre-programmed ballistic movements (Alpern, 1962), the trajectories of which are not visually influenced. The increase of visual threshold during a saccade (Latour, 1962) supports this view. Furthermore, the afferent transit time from the retina to the cerebellum (in the cat, Fadiga & Pupilli, 1964) or to the cerebral cortex (in man, Kooi & Bagchi, 1964) is about 30 msec. However, 30 msec is the duration of a 5 degree saccade (Robinson, 1964) making it temporally impossible for any visual regulation to occur. However, Vossius (1960) has suggested that saccadic trajectories could be regulated by a short latency proprioceptive feed-back loop from the extraocular muscles. Although muscle spindles do exist in human eye muscles (Cooper, Daniel & Whitteridge, 1955) various EMG studies seeking either a stretch reflex or other evidence of proprioception have yielded conflicting results.

The present investigation in conjunction with observations on patients with atrophy of the cerebellar cortex (Kornhuber, 1968) supports the hypothesis of a proprioceptive regulation of saccadic eye movements mediated by the cerebellum. Patients with cerebellar atrophy have normal smooth pursuit movements but exhibit two abnormalities in their saccadic responses. First, some saccades have a longer duration than normal with the eye approaching the target by a heavily overdamped trajectory. Secondly, such patients are unable to make a large saccade (say 40 deg) but instead execute a series of smaller saccades to reach their goal. If we assume that, as in the cat, proprioceptive information from the extra-ocular muscles reaches the cerebellum of man and further that such information helps control the saccadic trajectory, then lesions of the

cerebellum could result in the increased durations described by Kornhuber. However, the proprioceptive impulses apparently have functions other than simply controlling the saccadic trajectory as postulated by Vossius (1960). The second symptom described above may suggest that the cerebellum, probably with help from its proprioceptive input, helps to determine the magnitude or alternatively the end point of the saccade. When this control is eliminated in patients with cerebellar atrophy, the oculomotor system is reduced to using a series of 'exploratory' movements to realize its goal. Even the visual feed-back loop which is undoubtedly still intact in such cases is unable to improve the tracking performance.

Is the short latency cerebellar pathway fast enough to affect the saccadic eye movement? Vossius (1960) has postulated a model with an internal proprioceptive feed-back loop to account for the five types of human saccades he records. If the loop has a delay of 6–8 msec, the model can simulate by parametric changes all of the observed rapid eye movements. It is shown above that the minimum afferent transit time for extraocular proprioceptive impulses reaching the cerebellum is 4 msec. This figure agrees well with the 5–8 msec delay obtained by stretching the rat quadriceps femoris (Dow & Anderson, 1942). Cohen *et al.* (1965) have found a lateral rectus muscle potential with a latency of 5·5 msec upon stimulation of the cerebellar nuclei. Hence, the over-all delay from receptor back to extrafusal fibre would be less than 10 msec, a figure close to the values suggested by Vossius (1960). Furthermore, the duration of microsaccades as small as 2·25′ is no less than 20 msec (Zuber & Stark, 1965) so that at least the terminal portions of even such small movements could be influenced through a proprioceptive cerebellar feed-back loop.

Electrical stimulation of the cat nodulus inhibits vestibular nystagmus (Fernandez & Fredrickson, 1964). In spite of its effect on vestibularly induced eye movements, the nodulus appears to be lacking in eye muscle afferents. It is possible that such afferents are only directed to areas concerned with voluntary movements.

From our study, it is clear that the extraocular muscles are represented in lobule V of the anterior lobe. Cohen *et al.* (1965) obtained upward vertical eye movements from the culmen and Fadiga & Pupilli (1964) evoked visual potentials in the caudal—most folia of lobule V. Hence, the double cerebellar representation of Hampson *et al.* (1952) should be extended to include an extraocular muscle projection anterior and posterior to the primary fissure. In so far as our potentials obtained with natural stimulation can be compared with those of Eccles, Provini, Strata & Taborikova, (1968) obtained by electrical stimulation, the short latency of responses to stretch of the eye muscles suggests they are subserved by mossy fibre inputs.

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