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DISCHARGES OF INTRACEREBELLAR NUCLEAR CELLS IN MONKEYS

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SUMMARY

1. Conscious monkeys were trained with food rewards to perform movement tasks with the left forelimb and to accept manipulation of the joints and muscles and natural non-noxious stimulation of the skin of all four limbs.

2. Recordings were made from 217 cells situated in the left interpositus and dentate nuclei of the cerebellum. The identity of seventy-seven cells as cerebellar projection neurones was definitively established by activating them antidromically from the brachium conjunctivum near the contralateral red nucleus.

3. Modulation in the natural activity of 129 of these cerebellar nuclear cells (sixty in interpositus; sixty-nine in dentate) occurred in a reproducible manner in temporal association with a phase of the self-paced movement tasks performed by the animal using the ipsilateral arm and hand. The discharges during motor performance of forty-two dentate and forty-five interpositus cells were shown to be associated with movement about a particular joint or region of the forelimb whenever that movement occurred.

4. Cells whose discharges were related to proximal joint movements (shoulder, elbow) and cells related to distal joint movements (wrist, fingers) were encountered in both the dentate and interposed nuclei.

5. The cells were tonically active at rest. Most commonly, accelerations in the discharge were related to movement of a joint or the limb in one direction and a reduction or cessation of activity accompanied movement in the opposite direction.

6. For some cells, variation of the amount of discharge demonstrated during movement performance could be related to the range of the movement or its duration, more activity being characteristic of more prolonged movement performance through larger angles of joint displacement.

7. The dentate and interpositus cells whose discharges were most strongly and consistently related to movements of the forelimb were concentrated in the mid region and caudal half of either nucleus.

8. None of seventy-three dentate neurones examined showed appreciable responses to stimulation of the skin or manipulation of joints and muscles of the fore- or hind limbs and only two cells responded to unexpected perturbation of movement performance.

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9. No influence resulting from peripheral afferent input from the ipsilateral forelimb was detected in any interpositus cell whose firing was unchanged during ipsilateral arm movements.

10. Of the sixty interpositus cells whose discharge rates changed during motor performance, twenty-eight were demonstrated to be in receipt of input from receptors in the ipsilateral hand or arm, which could be activated by brisk tapping of the skin and sometimes by gentle squeezing of the forearm.

11. In the passive relaxed animal, manipulation of joints was ineffective in modifying the discharges of most interpositus neurones and, in all cases, prolonged pressure upon the skin elicited only transient responses. Imposed brief perturbation of movement performance introduced unexpectedly during execution of a movement task provoked changes in the discharge of only five interpositus cells in relation to the task.

12. The possibility is discussed that the firing of interpositus cells in relation to learned, stereotyped movement performance is regulated primarily by signals issuing from the sensorimotor cortex.

INTRODUCTION

Clinical observations and the results of numerous ablation and stimulation studies in experimental animals clearly indicate that paravermal and lateral regions of the cerebellum are heavily implicated in the control of voluntary limb movements (see Holmes, 1939; Chambers & Sprague, 1955*a*, *b*; Dow & Moruzzi, 1958; Brooks, 1975).

The paravermal region (paravermal or 'intermediate' cortex and nucleus interpositus) receives major afferent inputs from the sensorimotor cortex and from spinocerebellar pathways (for references, see Oscarsson, 1973; Allen, Gilbert, Marini, Schultz & Yin, 1977). Nucleus interpositus provides the efferent outflow of this cerebellar region which projects mainly to rubrospinal cells and (via ventral thalamus) to pyramidal cells of the motor cortex. Thach (1968) recorded the activities of individual interpositus neurones during motor performance in conscious monkeys. He detected neurones whose discharge rates underwent brisk, phasic changes in relation to self-paced, alternating ballistic wrist or shoulder movements of the ipsilateral limb. When ballistic wrist movement was initiated in response to a light signal, Thach (1970) also detected a correlation between interpositus discharge and the onset of movement. About one half of cells studied changed frequency about 10–70 ms before movement onset, while the remainder discharged only after movement occurred. Cells of this latter kind could have responded to changes in peripheral afferent input from the forelimb and they might be involved in correcting movement already initiated by the motor cortex (see Eccles, 1967, 1973).

The lateral cerebellum (hemispheral cortex and dentate nucleus) receives its major afferent inputs from association areas of cerebral cortex with lesser but significant input from sensorimotor cortex (Evarts & Thach, 1969; Allen, Gilbert & Yin, 1978). The outflow of the lateral cerebellum is provided through the dentate nucleus which projects heavily to the motor cortex after relaying in ventral thalamus. Thach (1968, 1970) showed that firing of dentate neurones accelerated or decelerated in relation to brief alternating wrist or shoulder movements in a manner similar to

that of interpositus neurones, but that the discharge of the majority of dentate neurones preceded movement onset by as much as 50–100 ms. However, Thach (1975) was unable to establish definitely whether discharge of dentate cells preceded or followed that of cells in the motor cortex because the timing of the discharges of two populations of neurones sampled from these sites overlapped considerably in relation to execution of the same movement task. Grimm & Rushmer (1974) recorded the responses of dentate neurones to performance of a complex, sequential movement task in which the animal used its ipsilateral forelimb to reach and touch a series of three buttons. Some neurones discharged high-frequency bursts in relation only to a specific phase of the movement task.

In the work to be reported here we have recorded the activities of both dentate and interpositus neurones in conscious monkeys trained with food rewards to perform a lever pulling task with their ipsilateral forelimb. They were also trained to allow manipulation of the forelimb by the experimenter. Our main aim has been to describe the firing of these neurones in relation to a complex but natural stereotyped movement and to seek evidence for influences resulting from peripheral afferent input by applying brief disturbances to the motor performance and by applying natural stimuli to receptors in the forelimb. As well as using their forelimb to execute a specific learned motor task the animals were also encouraged, with food rewards, to make a variety of other movements with the limb (such as reaching for a piece of food presented in a particular place) so that cellular activity associated with different degrees, durations and combinations of joint movements could be assessed.

In previous studies in awake monkeys, intracerebellar nuclear neurones have been identified solely on histological grounds but it is now known that the nuclei contain interneurones as well as neurones projecting outside the cerebellum (Chan-Palay, 1977). We have therefore routinely tested cells for the presence of an antidromic impulse following stimulation of the brachium conjunctivum in the region of the contralateral red nucleus. On this basis, a substantial proportion of our recordings were shown to be from nuclear cells projecting axons into the midbrain and possibly beyond.

METHODS

The discharges of single intracerebellar nuclear neurones were recorded in seven awake monkeys (*Macaca fascicularis*) trained with food rewards to perform simple stereotyped motor tasks with the left forelimb. Five of the animals were also employed to obtain recordings of cerebellar Purkinje cell discharges during voluntary movement performance and a full account of the methods relevant to the present study can be found in a report on the Purkinje cell responses (Harvey, Porter & Rawson, 1977).

Six animals were trained to pull a horizontally mounted lever forwards about 1·5 cm into a narrow target zone against a ramp force of 1·0–4·5 N. Entry of the lever into the target zone was signalled by a 600 Hz tone and the animal then released the lever to use its left forelimb to collect a small piece of food (a cube of apple, carrot, a currant, etc.) presented by the experimenter for the completion of a successful pull. The animal placed the food reward in its mouth and then lowered and extended its arm to grasp and pull the lever again. Each full movement sequence was completed in about 2 s (see Harvey *et al.* (1977) for details of movement analysis). The position in which the food reward was presented to the animal after each lever pull could be varied, allowing different degrees of shoulder, forearm, wrist and finger movements to be

studied, Brief perturbations of movement performance could be introduced by applying a sudden current step to the solenoid against which the monkey pulled.

The seventh animal was trained to flex its finger against a rigid lever and maintain an almost isometric contraction of 3·5–4·0 N (Porter & Rack, 1976). Perturbation of motor performance was accomplished by suddenly releasing the lever which caused the fingers to flex unexpectedly against little resistance through a distance of 1 cm. No perturbations were introduced to either lever during the training period prior to implantation of a recording headpiece, so the animals were not trained to anticipate the perturbation and to respond to it in any particular manner.

Stereotyped performance of the motor tasks was normally accomplished after a period of 3–6 weeks of daily training and during this time the animal was encouraged with food rewards to also remain passive and relaxed while accepting non-noxious stimulation of receptors of the limbs and body surface by the experimenter (see Harvey *et al.* 1977, for details). As well as studying different degrees of movement about forelimb joints by requiring the animal to reach with its limb to different positions to obtain a food reward after lever pull, an attempt was made to study more restricted movements of the limb to establish whether impulse activity of dentate and interpositus neurones covaried with movement about a particular joint. This was done by applying gentle manual restraint to immobilize a joint or joints and encouraging the animal to use the remaining free joints of its forelimb to obtain a piece of food moved in an arc just out of the animal's reach. Beginning proximally with the shoulder joint (restraining the upper arm) and progressing distally to immobilize also the elbow joint and then also the wrist joint, it was possible to study movements limited to progressively more distal joints, and hence to attempt to ascertain whether a discharge modulation disappeared upon immobilization of a particular joint. All animals rapidly became accustomed to these procedures during training sessions and usually made no palpable effort to move the joints restrained by the experimenter.

When the animal was fully trained, a specially designed headpiece was fixed to the skull of the monkey with the cylinder, through which micro-electrodes could be advanced into the brain, situated over a craniotomy 16 mm in diameter overlying the left cerebellar hemisphere (centre of craniotomy 5 mm from mid line and 8 mm posterior to the interaural line). This procedure was carried out at an aseptic operation under thiopentone anaesthesia. At the same operation, pairs of flexible stainless-steel wires were sutured into the bellies of representative muscles used during the task, and in one animal a cuff stimulating electrode was implanted around the left median nerve at the wrist. Electrode leads were brought subcutaneously to the scalp. A concentric stimulating electrode (outer diameter 0·5 mm) was implanted under stereotaxic guidance into the brachium conjunctivum at the level of the right red nucleus to allow for electrical stimulation of ascending axons of dentate and interpositus neurones. All electrode leads were connected into a multipin receptacle firmly cemented to the headpiece and the animal was allowed to recover from the operation.

On the day following operation the animal was retrained on the lever and on each day thereafter for 4–6 weeks, in once- or twice-daily sessions lasting from 1 to 3 h, extracellular recordings were made with glass-coated tungsten micro-electrodes (10–25 μm of tip exposed) of the activity of single dentate and interpositus neurones accompanying many repetitions of the motor task. Magnetic-tape recordings were made of this activity along with simultaneous registrations of signals of lever displacement and e.m.g. activity. The lever displacement signal was used to determine an 'analysis period time' during which peri-response time histograms (centred around the onset of lever displacement, the perturbation of the lever, or the release of the lever) of neuronal discharges were generated on-line by a PDP/11 computer. Analysis of the relationship between dentate and interpositus nuclei activity and movement employed these histograms and also photographic and fibre optic records of data displayed on an oscilloscope at the time of the experiment or replayed from magnetic tape at a later time. Peristimulus time histograms of neuronal discharges in response to peripheral stimuli (a tap to the hand, shock to median nerve, etc.) were also compiled during the experiment with the aid of the computer.

Stimulation of the brachium conjunctivum was with constant current pulses, 0·2 ms in duration and not exceeding 2 mA in amplitude. The median nerve was stimulated at 2 s intervals with single 0·2 ms duration pulses whose intensity was sufficient to produce a just visible twitch of the thumb. Neither the nerve stimulation nor the intracranial stimulation caused the animals any apparent discomfort.

Upon completion of the periods of recording, the animal was again anaesthetized and marker electrodes coated with Indian ink were inserted through the headpiece into the cerebellum at the same angle as the recording electrodes to delimit the area penetrated by the micro-electrodes during recording sessions. Several marker tracks were also made a few millimetres rostral to all recording tracks. These were used as an aid in aligning the cerebellum for sectioning in the plane of micro-electrode penetration. The animal was perfused with fixative and the head then mounted in a stereotaxic frame. The headpiece and underlying skull were removed and the brain transected under stereotaxic guidance at the level of insertion of the brachium conjunctivum stimulating electrode. The position previously occupied by the electrode tip in the mid-brain could then be examined by visual inspection of the electrode track in the bisected brain. In all cases, the electrode tip was confirmed to have been within or near to the caudal part of the red nucelus. Serial frozen coronal sections of the cerebellum were cut at 50 μm intervals. Each fourth section was collected and stained with cresyl violet to visualize the electrode tracks so that the locations of cells whose activities had been studied could be defined.

RESULTS

Location and identification of neurones

The interposed and dentate nuclei were localized during the recording sessions by their depth below the cerebellar surface and their distance from the cerebellar mid line. The final determination of the site from which a given set of recordings had been obtained was, however, made after detailed study of the histological sections at the end of the experiment. Recordings from neurones allocated to interpositus and dentate nuclei were collected between 2·0 and 6·0 mm from the mid line, and from 5·0 to 10·0 mm below the surface of the cerebellum. Entry of the recording electrode into the cerebellum (after passing through 14–18 mm of occipital lobe tissue) was signalled by an electrical transient attributable to penetration of the tentorial membrane and a subsequent sharp increase in background neuronal activity. The characteristic complex and simple spike activity of individual Purkinje cells could usually be isolated within a short distance (about 0·25 mm) of further micro-electrode travel after entry into the cerebellum, thus confirming penetration of the cerebellum. Because of the long distance of micro-electrode travel needed to reach the intracerebellar nuclei and the possibility of electrode deflexion at the tentorial membrane, an attempt was made to check for gross deviations in direction of intended travel of the electrode by assessing its location in relation to the position of surface penetration of the cerebellum. The recording headpiece used in these animals was aligned so that electrodes penetrated the brain at an angle close to that of the stereotaxic vertical axis. This meant that to reach the dentate and interpositus nuclei, the recording electrodes had to pass directly through areas of paravermal cerebellar cortex (lobules IV, V and VI) which receive a somatotopically organized tactile input from the periphery. This input is arranged rostrocaudally so that afferent signals from the hind limb are directed most rostrally into the folia of lobule IV and signals from the face most caudally into lobule VI (Adrian, 1943). In the present animals, natural stimulation of tactile receptors was routinely performed as the cerebellar cortical layers were encountered (see Harvey *et al.* (1977) for details) so that the presence of a response from either hind limb, forelimb or face provided a useful guide to electrode location upon cerebellar penetration.

A study was made of the activities of 217 intracerebellar nuclear neurones of which

118 were assigned to the dentate and ninety-nine to the interpositus nucleus on the basis of histological inspection of the recording and marker tracks in serial sections cut through the whole region. The identity of seventy-seven neurones (thirty-six in the interpositus and forty-one in the dentate) as cerebellar projection cells was definitively established by the demonstration of antidromic responses following delivery

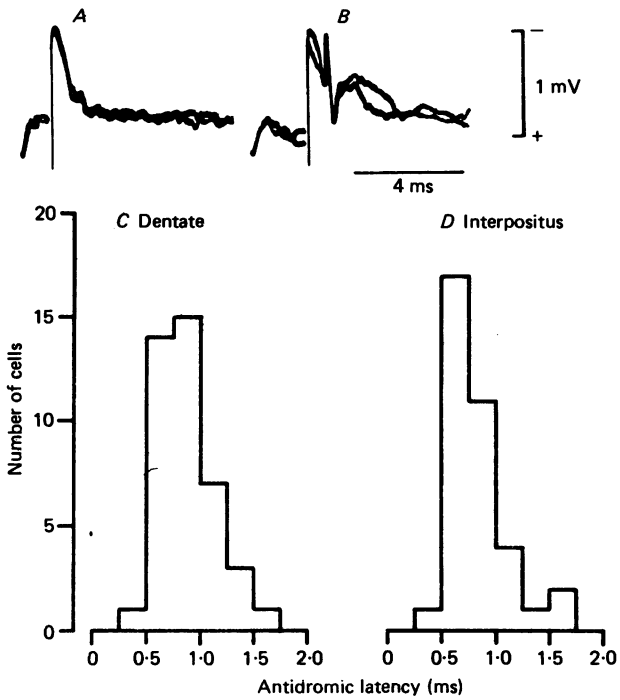

Fig. 1. Antidromic responses of intracerebellar nuclear cells to stimulation of the contralateral brachium conjunctivum. Trace *A* shows, in superimposed records, the occlusion of an antidromic spike in a dentate neurone by a spontaneous action potential (positive phase of the spontaneous spike is at beginning of the trace). The spike discriminator pulse obtained from this spontaneous action potential was used to trigger an antidromic stimulus after a delay of 1 ms and no antidromic response occurred. In *B*, a spontaneous spike triggered an antidromic stimulus after a delay of 2 ms in each of the superimposed records, and in this case there was no occlusion of the antidromic response which had a latency of 0·7 ms. Two superimposed sweeps are recorded in both cases. Twice threshold stimuli were used in all cases. *C* and *D*, latencies in ms of antidromic spikes of interpositus and dentate cells respectively. Measurements used in constructing these histograms were obtained from responses to just suprathreshold stimuli.

of stimuli to the brachium conjunctivum. In these cells, a single shock to the midbrain evoked a single impulse at short fixed latency. The latencies ranged from 0·4 to 1·7 ms and the majority of values lay between 0·5 and 1·0 ms as can be seen from the histograms of Fig. 1. The neurones were able to respond to each of two or three stimuli delivered at frequencies of 600–800/s and the antidromic nature of the response could be confirmed (in all of sixteen cells tested) by the demonstration of occlusive interaction of the antidromic spikes with spontaneously generated action

potentials. The occlusion followed a time course indicative of impulse collision in the axon and a representative example is shown in Fig. 1. The conduction velocity of the efferent axons was calculated to range from about 11 to 45 m/s by assuming an approximate conduction distance of 18 mm between recording and stimulating sites.

The antidromic spikes displayed no obvious *A–B* inflexions which would signify that the recordings arose from cell bodies, but these (and other) unitary potentials recorded within the intracerebellar nuclei were presumed to arise from cell bodies because the spikes were usually monophasic negative, or biphasic in wave form and discharges of individual units could be recorded over quite long distances (50–150 μm) of micro-electrode travel. Moreover, the potentials could be recorded in isolation for quite long periods of time (up to 2 h) and the neurones would display prolonged injury discharge in response to pressure by the micro-electrode. These properties contrasted with those of potentials which could be isolated from fibres in white matter above the nuclei. Their discharges were usually monophasic, positive in wave form and had very small micro-electrode 'seeing' distances. They also were difficult to record for any length of time and disappeared abruptly without obvious injury discharge upon slight advancement of the micro-electrode. Therefore, it is unlikely that the presumed antidromic spikes might have arisen from fibres belonging to an afferent projection from the mid-brain to the cerebellum.

An attempt was made in all animals to identify intracerebellar nuclear neurones as cerebellar projection cells by the demonstration of antidromic responses to electrical stimuli delivered to their axons at an extracerebellar site. In the first two animals it was hoped to identify cells projecting in particular to the ventrolateral division of the contralateral thalamus. This proved to be unsatisfactory in our hands, as a site for which to aim electrodes solely by stereotaxy. In these monkeys the stereotaxic location was found to vary by up to 2 mm from animal to animal. The electrode failed to reach the target site in one animal and in the other, the tip was located too far rostrally to evoke responses (other than in one neurone) with reasonable intensities of stimulation (up to 1 mA). More reliable results were obtained by aiming electrodes for the brachium conjunctivum at the level of the caudal pole of the contralateral red nucleus, presumably because of the high concentration of axons of intracerebellar nuclear neurones in this region. Of course stimuli delivered here activate axons terminating in the mid-brain as well as those *en route* for the thalamus. Nevertheless, the presence of an antidromic response evoked from this site allowed the conclusion to be drawn that the neurone sent a projection that ascended rostrally as far as the mid-brain and was not therefore a cerebellar nuclear interneurone with a locally ramifying axon.

Natural activity of dentate and interpositus neurones

Background activity. Both nuclei were characterized by ongoing neural activity that was evident even when the animal was sitting with its limbs stationary. Although not studied in detail (discharge rate was estimated from storage oscilloscope displays of spike trains), the tonic discharge of individual neurones was seen to range from about 10 to 100 impulses/s with the majority of neurones firing impulses in a fairly irregular manner over a range from 30 to 50/s. Most cells selected for study were picked out on the basis of their ongoing activity but, in a number of tracks, cells were isolated solely by their antidromic response to stimuli delivered to the brachium conjunctivum. Only three cells out of twenty isolated in this manner displayed no natural spike activity (over 1–3 min periods of study) indicating that only a small percentage of projection neurones are inactive in the awake non-moving animal and could therefore be missed by a recording electrode.

Movement related activity. Of 174 cells studied during performance of the stereotyped lever pulling task, the ongoing activity of 129 was modulated in a consistent manner in relation to one or more phases of the movement sequence. Relationship

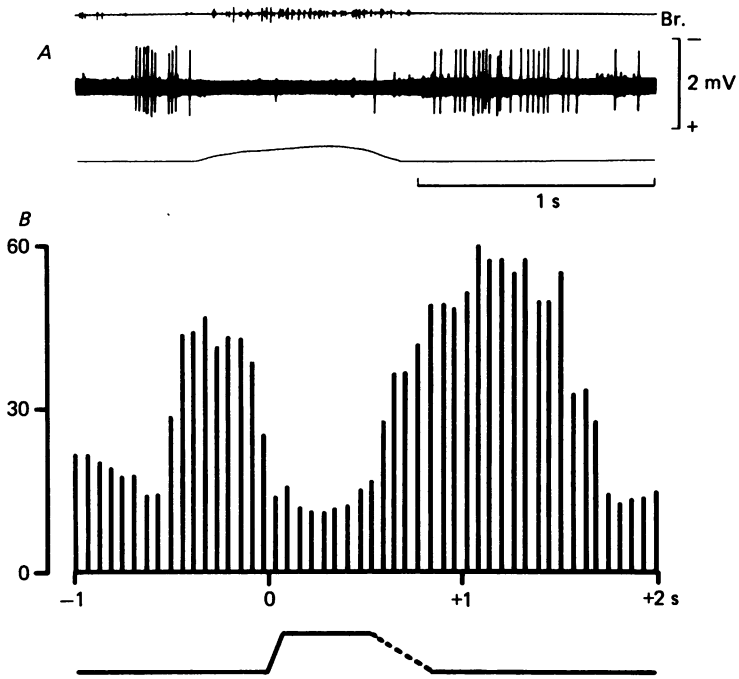

Fig. 2. Discharges of an identified interpositus projection cell during motor performance. *A* shows representative spike activity associated with the occurrence of a single lever pulling performance. The top trace illustrates the e.m.g. activity of the brachialis muscle (Br.), which is active during the pull or flexion phase of the motor task. Upward deflexion of the lowermost trace in this panel indicates the lever displacement. *B*, peri-response time histogram of the discharges of the same interpositus cell in relation to twenty repetitions of the lever pulling movement. Upward deflexion of the trace underneath the histogram indicates the average time of lever displacement during the movement repetitions. By studying a variety of other movements which were limited in action to particular forelimb joints (see text) it was possible to show that the discharges during motor performance of this cell occurred in association with extension of the upper arm. After each lever pull indicated above, the animal fully extended its arm to obtain a food reward presented at arm's length in front of its body and the duration of upper arm extension in this movement lasted about one second. It can be seen that an increased extent and duration of the movement with which the cell's discharge was characteristically related was accompanied by an increased amount of activity by the cell. Ordinate: number of action potentials in each time period. Abscissa: time in seconds.

between movement and impulse activity for these neurones was first assessed in a peri-response time histogram constructed for ten or more trials in which discharges were averaged in time bins around the onset of lever movement. An example is shown in Fig. 2 of the activity of an interpositus projection neurone during twenty repetitions of the task. The discharges of this cell increased markedly just before lever displacement when the animal extended its arm to grasp the lever; impulse activity subsided during the period when the animal grasped and pulled the lever. Discharge rate then increased again as the animal released the lever and extended its arm to collect a food reward positioned just beyond the lever. Shown above the

peri-response time histogram is a representative sample of spike activity occurring about a single performance of the lever pull task, which illustrates that the modulation revealed in the peri-response time histogram could clearly be observed in a single movement sequence.

When a consistent relationship between movement and neural activity was ascertained in a peri-response time histogram, an attempt was made to establish with which aspect of forelimb movement the cell's discharge was characteristically or best related. This was done by encouraging the animal to make a particular movement to obtain a food reward together with manual restraint of particular joints (see Methods). But it was necessary to exclude the possibility that discharge modulation was not related to movements of the other limbs or the eyes which might occur synchronously with particular movements of the ipsilateral forelimb. For example, rather than being related to actual forelimb movements, the periods of increased discharge of the cell in Fig. 2 might be associated with direction of gaze to lever and to food or with slight movements of the legs occurring in tempo with forearm extension. Variations in neuronal activity with eye movements were assessed by persuading the animal to track with its eyes, a morsel of food moved across, and up and down, or to a particular point in its visual field. Discharges associated with leg movement could be assessed by manually moving a hind limb away from its customary resting position and then allowing the animal to make a postural readjustment of the limb. Eight movement-related neurones were excluded from further study because it was suspected that their discharges were related to movements of the eyes or the ipsilateral hind limb. Four other neurones (all located in the dentate) displayed modulation in discharge with movements of either forelimb but no effort was made to study in detail activity related with the contralateral limb. These neurones were not excluded from the sample, though care was taken to ensure that the contralateral arm remained stationary when movements of the ipsilateral limb were studied.

For fifty neurones the changes in firing rate displayed during performance of the motor sequence could be shown to occur in association with movement in a particular direction about a particular joint. Details of the movement relationship of these neurones are presented in the first four rows of Table 1. In the case of the cells whose discharges were observed to covary with finger flexion or extension it should be noted that the movements studied involved extension or flexion of all the fingers together (such as closing the fingers into the palm to attempt to trap a small piece of food) and often the thumb also moved in concert with the fingers. Whether or not dentate or interpositus neurone activity is related to movements of a single digit or movement about particular interphalangeal joints was not ascertained.

For neurones in each of the categories of movement listed in these rows, the discharge could increase when the joint moved in one direction (e.g. wrist extension) and decrease with movement in the opposite direction (wrist flexion). This reciprocal type of behaviour was observed in about a half of the cells whose discharges could be shown to be characteristically related to a particular movement. In most of the remainder, the modulation consisted of an increase in discharge in association with movement in one direction (in three cases the modulation consisted simply of a decrease in discharge). Two interpositus neurones were unusual in that they fell silent when the animal's limb came to rest: they discharged only when the wrist was actively extended.

For the interpositus and dentate neurones whose discharges were related to a particular movement, it should be noted that the change in discharge occurred whenever the animal made that particular movement regardless of the position of the forelimb or the intent of the movement. Thus, if a neurone increased its discharge

in association with wrist extension when reaching for the lever, increase in discharge of the neurone would also occur if the wrist were extended for food presented in positions requiring the animal to reach up, down, across, or whenever the wrist was extended during more casual natural movements.

For some of these neurones, amount of discharge and duration of modulation was shown to covary with range and duration of movement. This could be demonstrated by varying the range and duration of the extensor movement the animal had to make to obtain its food reward or by correlating discharge modulation with the duration of lever pull (for cells related to flexion movements; see Harvey *et al.* 1977). The example shown in Fig. 2 is of a neurone whose discharges increased in association with upper-arm extension. A small peak in activity which coincides with a small amount of upper-arm extension necessary to reach the lever is evident just prior to lever movement in the peri-response time histogram of this neurone. Upon lever release, food was presented for the twenty trials in a position that required the animal to fully extend its upper arm (to bring it level with shoulder height) and this increased range and duration of movement was associated with an increased amount of activity of the cell.

TABLE 1.

Movement relationship	Number of neurones	
	Interpositus	Dentate
Upper arm flexion/extension	7	4
Elbow flexion/extension	9	5
Wrist flexion/extension	7	8
Finger flexion/extension	4	6
Proximal (forearm/upper arm/shoulder)	14	6
Distal (wrist/fingers)	4	13
Unclassified	15	27

Covariation of cellular activity with amount of movement was observed in seventeen out of twenty-two interpositus neurones tested but in only seven out of sixteen dentate neurones. While the activity of the other fourteen neurones appeared clearly to change whenever the animal made a particular movement, no appreciable variation in activity with different amount of movement was evident. This behaviour is exemplified by the three dentate projection cells illustrated in Fig. 3. Each of these cells discharged when the animal extended its wrist and a brief peak in activity associated with a brief phase of wrist extension can be seen to begin in each peri-response time histogram just before lever displacement. However, much the same amount and pattern of discharge occurred with wrist extension upon lever release even though the animal kept its wrist extended for at least one second while reaching towards a withheld food reward.

Attempts to relate neuronal discharge to a particular phase of movement met with only partial success in thirty-seven cases in which activity could be reliably related only to distal (wrist/digits) or to proximal (forearm/upper arm) movement. The results for these neurones are listed in rows 5 and 6 of Table 1.

For the remaining forty-two neurones studied in relation to the lever pulling task, we were unable to relate their changes in discharge to movement about any particular region of the limb even though some of the cells were studied for substantial periods of time. This may have been because the activities were associated with movements not tested (e.g. trunk movements) or it may be characteristic of some cells that they discharge in relation to movements involving a particular combination of joints.

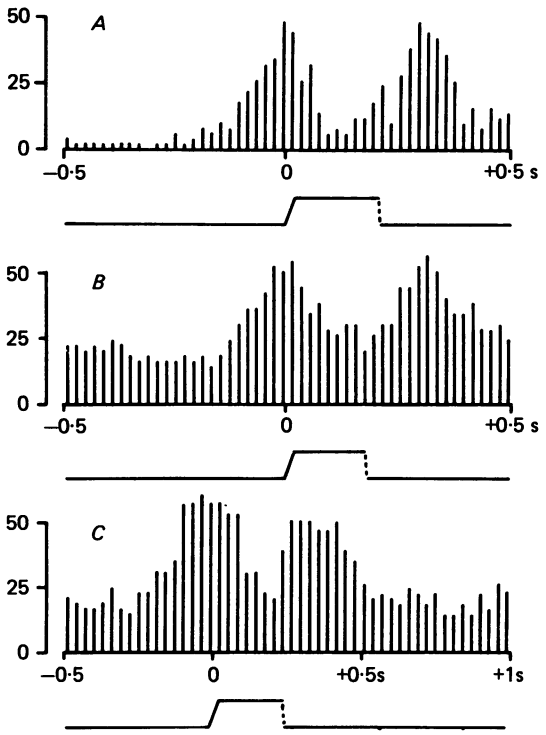

Fig. 3. Peri-response time histograms of the discharges during movement performance of three dentate projection cells which were isolated within a distance of 500 μm during a penetration through the caudal half of the dentate nucleus. There are differences in the background activity of the cells, but each behaved similarly in relation to movement. These cells discharged whenever the animal extended its wrist and a period of increased activity for each cell is associated with a brief phase of wrist extension before displacement of the lever. In order for the animal to obtain a food reward after return of the lever to its rest position, it had to extend fully its wrist and keep it extended for at least 1 s. The increased extent and duration of the extension movement occurring after lever displacement was not associated with a prolongation of discharge in relation to the movement in any of these cells. Each histogram was compiled from the events associated with twenty trials. Note extended time scale in *C*.

Topographic arrangement of neurones

Although systematic tracking through the nuclei with uniform sampling of cellular activity was not feasible in the present experiments, several aspects of spatial organization of responsive neurones were noted with enough regularity to merit description. Cells related to forelimb movement were most frequently en-

countered in penetrations directed into the middle and posterior parts of the dentate and interpositus nuclei. The locations of penetrations projected on to diagrams of horizontal sections of the nuclei of two representative animals are shown in Fig. 4. The filled circles denote penetrations in which there were neurones related to forelimb movement, and tracks in which cells displayed no apparent consistent relationship with forelimb movement are indicated by the open circles. Forelimb related neurones were frequently encountered in about the dorsal half of the interpositus, whereas in the tracks indicated in the dentate such neurones were not often detected in the dorsal mm or so of the nucleus.

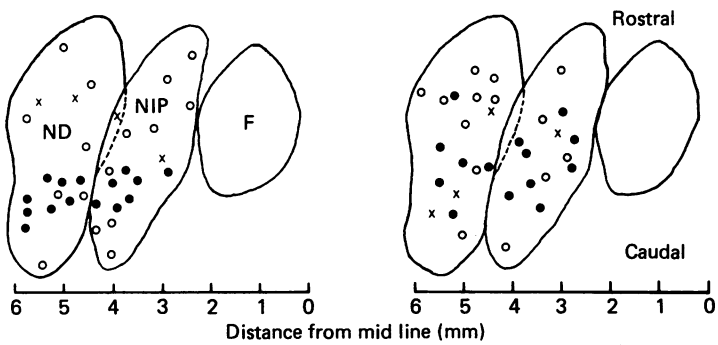

Fig. 4. Diagram of the location of penetrations into horizontal sections of the intracerebellar nuclei in two monkeys. ●, electrode tracks in which cells whose activities were consistently related to forelimb movement were located. ○, electrode tracks in which cellular activity displayed no apparent consistent relationship with arm movements. The crosses denote electrode tracks in which no successful recordings were made. (F = fastigial nucleus; ND = dentate nucleus; NIP = interpositus nucleus.)

We failed to encounter nuclear cells related to forelimb movement at any depth in penetrations made through the most rostral and most caudal poles of either interpositus or dentate. Within those regions of the former in which neurones related to limb movement were collected, there was a slight tendency for the upper limb to be represented more towards the middle parts of the nucleus with progressively more distal joints represented progressively more caudally. However, different cells related to proximal upper limb or to distal limb movements were sometimes encountered in the same penetration, indicating that there is not a strict rostrocaudal somatotopic organization within this structure. A general tendency was noted in both nuclei for neurones with similar properties to be grouped together and often three or four neurones each with a similar relationship to movement would be picked out over 500–700 μm or so of micro-electrode travel. Nearby neurones also behaved similarly as judged from samples of multi unit activity. Three dentate neurones each related to wrist extension serve to illustrate this point. Potentials from these cells were isolated within a distance of 500 μm (approximately in the mid depth of the nucleus) and cells encountered directly above and below this region were not apparently arm-movement related (Fig. 3).

Responses of dentate and interpositus neurones to peripheral afferent inputs

Influences resulting from natural stimulation of peripheral receptors were investigated in seventy-three dentate and eighty-seven interpositus neurones. As a whole, the dentate neurones were unresponsive to the procedures employed here (palpation of muscles, movement of joints and tactile stimuli). Emphasis was placed on stimulating receptors in the ipsilateral forelimb but often tactile stimuli were delivered to

all limbs and to much of the remainder of the body surface. Variations in discharge in apparent synchrony with joint movement were occasionally seen in individual trials for some cells. However, the summation of discharges over ten or so trials (in a peri-stimulus time histogram) of joint movement over periods when the animal appeared to be fully relaxed, failed to demonstrate significant modulation, indicating that little if any spinocerebellar input generated by this manoeuvre is directed to the dentate neurones. In one animal a stimulating cuff electrode was implanted around the ipsilateral median nerve at the wrist, and a feeble, poorly defined response was observed in two neurones following nerve stimulation at an intensity sufficient to produce a just visible twitch of the thumb.

In contrast to the scarcity of responses of the dentate neurones to peripheral input, influences from receptors in the ipsilateral forelimb were detected in about one third (twenty-eight) of interpositus cells tested. Weak activation of these neurones could be heard in response to taps of the palm or brisk flicks of the fingers, and in fewer cases there was a response also to squeezing the forearm. In most of the responsive neurones, stimulation of the ipsilateral forelimb only was effective but in four cases a weak response was also detectable when receptors in the contralateral forelimb were stimulated. For twelve of the most clearly responsive interpositus neurones estimates of the latency of response were obtained in peri-stimulus time histograms compiled by tapping the hand (or arm) with a probe capable of producing a computer trigger-signal upon contact with the skin. Latencies for activation ranged from 12 to 50 ms or even longer, but most spikes occurred within 25–40 ms after stimulation. In some neurones the pattern of response revealed in the histogram consisted simply of a transient facilitation, but more complex responses consisting of one or two sequential phases of facilitation and depression were observed in other cells. A histogram of one cell responding with two such phases is illustrated in Fig. 5*A*. Although some evoked responses were quite prolonged, as in this example, they were invariably of a rather weak nature. The magnitudes of the peaks in activity (amounting to about 1 spike or so per stimulus) evoked in the neurone illustrated are typical of those generally evoked in forelimb related interpositus neurones by phasic changes in peripheral input. In one animal the effect upon activity of such neurones of weak electrical stimulation of the median nerve was routinely tested. The results of nerve stimulation confirmed the pattern and strength of response observed in relation to natural stimulation of peripheral receptors in the limb and also revealed the presence in two neurones of weak inhibitory responses (latency about 20–25 ms and similar in magnitude to the depressions shown by the cell indicated in Fig. 5*A*) which had been overlooked in the assessment of response to natural stimulation. As peri-stimulus time histograms were not compiled for every neurone tested, weak responses in other neurones might have been overlooked, so it is likely that the proportion of interpositus neurones considered to be in receipt of peripheral afferent input is an underestimate

All the interpositus neurones with a demonstrable input from the ipsilateral forelimb displayed modulation in discharge during volitional movement of that forelimb which suggested that sensory feedback from the limb might drive the discharges of these neurones during movement. However, prolonged changes in discharge were not evident in response to maintained tactile stimuli (squeezing the hand or maintained pressure upon the skin with a probe); only transient responses

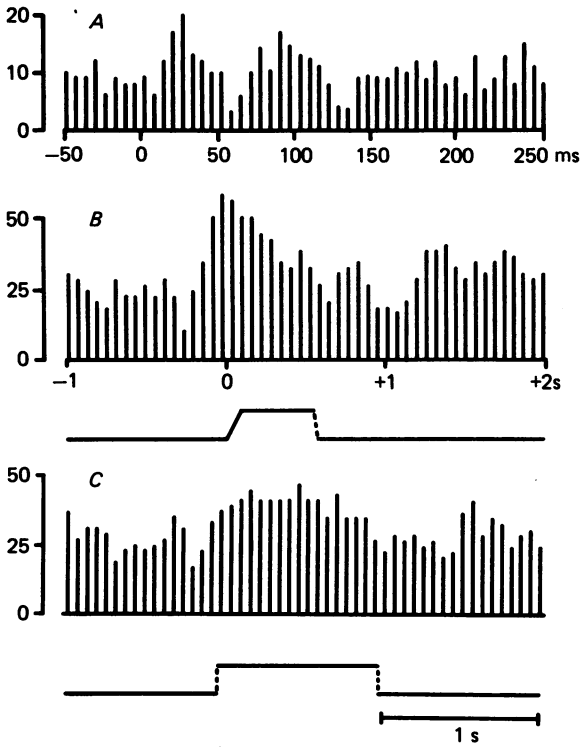

Fig. 5. *A*, peri-stimulus time histogram of the responses of an interpositus cell to thirty taps delivered to the palm of the ipsilateral hand. This was one of the largest and most prolonged responses seen to mechanical stimuli. The taps were delivered at the zero time mark on the abscissa.

B, peri-response time histograms of the responses to twenty repetitions of the lever pulling task of an interpositus cell which discharged whenever the animal flexed its fingers.

C, peri-stimulus time histograms showing responses of this same cell to twenty periods of passive flexion of the fingers. From the position of full extension, the fingers were passively flexed into the palm by the experimenter during the period indicated by upward displacement of the stimulus marker. Before movement the fingers were held fully extended and after movement they were held flexed. This cell's discharge increased during the periods occupied by the passive movement and was the only cell studied which exhibited a consistent and maintained appreciable response to imposed movement of the limb in the passive relaxed animal.

were appreciable upon application, and sometimes upon removal of stimuli. Movement of joints in the passive relaxed animal usually failed to produce any consistent change in discharge in interpositus neurones even when joints were moved in the direction in which intentional movement was associated with deep modulation in activity. One exception was an interpositus projection neurone related to finger flexion which reliably demonstrated an increase in discharge when the animal's fingers were passively flexed by the experimenter. A peri-stimulus time histogram of this response is illustrated in Fig. 5*C*, where the period occupied by passive finger flexion is indicated approximately by upward displacement of the trigger signal record (generated by a footswitch). Before flexion, the fingers were held steady in full

extension; they were then folded together into the animal's palm and were then held flexed and steady for a period of at least 1 s. It can be seen that this cell's discharge rate increased mildly while the fingers were being flexed but there was no readily appreciable difference in discharge rates between the periods when the relaxed fingers were held fully extended or were held flexed. The insensitivity of firing frequency displayed by this neurone to different joint positions (maintained by the experimenter) was typical of the other interpositus neurones examined.

Responses to unexpected perturbations of movement

The results of stimulation of peripheral receptors clearly revealed that a substantial number of interpositus neurones (and possibly a few dentate neurones) whose natural activity covaried with aspects of volitional movements of the ipsilateral forelimb received weak and transient afferent input from cutaneous and probably from deep receptors in the limb. However, there was little evidence to suggest that changes in peripheral afferent input generated by movement were directly responsible for the movement-related activity. A reason for the failure of peripheral afferent input to provoke vigorous or maintained responses could have been that transmission of information from pressure and movement sensitive receptors to the cerebellum was being depressed under the conditions in which the tests had been carried out. The animals had been conditioned over many weeks of training to accept calmly and without movement response the procedures employed here for 'sensory' examination of the limb, and this conditioning might have resulted in a depression of spinocerebellar transmission. During voluntary movement, however, transmission might well have taken place (and even have been facilitated) and to test whether or not this was the case, changes in afferent input were generated by disturbing the position of the lever during performance of the learned motor tasks. This was done either by applying a backwards jerk (10 N force; 8 ms duration) to the horizontal lever as the animal pulled it towards the target zone, or by suddenly releasing the lever in the case of the animal trained to exert a steady force on the lever by making an almost isometric contraction of its finger flexors.

The behaviour of fifty-three dentate and forty-six interpositus neurones was studied in relation to perturbations introduced during the lever pulling task and although these pertubations sometimes jerked the arm forwards by 0·5–1·0 cm (and should therefore have been effective in stimulating many receptors) they usually failed to provoke any consistent, appreciable change in dentate and interpositus neurone activity. Only one cell (an interpositus projection neurone) demonstrated a response that was clear and reproducible from run to run. This cell produced an increase in discharge which is collected into a histogram bin of 60 ms duration about half-way up the ramp-phase of the pull in a peri-response time histogram of twenty movement repetitions (Fig. 6*A*). This response was produced by the introduction of fourteen disturbances and added fifteen extra spikes to the discharges associated with lever pull in this neurone. Thus the average response was about 1 spike per stimulus, which was about the order of magnitude of responses evoked by taps to the forearm of the relaxed animal. Latency of the response was estimated to be about 40–60 ms for most spikes by constructing a peri-stimulus time histogram around the onset of the disturbances.

Sudden release of the lever in the lever-holding task allowing the fingers to flex unexpectedly against little resistance through a distance of 1 cm, produced mostly weak and transient responses in four out of sixteen interpositus neurones and in two out of twenty-seven dentate neurones tested. In five out of six neurones the response consisted of an increase in discharge (about 1 spike/release) which occurred mostly

within 30–50 ms after lever release, but an occasional spike occurred with a latency as short as 15 ms in one interpositus neurone. In the other cell (in interpositus), lever release provoked a more prolonged and complex response (Fig. 6*B*).

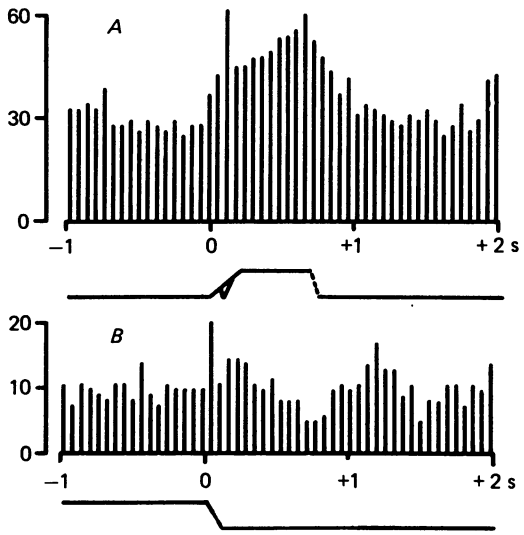

Fig. 6. Responses of interpositus cells to perturbation of motor performance. *A*, the responses of a cell to perturbations introduced during the ramp phase of the lever pull in fourteen out of twenty movement repetitions. This cell's discharges increased during arm flexion and the perturbation added an extra fifteen impulses to the activity associated with pulling the lever. *B*, activity of another interpositus cell in relation to sudden release of the lever during twenty repetitions of the lever holding task. This was the largest and most prolonged response seen in response to perturbations of movement performance. Downward displacement of the lever position trace indicates lever release through a distance of 1 cm.

DISCUSSION

Location and identification of neurones

Recordings were made in awake monkeys from neurones located in the cerebellar dentate and interposed nuclei. A substantial proportion of these neurones was shown to be a population of cerebellar projection cells by activating them antidromically from the brachium conjunctivum near the contralateral red nucleus. The nucleofugal cells we studied therefore projected as far rostrally as the midbrain. No direct indication of projection was obtained for nuclear cells not activated antidromically, but in an animal in which the implanted electrode was optimally located for stimulating the brachium conjunctivum, the thresholds for antidromic invasion ranged mostly from about 40–200 μA, and it was possible to evoke antidromic responses in 87% of cells found to be related to arm movements. This suggests that the great majority of forelimb-related dentate and interpositus neurones sampled by a microelectrode in the awake monkey contribute axons to the ascending limb of the brachium conjunctivum.

Background activity in the nuclei

In the awake, non-moving monkey, neurones in both dentate and interpositus nuclei discharged continuously in a fairly irregular manner at rates similar to those previously reported for awake animals by Thach (1968, 1970) and Armstrong & Rawson (1979). None of the dentate neurones we were able to identify positively as cerebellar projection cells displayed background impulse activity in the clear burst-like manner of the presumed dentate projection neurones studied in the awake squirrel-monkey by Grimm & Rushmer (1974) and Robertson & Grimm (1975).

It has been generally assumed that all intracerebellar nuclear neurones display background activity (see, for example, Eccles, 1973), but in most previous studies of the nuclei in awake animals (Thach, 1968, 1970, 1975, 1978; Grimm & Rushmer, 1974; Burton & Onoda, 1978) cells have been picked out on the basis of their ongoing activity, making it difficult to detect silent neurones. Using antidromic stimuli to search for cells, we found few which were quiescent and were able to confirm that in the awake monkey at rest, the great majority of dentate and interpositus projection neurones display continuous background activity. These findings for the primate dentate and interpositus substantiate similar observations on interpositus projection neurones in the awake cat (Armstrong & Rawson, 1979).

Topography of movement-related neurones

The ongoing discharge of some dentate and interpositus neurones underwent modulation that was in consistent temporal association with selfpaced movements of the ipsilateral forelimb. Cells whose discharges were related to proximal joint movements and cells related to distal joint movements were detected in both interpositus and dentate nuclei. In both nuclei, a fairly clear pattern was evident in which cells preferentially related to forelimb movements were concentrated in the mid regions and caudal halves of the structures. Our findings correspond with the recent observations by Thach (1978), who reported that cells related to ipsilateral wrist movements were concentrated in the mid portions and the caudal two thirds of the nuclei. These regions of nuclei coincide with those shown in the anaesthetized monkey to receive afferent projections from the forelimb and/or inputs from cerebral areas concerned with the forelimb representation (Allen *et al.* 1977, 1978). Cells preferentially in receipt of hind-limb inputs were concentrated in the rostral halves of the dentate and interpositus nuclei (Allen *et al.* 1977, 1978). We made no particular study of hind-limb movement, but it can be noted that cells whose discharges appeared to be related to hind limb, but not to forelimb movement, could be detected in the rostral halves of both nuclei, and further, such cells in interpositus responded quite clearly to peripheral afferent input from the hind limb. Thus, the locations of nuclear neurones related to volitional movements in the awake animal found by Thach (1978) and by ourselves agree well with the somatopy of inputs revealed by electrophysiological methods in the anaesthetized animal.

Our results perhaps indicate that more neurones in the dentate nucleus are related to movements about distal joints than are neurones in interpositus (see Table 1), but it should be kept in mind that these data provide at best only a rough guide because of the difficulties in obtaining reliable sampling of cellular activity throughout

the nuclei. However, such a bias towards distal limb representation in the ascending projection of dentate neurones is consistent with the observations of Sasaki, Kawaguchi, Oka, Sakai & Mizuno (1976), who found that potentials evoked in the cerebral cortex by dentate nucleus stimulation were predominant in areas of precentral cortex concerned with the distalmost parts of the forelimb, whereas cerebral responses produced via interpositus nucleus were concentrated in areas related to proximal forelimb movements.

Movement-related activities of interpositus neurones

The question of how cerebellar output relates to movement and muscle activity is of critical importance in understanding cerebellar contribution to motor performance. Thach (1968, 1970) showed that the firing of interpositus neurones accelerated or decelerated in consistent relation to rapidly alternating ballistic movements of the wrist or shoulder. Some of the neurones discharged only in relation to one direction of movement and a correlation of interpositus discharge with the timing of onset of movement in one of these ballistic movement tasks was also demonstrated. Recently Thach (1978) showed that interpositus neurones might encode joint position and force and pattern of muscular activity in their discharges in relation to wrist movements. Our results add to these findings by showing that in a slowly executed movement task, modifications in this neuronal activity could often be associated with movement of one joint of the forelimb in one direction, and further that the modifications of some of the neurones could covary with the range of movement and its duration which could extend for several hundreds of milliseconds. Moreover, these changes in discharge accompanying motor performance could be shown to take place when the movement formed part of a specific learned motor task or when the movement took place during more casual natural behaviour.

Together with the knowledge that the interpositus nucleus provides a very powerful monosynaptic excitatory input to rubrospinal cells (Toyama, Tsukuhara, Kosaka & Matsunami, 1970), these data suggest there might be a relationship between the interpositus nucleus and muscle activity during the execution of movement. But none of the observations listed here necessarily indicates that any functional relationship exists between the neuronal and muscle activities. Even though discharge of some cells changed in association with movement about a particular joint, and discharge could apparently covary with e.m.g. activity of a muscle involved in the movement, other muscles were also active about that joint. Hence, we could not establish a precise relationship between discharge of the interpositus neurones and activity of any particular muscle. Further studies are needed in which correlations between cerebellar activity and muscle contractions can be adequately assessed in order to establish the nature of the associations between activity in interpositus neurones, α-motoneurones and intercalated descending spinal tract neurones in the primate.

Afferent input to interpositus neurones

Changes in interpositus neural activity in relation to arm movements are likely to result from signals issuing from the sensorimotor cortex, and/or from peripheral input along spinocerebellar paths. By manipulating joints and muscles of limbs and

by applying non-noxious stimuli to the skin over much of the body surface in the relaxed co-operative animal we were able to demonstrate that a substantial proportion of interpositus neurones whose firing rates were modulated during intentional movement could receive input preferentially from receptors in the ipsilateral forelimb. However, the generally weak and fleeting nature of neuronal responses brought about by manipulation of the limb or by perturbing the limb during movement indicated that peripheral sensory feed-back generated by limb movement alone was insufficient to account for the movement related activities of most of these neurones.

Although our observations indicate that only a few interpositus neurones are likely to be strongly driven by spino-cerebellar inflow resulting directly from peripheral afferent input (but see Burton & Onoda, 1978, for cat interpositus neurones), they do not necessarily exclude the spinal cord as a substantial source of afferent input during volitional movement. In the cat, many cells belonging to the ventral spinocerebellar tract, the spino-reticulocerebellar path (via the lateral reticular nucleus) and to most spino-olivocerebellar paths respond very weakly, if at all, to somatosensory input (Oscarsson, 1973; Clendenin, Ekerot & Oscarsson, 1974). These tract cells are considered to forward information relating to excitability levels produced by descending signals in collections of interneurones within the spinal cord, rather than primarily to changes in peripheral afferent input (Oscarsson, 1973; Lundberg, 1971). Certainly a considerable afferent cerebellar drive resulting from interaction of descending signals with intraspinal circuits in the present animals would not be inconsistent with our observations that the deepest modulations in interpositus neurone activity were usually associated with intentional movement, but no indication of the extent of any such movement-dependent segmental influence could be obtained from our experiments.

The results suggested that transmission of some peripheral signals to the cerebellum might be depressed during intentional movement because responses to disturbances applied to the lever were not detectable in some cells which had earlier been shown to respond to taps delivered to the relaxed hand. Certainly, anatomical connexions exist for descending influences to exert effective control over spino-cerebellar transmission (see Oscarsson, 1973; Bloedel, 1973; Armstrong, 1974). In relation to the dynamic loop concept of cerebellar operation in the correction of ongoing movement (Eccles, 1967, 1973), our results indicate that brief and unexpected changes in peripheral afferent input need not invariably lead to obvious changes in firing pattern of cerebellar output neurones. This could mean that the cerebellum automatically formulates corrective motor signals only in relation to changes in peripheral input resulting from fairly prolonged or gross disturbances of ongoing movement.

The conclusion we draw from these results is that discharges of many interpositus neurones in relation to volitional forelimb movements depend largely upon influences resulting from issue of supraspinal signals. Information about movement is presumably transmitted from cerebrum (via nuclei in the pons and brain stem) to cerebellum throughout the course of voluntary motor performance, and our recordings might have sampled the behaviour of interpositus neurones predominantly in relation to signals produced by the sensorimotor cortex. Studies employing electrical stimulation of the cerebral cortex and limb nerves in anaesthetized monkeys reveal that inputs from homotopic regions of sensorimotor cortex and periphery frequently converge on to individual neurones (Allen *et al.* 1977; Rawson, unpublished observations); so the opportunity exists for a neurone demonstrably in receipt of spinal input also to respond to descending signals. However, from comparisons between recordings obtained to date from neurones in cerebrum and cerebellum during motor performance it has not been possible to define clear relationships between discharges of intracerebellar nuclear neurones and those of cells in the motor cortex. Sequential recordings made by Thach (1975, 1978) in relation to onset of movement

did not indicate clearly whether discharge of cerebellar neurones preceded or followed that of motor cortex cells. There is a need in further study of cerebro-cerebellar interactions for recordings to be made simultaneously from appropriate neurones in both regions of the nervous system in order that their behaviour in relation to movement can be directly compared.

Movement-related activities of dentate neurones

In the present study, the firing of some dentate neurones changed in temporal association with aspects of volitional movement about forelimb joints. These findings for slowly executed movements confirm those made by Thach (1968, 1970) in relation to brief movements of the wrist or shoulder. Most of the nuclear cells studied by Thach (1968) discharged in relation to both the wrist and shoulder movements but a few cells were preferentially related to one movement or the other. Our results also indicate that a degree of somatotopic specificity exists in the movement-related activities of dentate neurones because some cells discharged in association with movement about a particular joint or region of the limb and displayed no apparent consistent relationship with movements about other joints.

Compared with the interpositus neurones, the discharges of fewer dentate neurones studied appeared to be related to aspects of ongoing movement such as its range and duration. More than one half of cells thoroughly examined discharged in apparent relation only to the occurrence of a particular movement, but we detected none which discharged discrete high frequency bursts in relation only to a single specific phase of the motor task in the manner described by Grimm & Rushmer (1974) for presumed dentate neurones during performance of a complex sequential movement task. The characteristics of these task-related bursts were uninfluenced by different trajectories of the limb (Robertson & Grimm, 1975) and the conclusion was drawn that dentate output was little concerned with the actions of muscles and joints during movement execution but rather with some higher function or general strategy of movement.

However, Thach (1978) has recently demonstrated that discharge patterns of some dentate neurones during motor performance could encode joint position and pattern of muscular activity. He also detected a category of neurone which discharged in relation to the intended direction of movement (flexion or extension of the wrist in response to a light signal). Added to our finding that discharge of some dentate neurones could covary with amount and duration of movement and to the lack of clearcut evidence to indicate whether discharge in dentate precedes or follows that in the motor cortex (see Thach, 1975), these recent observations make it clear that it is difficult at present to relate dentate output preferentially to any particular movement variable or function. Moreover, Bantli & Bloedel (1976) have demonstrated a dentate projection to reticulospinal cells which provides a means by which the lateral cerebellum could influence proximal musculature independently of a projection that involves the motor cortex. These findings indicate the need, in future studies, for the projections of dentate cells to be accurately determined in order to establish whether neurones discharging in a particular manner during motor performance send their axons to particular target sites.

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