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Convergence of Cerebral Inputs onto Dentate Neurons in Monkey

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Summary. The patterns of convergence of inputs from different areas of the cerebral cortex and the peripheral nerves onto single dentate neurons was studied in cebus monkeys. Dentate neurons receive their strongest and most numerous inputs from the premotor and supplementary motor regions of area 6. The sensorimotor and frontal cortices have weaker projections to the dentate nucleus, while peripheral nerves and many other association cortical areas were found to be ineffective in influencing cells of the lateral cerebellum. Dentate cells that respond to stimulation of hindlimb regions of the sensorimotor cortex tend to receive their principal input from the supplementary motor area and medial premotor regions, while neurons responding to forelimb sensorimotor cortex tend to receive lateral premotor inputs. In addition there is a topographical organization within the ventral pole of dentate with the hindlimb represented in the anterior regions and the forelimb in the posterior regions. These results are compared with those of similar studies of interpositus and dentate neurons in cat and monkey. The differences between the afferent inputs to dentate and interpositus are consistent with the suggestion that the lateral cerebellum is involved in programming movement parameters before movement initiation while the intermediate zone is involved in up-dating the evolving movement.

Key words: Cerebrocerebellar – Dentate – Monkey

Three functional sagittal zones have been proposed for the cerebellum: the medial, consisting of the vermis and flocculus; the intermediate, consisting of the pars intermedia of the anterior lobe and the paramedian lobule; and the lateral, consisting of the cerebellar hemisphere (crura I and II, paraflocculus)

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(Chambers and Sprague, 1955). The intermediate and lateral zones of the cerebellum receive the strongest cerebral projections. The medial zone receives a weak cerebral input; its major input is from peripheral nerves and its chief efferent projection is to the spinal cord via reticulospinal and vestibulospinal pathways. It is likely that this zone is involved in the control of posture (Eccles et al., 1974b).

It has been shown in the cat and monkey that the neurons of nucleus interpositus, the outflow nucleus of the intermediate zone, integrate inputs primarily from peripheral nerves and sensorimotor cortex (i.e., that region comprised of primary motor and somatosensory cortex) (Eccles et al., 1974a; Allen et al., 1977; Allen et al., in preparation). Nucleus interpositus projects down the spinal cord via the rubrospinal tract and to the motor cortex after relaying in ventrolateral thalamus (VL). In contrast, the lateral cerebellar nucleus integrates inputs primarily from association areas of the cerebral cortex, with significant input coming from the sensorimotor cortex but weaker input from the peripheral nerves (Allen and Ohno, 1973; in preparation). The outflow from the lateral cerebellum (n. dentatus) projects primarily to the motor cortex via VL but also to the adjacent premotor cortex in area 6 (Sasaki et al., 1976). Based upon these observations and neurological studies of patients with cerebellar lesions (Dow, 1969), the suggestion has been made that the lateral cerebellum is involved in the programming of movement parameters before movement initiation, while the intermediate zone is involved in up-dating the evolving movement (Evarts and Thach, 1969; Allen and Tsukahara, 1974). This sequence of events agrees with observations made on monkeys trained to perform specific movements (Thach, 1970, 1975; Robertson and Grimm, 1975a; Strick, 1976). Experiments by Kornhuber and co-workers (Deecke et al., 1969) have shown that in man large regions of the cerebral cortex become active bilaterally up to 800 msec before initiation of a simple voluntary movement.

In view of these findings it becomes important to know which of the primary and association cortical areas involved in movement influence the dentate nucleus and how the different areas cooperate in producing its output. The present experiments were initiated in order to gain a better understanding of the way in which information is processed by the lateral cerebellum. Primates were chosen for this study because of their better developed dentate nucleus, motor cortex and association cortex. Association cortical areas with presumed motor function, as well as primary motor and somatosensory areas and nerves, were stimulated while recording from single dentate neurons. We found striking differences between the responses of dentate and interpositus neurons which lend support to the hypothesis that the lateral cerebellum is involved in the pre-programming of volitional movements.

Methods

The experiments were performed on 14 Cebus monkeys (1.5–3.0 kg) which were anesthesized with nitrous oxide (80%, in oxygen) and halothane during the surgical preparation and maintained under nitrous oxide anesthesia during the period of recording. The monkeys were mounted on a stereotaxic frame in the prone position, immobilized with Flaxedil and artificially ventilated.

Expired CO_2 was maintained at 3–4%, while blood pressure was kept above 90 mm Hg by infusing a vasoconstrictor Aramine when needed. The body temperature was maintained between 37 and 38 ° C.

A craniotomy was performed over the left cerebellum and the right cerebral hemisphere. For stimulation purposes, insulated steel needles exposed at the tip were inserted into each of 10–22 cerebral sites and anchored firmly to the skull with dental acrylic. The needles were inserted to a depth of about 3 mm so that they would stimulate cells which were in the deep layers of the cortex or fibers just at the point of exit of the grey matter. Figure 1 shows a diagram of a lateral and medial view of the right cerebral hemisphere with all sites of cortical stimulation except insular and orbital cortices shown superimposed onto one brain. Stimulation sites were chosen according to the cerebral areas found by Dow (1942) as the most effective in evoking surface potentials over the cerebellar hemispheres. At least two sites in the primary motor (MI), two in the somatosensory (SI), three in the premotor (PM), and one in the supplementary motor (SMA) cortices were stimulated in all of the experiments. See Allen et al. (1977) for a detailed description of the placment of SMA and PM electrodes. The frontal, temporal, and cingulate cortices and common radial and sciatic nerves were tested in most experiments, while the prefrontal, posterior parietal, secondary visual, orbital, and insular cortices were tested in a few animals. The hand and foot areas of the precentral gyrus (MI) were located using surface stimulation. The corresponding points on the postcentral gyrus (SI) were verified by observing the potentials evoked by nerve stimulation. Lesions were made at each stimulus site after the experiment, and the location of each electrode was confirmed by histological examination. Results obtained from electrodes misplaced or stimulating deeper association fibers were eliminated. For stimulating each cortical site a pair of cathodal pulses (duration, 0.1 msec; interval, 1.3 msec) at an intensity of 1.0 mA was applied to the cortical needles. A large electrode on nearby muscles served as the indifferent. A pair of steel needles insulated except at the very tips was placed stereotaxically (Manocha et al., 1968) into the right red nucleus and bipolar stimulation was used to test for antidromic activation. The common radial and sciatic nerves on the left side were stimulated with a pair of pulses (duration, 0.1 msec; interval, 2 msec) at 7–10 times threshold.

Extracellular recordings of dentate cell discharges were obtained using 3–4 MΩ glass micropipettes filled with 2 M NaCl. The micropipette was inserted into the left dentate nucleus aiming from posterior to anterior in the horizontal plane (H: 0 to –3.0, L: 3.0 to 7.0). Mechanical stability was achieved by covering the exposed cerebellar cortex with 4% agar gel and performing a bilateral pneumothorax. Each dentate neuron was identified by antidromic activation from red nucleus and by subsequent histological verification of its location within the nucleus. The recording microelectrode was coupled through a cathode follower (a.c. time constant, 0.2 sec) to an oscilloscope for photography. In addition, the spikes were filtered and converted to standard pulses by a Schmitt trigger for use by an instrument computer (Fabri-Tek 1062) in producing post-stimulus time histograms (PSTHs). Once the PSTH was computed, it was possible to add to every memory address the contents of all preceding addresses, thereby converting the PSTH to a cumulative frequency distribution (CFD).

At the end of one or more tracks in each experiment, the microelectrode was cut and its shaft left in the cerebellum for later histological examination. After the experiment, the brain was fixed in 10% formalin and saline, embedded in celloidin, cut at 150 μm thickness and stained with thionin. The tracks were reconstructed and the position of each dentate neuron was located on the appropriate histological section.

Results

This paper describes the results of a study of dentate neurons recorded by microelectrodes during tracks through the cerebellum of the monkey while stimulating various regions of the cerebral cortex. Two hundred fifty-five cells, which were stable enough to permit testing their responses to stimulation of at least 5 cortical sites, were selected from a larger total for analysis. Of the cells which were tested by stimulation of the contralateral red nucleus, 82% (163/200) were identified as projection neurons by antidromic activation at an

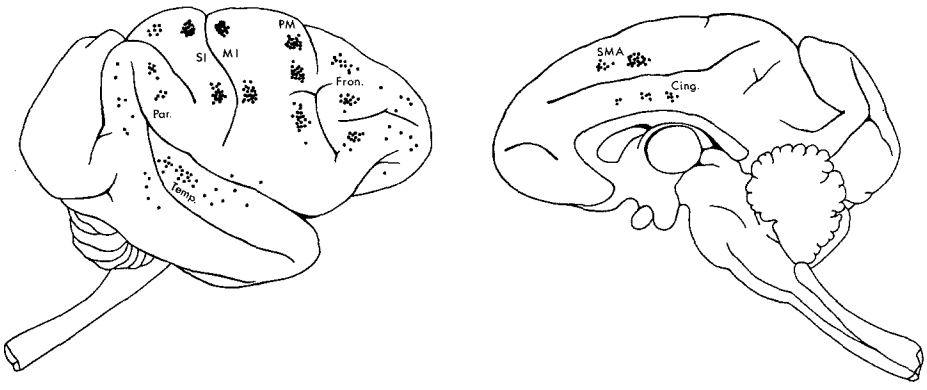

Fig. 1. Sites of stimulating electrodes in the cerebral cortex. The sites of stimulation are shown on a lateral (left) and medial (right) view of the right hemisphere of the Cebus monkey. The locations of all cortical electrodes are shown superimposed and normalized upon one brain, with the exception that the sites in the insular and orbital cortices are not shown. The number of dots within each cluster indicates the number of experiments in which that particular site was stimulated. MI: primary motor, SI: primary somatosensory, PM: premotor, SMA: supplementary motor area, Temp: temporal, Cing: cingulate, Fron: frontal, Par: posterior parietal. The locations of electrodes inserted into the prefrontal and secondary visual areas are shown but not labeled

average latency of 1.3 msec (S.D. 0.3). No differences in the response characteristics were observed between those cells antidromically activated from red nucleus and those that were not. All recordings were made from the cell somata as judged by conventional criteria.

Basic Responses of Dentate Neurons to Stimulation of the Cerebral Cortex

Penetrations with the microelectrode were made in such a way as to sample all portions of the dentate nucleus in the course of these experiments. Each dentate neuron was tested to stimulation of several cortical sites. The responses to stimulation of the different cortical zones could be classified into a few basic patterns as illustrated in Figure 2. Figure 2A shows the results of a study of a dentate neuron which responds to stimulation of the cerebral peduncle with inhibition starting at 9 msec and lasting until a late excitation starts at 27 msec. The neuron of Figure 2B responds with inhibition starting at 11 msec. A brief, weak excitation at 18 msec is followed by inhibition at 21 msec; a further strong late excitation begins at 26 msec and is followed by late inhibition at 35 msec.

From the responses of the entire population of dentate neurons, of which the two cells in Figure 2 are representative examples, several basic response components (see Fig. 2C) can be identified on the basis of latency measurements (see Allen et al., 1977). These components correspond to those reported in the cerebellar cortex (Allen et al., 1974; Sasaki et al., 1975) and in the deep cerebellar nuclei (Eccles et al., 1974c; Allen and Ohno, 1973; Allen et al., 1976,

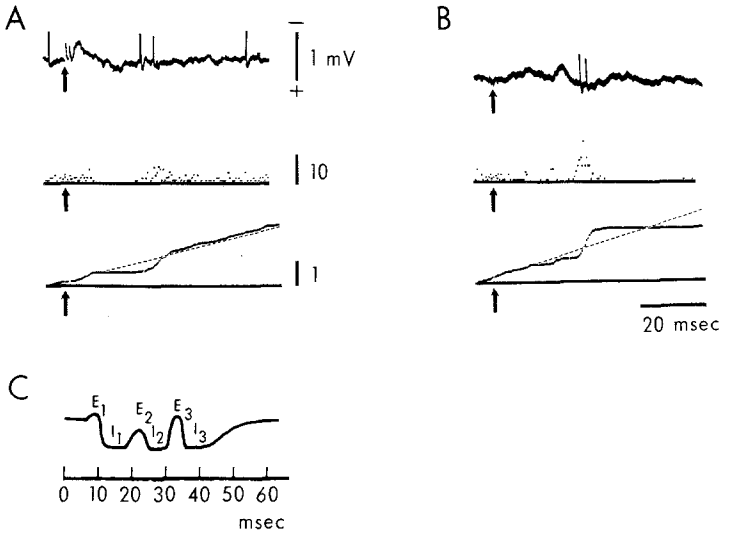

Fig. 2. Basic response of dentate neurons. **A** Response of a dentate neuron to stimulation of the cerebral peduncle. **B** Response of another dentate cell to stimulation of the SMA. In both **A** and **B** the upper trace is a specimen record, the second row is the post-stimulus time histogram (PSTH) obtained from 64 consecutive responses and the bottom row is the cumulative frequency distribution (CFD) obtained by integrating the PSTH. The solid arrow marks the onset of the stimulus which in both A and B was a pair of 1.0 mA pulses. The dotted line in the CFD represents the average background discharge. The time scale of 20 msec applies to all records. The calibration of 1.0 mV applies to the specimen records, 10 counts to the PSTH, and 1 count added per stimulus to the CFD. **C** A schematic diagram of all the response components found in dentate cells in the form of a PSTH

1977) of cats and monkeys. These components are the following: an early weak excitation with a mean latency of 8.4 msec (termed E_1; S.D., 1.5 msec; n, 43), early inhibition at 10.7 msec (I_1; S.D., 3.4 msec; n, 63), weak excitation at 19.7 msec (E_2; S.D., 3.6 msec; n, 55), inhibition at 25.4 msec (I_2; S.D., 4.8 msec; n, 54), late excitation at 33.1 msec (E_3; S.D., 5.5 msec; n, 30), and late inhibition at 36.6 msec (I_3; S.D., 6.1 msec; n, 17). Not all of these components are present in every response, and the above latency measurements are only taken from cells which had multiple components. For example, in Figure 2A the response appears to consist of I_1, I_2, and E_3 without an E_2. Careful inspection of Figures 2A and 2B shows a suggestion of E_1 preceding I_1 in each case. In the Discussion it will be concluded that the ponto-cerebellar fibers mediate E_1, I_1, and most of E_2, whereas the olivo-cerebellar fibers contribute to E_2 and mediate I_2 and E_3.

The changes in the pattern of response of a dentate neuron are shown in Figure 3 as the strength of stimulation and number of shocks in the stimulus train are varied. The dentate cell is sensitive to both the number and the intensity of the shocks. A sequence of weak inhibition, excitation, and inhibition (I_1, E_2, I_2) can be elicited by either 2 shocks at 0.2 mA or 1 shock at 0.3 mA. Increasing the strength or the number of shocks produces an increase in both the amount of inhibition and excitation. It is apparent from the sequence shown in

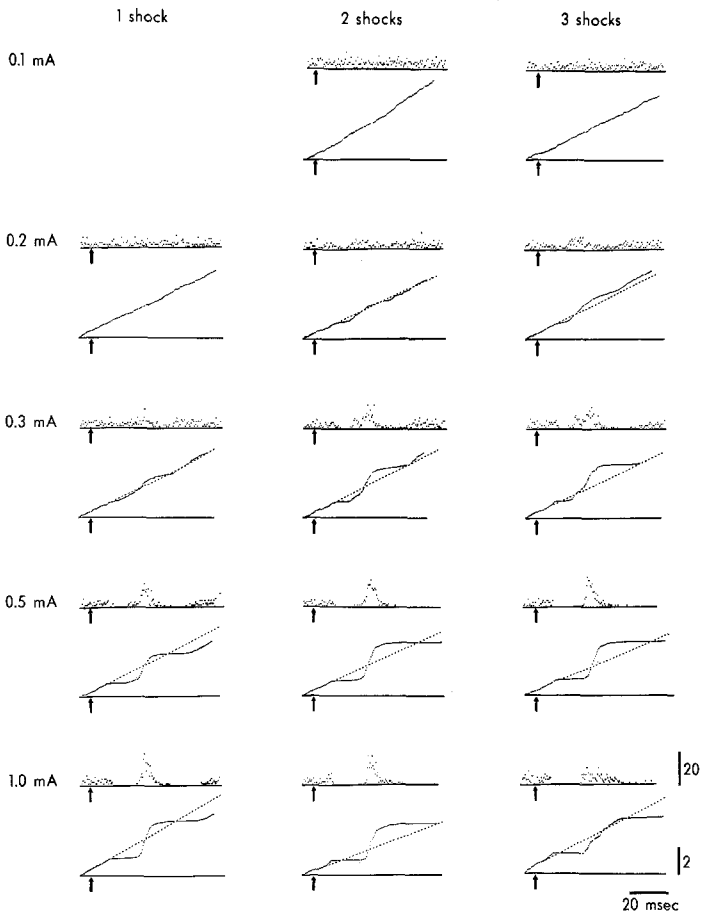

Fig. 3. Relationship between the response of a dentate cell and the intensity and number of shocks. The PSTH and CFD are shown for a dentate cell to stimulation of the SMA with a variable number of shocks as shown on top and a variable intensity shown to the left. The calibrations of 20 msec applies to all records, the 20 counts to all PSTHs and 2 counts added per stimulus to the CFDs

Figure 3 that E_2 can be produced both by increasing the number of shocks (from 1 to 2 shocks at 0.3 mA) or by increasing the intensity of stimulation (from 0.3 to 0.5 mA at 1 shock). A clear early excitation (E_1) can also be seen along with the other three components for 2 and 3 shocks at 1.0 mA. For the results given in this paper, the cortical sites were all stimulated with 2 shocks at 1.0 mA.

There are no apparent systematic differences in the temporal response patterns elicited from different cerebral areas.

Cortical Areas Projecting to Single Dentate Neurons

Each dentate cell responds to stimulation of a specific subset of cerebral areas. The response pattern of a typical dentate cell is shown in Figure 4. This cell

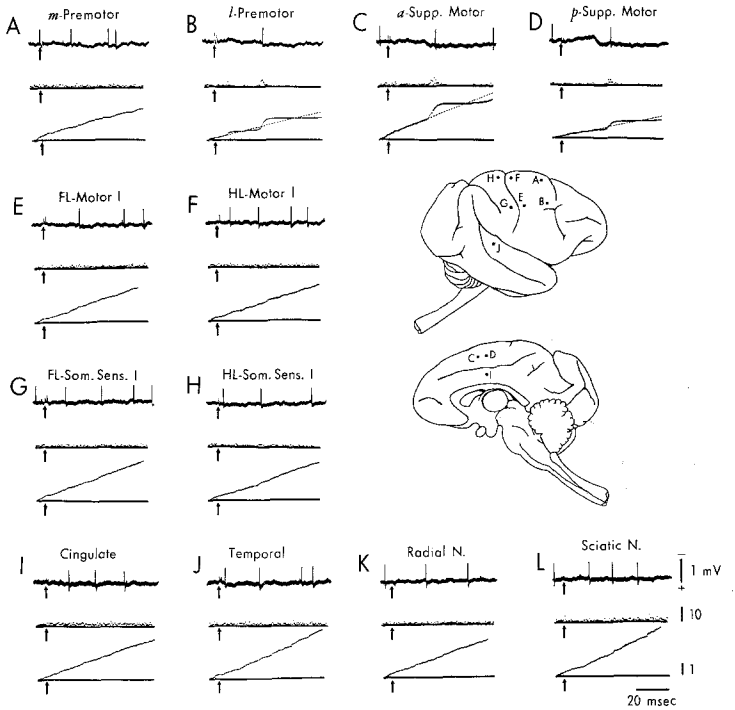

Fig. 4. Responses of a dentate neuron to stimulation of 12 different cortical areas. For each stimulus site **A–L**, one specimen record, one PSTH, and one CFD are shown. The cortical stimulus sites are shown on the two inset diagrams of the right cerebral hemisphere. Many other sites were stimulated in this experiment but are not shown. The 20 msec calibration applies to all records, the 1.0 mV to the specimen records, the 10 counts to the PSTHs, and the 1 count added per stimulus to the CFDs

responds to stimulation of the anterior SMA (4C) with a strong excitation E_3 at a latency of 26 msec, followed by a long lasting inhibition I_3 at 35 msec. Stimulation of the posterior SMA (4D) produced a sequence of weak inhibition I_2 at 22 msec, weak excitation E_3 at 28 msec and a strong long lasting inhibition I_3 at 39 msec. A similar response pattern was evoked by stimulation of the lateral PM (4B) area: there is a trace excitation E_1 at 8.5 msec, two strong inhibitory components I_1 and I_2 at 11 msec and 20 msec, a strong excitation E_3 at 27 msec, followed by a strong long-lasting I_3 at 35 msec. Stimulation of the four areas in the primary motor and somatosensory cortex (4E, 4F, 4G, 4H), two peripheral nerves (4K, 4L), cingulate (4I), and temporal (4J) cortices did not affect the activity of this neuron. Thus, this dentate neuron receives inputs only from the two regions of area 6, the premotor and supplementary motor areas, and not from the sensorimotor cortex or peripheral nerves.

Other dentate cells, however, did respond to stimulation of the sensorimotor cortex as well as to area 6. Figure 5 shows an example of such a neuron in which many more areas of the cerebral cortex were stimulated. This cell responds strongly to stimulation of the supplementary motor area (5C, 5D), hindlimb

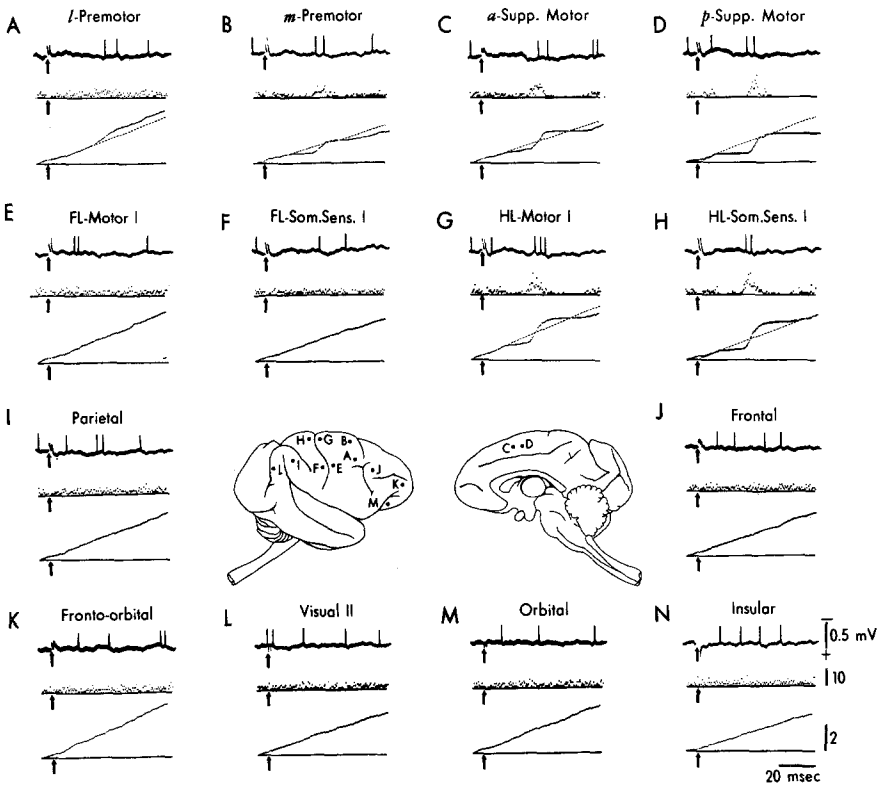

Fig. 5. Responses of a dentate neuron to stimulation of 14 different cortical areas. For each stimulus site **A–N**, one specimen record, one PSTH, and one CFD are shown. The cortical stimulus sites are shown on the two inset diagrams of the right cerebral hemisphere. In this experiment many other sites were stimulated, but only the most representative are shown. The 20 msec calibration applies to all records, the 0.5 mV to the specimen records, the 10 counts to the PSTHs, and the 2 counts added per stimulus to the CFDs

motor cortex (5G), and hindlimb somatosensory cortex (5H), with weaker responses to stimulation of premotor cortex (5A, 5B). Most of the responses consist of a sequence of early inhibitions (I_1, I_2), late excitation (E_3), and late inhibition (I_3) although not all components are present or have the same properties in each case. This neuron receives inputs from all four regions of area 6 shown and the hindlimb regions of the sensorimotor cortex. In addition to those areas, several other cortical areas were stimulated which are: 1. known to project to the pons in the monkey (Sunderland, 1940; Nyby and Jansen, 1951); 2. homologous to cortical areas influencing dentate neurons in the cat (Kaada, 1960; Allen and Ohno, 1973); 3. important cortical areas in processing somatosensory information (Jones and Powell, 1970; Nauta, 1971); or 4. other cortical areas involved in the control of movement. Some of these are shown in Figure 5 and include several points in the parietal (5I), frontal (5J), fronto-orbital border (5K), secondary visual (5L), orbital (5M), and insular

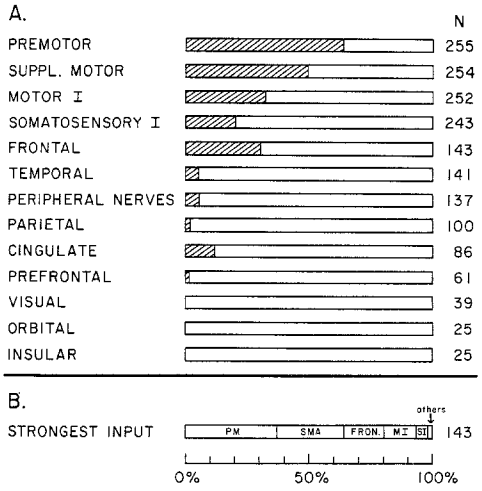

Fig. 6. Summary of percentage of dentate neurons that respond to stimulation of different cortical regions. **A** The percentage of dentate cells that responded to stimulation to at least one site of each cortical region is shown. Since not all the same cortical areas were tested in all experiments and for all cells, the percentages are based on the total number of cells, shown to the right, for which that cortical site was tested. Trace responses were eliminated in all calculations. **B** The percentages of cortical sites that elicited the strongest response in the 143 dentate cells for which the PM, SMA, MI, SI, and frontal cortex were all tested. The sites of the cortical stimulating sites are shown in Figure 1

(5N) cortices. None of these other association areas were effective in influencing the discharge of this dentate cell. These other association areas were not tested in all experiments.

The relative frequency of all the cortical and peripheral nerve inputs to all dentate cells can be seen in Figure 6. Since all cells were not tested with the same cortical inputs, the percentages shown are based upon the number of cells in which each cortical area was stimulated, shown to the right. It is apparent that the lateral cerebellum receives its most frequent projections from the premotor (PM) and supplementary motor area (SMA) of area 6. Other areas that provide a significant input are the primary motor and somatosensory cortex and the frontal cortex. All other association cortical areas and the peripheral nerves provided very little input to the population of dentate cells tested.

The strength of each response component was graded based upon the number of spikes added (excitation) or subtracted (inhibition) per stimulus (see Figs. 8, 9). Thus, it was possible to determine the relative influence of each cortical area upon a dentate neuron and the area that provided the strongest response, taking into account both excitatory and inhibitory components. Figure 6B shows the percentage of dentate neurons whose strongest input came from the cortical area listed. This was computed from a subset of the total population of cells in which at least PM, SMA, MI, SI, and frontal cortex were tested. Again it is apparent that area 6 provides the greatest influence on dentate cells, followed by the frontal and primary sensorimotor cortex. The strongest inputs to dentate came from premotor (37%) and supplementary motor (27%) whereas primary motor or somatosensory cortex provided the strongest input to only 17% of the neurons. Thus, those cortical areas that most frequently influenced the dentate neurons (Fig. 6A) also provided the strongest input (Fig. 6B).

For the dentate neurons that respond to stimulation of primary sensorimotor cortex or peripheral nerves, we defined as a convenience each neuron as hindlimb (HL), forelimb (FL), or mixed according to the somatotopy of these

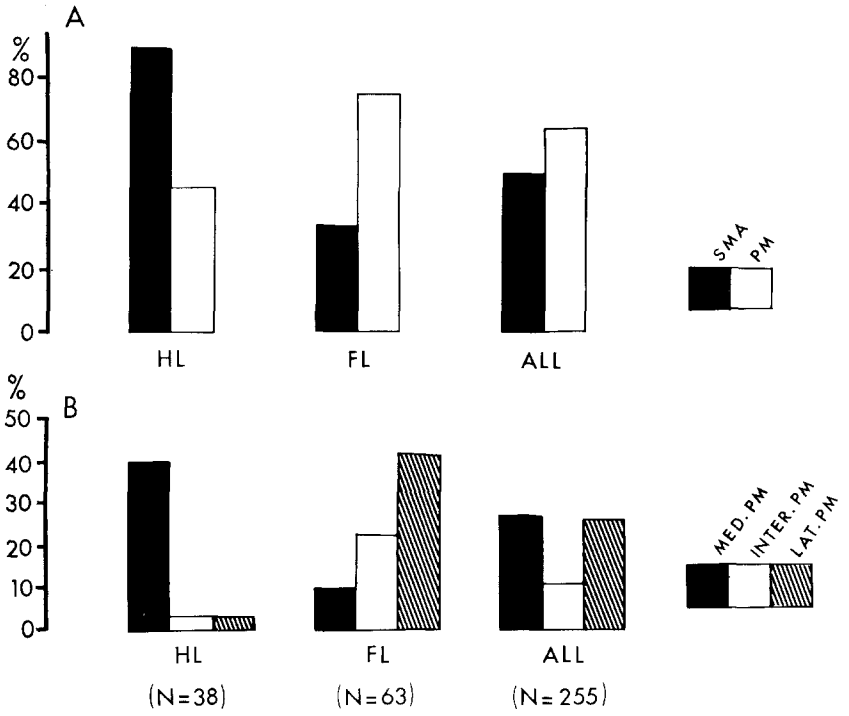

Fig. 7. Correlations between inputs from area 6 and dentate cells of fore- and hindlimb somatotopy. The somatotopy of each neuron was determined by its response to stimulation of the primary motor and somatosensory cortex and peripheral nerves. **A** The projection of the supplementary motor area (SMA) and premotor (PM) areas onto cells with hindlimb (HL) and forelimb (FL) somatotopy as compared with the total population (ALL) of dentate cells. A chi-squared analysis showed that the distribution of HL cells is significantly different from that of the total population at the 95% level of significance whereas the FL distribution is not, $X^2_{HL} = 13.2$, $X^2_{FL} = 4.1$, $X^2_{.95} = 6.0$ for 2 degrees of freedom. **B** The projection of three different stimulation points in the premotor cortex to dentate cells of hind- and forelimb somatotopy as compared with the total population. The chi-squared analysis showed both FL and HL distributions to be significantly different from the population, $X^2_{HL} = 12.3$, $X^2_{FL} = 20.1$, $X^2_{.95} = 7.8$ for 3 degrees of freedom

inputs. The cell whose response pattern is shown in Figure 5 is an example of one whose input from the sensorimotor cortex would identify it as a pure HL cell. Thirty-eight (15%) neurons received sensorimotor cortical and peripheral nerve inputs restricted to the hindlimb whereas 63 (25%) were pure FL cells. Only 7 cells (3%) showed a mixed input.

The correlations between inputs from sensorimotor cortex and from area 6 onto single dentate neurons is shown in Figure 7. Figure 7A shows the percentage of HL and FL cells that receive inputs from SMA and PM as compared to the total population of cells. Dentate cells receiving inputs from the hindlimb sensorimotor cortex tend to receive their primary input from the SMA, while those with input from forelimb cortex tend to receive greater input from the PM cortex. A chi-square analysis showed that the distribution of HL cells is

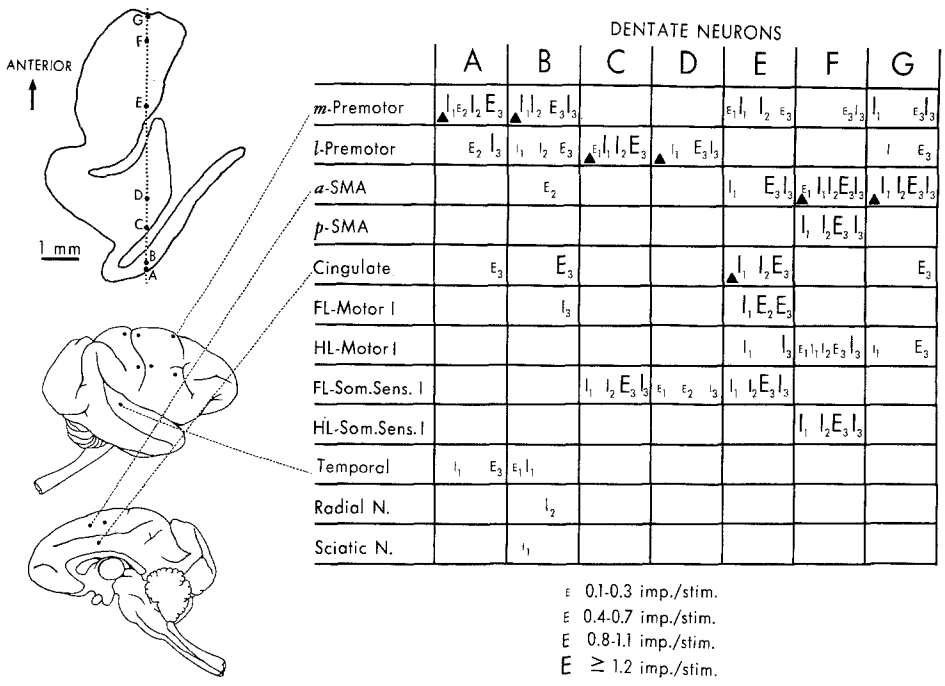

Fig. 8. Responses of seven dentate neurons recorded along one track through the left dentate nucleus in a horizontal plane. The location of each neuron is shown in the diagram of the dentate nucleus at the upper left. The microelectrode was introduced from posterior to anterior in the horizontal plane. The strength of the response of each neuron **A–G** is coded according to the number of impulses added or subtracted per stimulus as shown in the scale at the bottom of the figure. The response components are designated E_1, I_1, E_2, etc. according to the convention described in the text. The locations of the cortical stimulation sites are shown in the inset diagram of the cerebral cortex

significantly different from that of the overall population at the 95% level but that the distribution of FL cells is not. A topographical projection to HL and FL cells from the premotor region is revealed in Figure 7B. Here it is shown that the HL cells that do respond to PM stimulation do so chiefly in association with the medial portions of PM cortex, while FL cells tend to respond to stimulation of the lateral PM cortex. Both the FL and HL distributions are statistically different at the 95% level from the distribution for the total population, which is just about equally weighted for medial and lateral PM, as shown to the right. Thus, dentate cells receiving inputs from SMA and medial PM tend to receive a HL cortical input also; whereas cells responding to lateral PM receive their secondary input from FL sensorimotor cortex.

Topographical Projection of Cerebral Cortical Inputs to the Dentate Nucleus

It is possible to consider the topographical mapping of the cerebrum onto the dentate nucleus by reconstructing the microelectrode tracks on histological

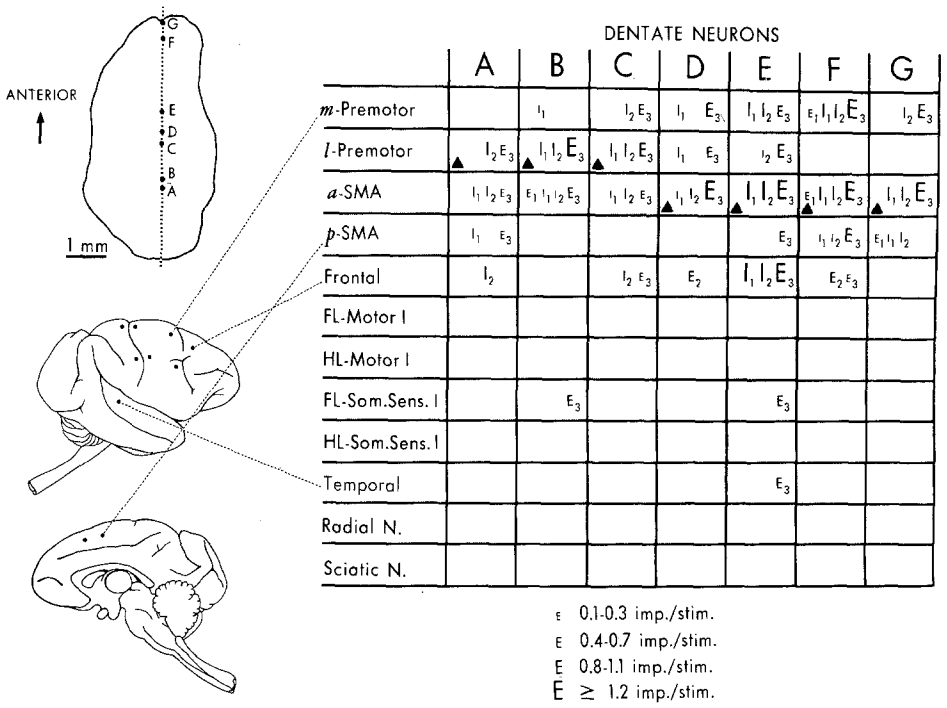

Fig. 9. Responses of seven dentate neurons recorded along one track through the left dentate. The locations of the seven dentate cells A–G in the ventral pole of the nucleus is shown in the diagram at upper left. The strength of the response is coded according to the scale at the bottom. Conventions are the same as for Figure 8

sections of the cerebellum. Figure 8 shows a study of the responses of seven dentate cells along a single microelectrode track in the horizontal plane. Here the responses have been coded according to the response components present; the size of each symbol represents the strength of the response component. For each neuron a solid black triangle denotes the stimulus judged to evoke the strongest response.

The regional differences in Figure 8 are very clear, suggesting that there might be "colonies" of neurons with similar operations. Cells A and B, located in the limb connecting dentate with interpositus, have similar response properties. Both receive their strongest inputs from medial premotor, with additional inputs coming from lateral premotor, cingulate, and temporal cortex. Neuron B receives additional weak inputs from forelimb MI, anterior supplementary motor area, and the peripheral nerves. Cells C and D, lying in the middle segment of the nucleus, are almost identical, with responses to the lateral PM and FL region of the postcentral gyrus. In the anterior limb of the nucleus, neuron E demonstrates a third pattern of afferent connections. For this particular cell the strongest input comes from cingulate, but additional strong inputs originate from anterior SMA, medial PM, forelimb and hindlimb pre- and

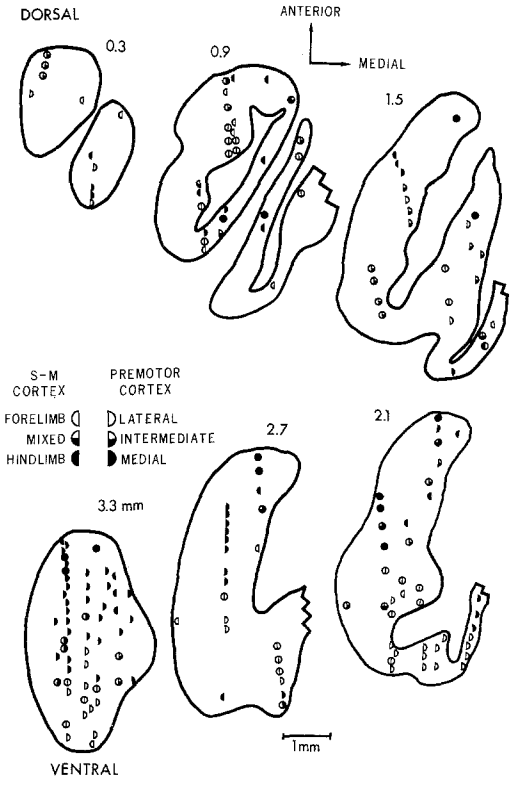

Fig. 10. Three dimensional reconstruction of the dentate nucleus showing the locations of all neurons that responded to stimulation of the sensorimotor cortex (MI and/or SI) or the premotor cortex. The locations of all neurons from all experiments are superimposed upon horizontal drawings of a standard dentate nucleus. Each cell is coded by its response to the sensorimotor and premotor cortex. The cells that responded to the sensorimotor cortex are identified as forelimb, hindlimb, or mixed depending upon their somatotopy and the premotor input is identified as being strongest from the lateral, intermediate or medial stimulating electrodes. Since the nucleus is of different size and shape from one animal to another, the appropriate section on which to localize each penetration was determined by normalizing the size of the nucleus to that of the standard and measuring from the ventral pole

postcentral areas. Neurons F and G, although they both respond most intensely to stimulation of anterior SMA, receive otherwise different inputs.

Another reconstruction of a microelectrode track through a more ventral section is shown in Figure 9. Here the nucleus itself shows no obvious differences in general shape, yet certain properties of dentate integration can be discerned. Each dentate cell receives inputs from widely varying regions of the cerebral cortex. These seven neurons generally receive inputs from medial and lateral PM, anterior and posterior SMA, and the frontal cortex. Although there is a high degree of spatial integration, there is still a certain topographical pattern. For example, in proceeding from neuron A to neuron G, there is a progressive shift in the source of premotor input from the lateral region to the medial region. Although all of the neurons along this track respond to stimulation of the anterior part of SMA, the neurons in the anterior portion of the track respond much more strongly than do the neurons located more posteriorly. Similarly, the cells in the anterior part of this particular track respond more strongly to inputs from the posterior SMA and from the frontal cortex.

Within these topographical patterns, we often found groups of neurons with similar inputs. These groups appear to represent the colonies which Eccles and co-workers found in the fastigial and interpositus nuclei of the cat for peripheral

inputs (Eccles et al., 1974b, 1974d). Within each colony the neurons are similar in terms of their spectrum of inputs, but there is still individuality of the neurons because no two cells receive exactly the same inputs or respond in the same way to those inputs.

An attempt to determine the total topographical pattern of the cerebral projections to dentate was made by superimposing all of the tracks on the corresponding planes of a three dimensional reconstruction of the dentate nucleus. Part of the topographical pattern is shown in Figure 10. Here cells are coded as HL, FL or mixed according to their response to sensorimotor cortex and also coded according to their response to different regions of the premotor cortex. Since cells related to the forelimb tend to be correlated with lateral PM input and hindlimb cells to medial PM (Fig. 7B), cells receiving inputs from lateral PM and/or forelimb sensorimotor cortex are coded by open half circles in Figure 10 while cells with medial PM and/or hindlimb inputs are shown with closed half circles. Each cell was then located on the appropriate histological section of an "average" dentate nucleus. Since the shape of the nucleus tends to vary from one animal to another, certain concessions had to be made for these differences. Nonetheless, it is apparent from Figure 10 that the medial PM-hindlimb cells tend to be located in the anterior portion and the lateral PM-forelimb cells in the posterior portion, especially in the ventral pole of dentate. This topography does not seem to hold for the more dorsal regions of the nucleus.

A similar correlation can be made between forelimb and hindlimb sensorimotor cortex and SMA. When this is done (not shown), as would be predicted from Figure 7, the dentate neurons receiving SMA inputs tend to receive hindlimb inputs and be located anteriorly in the nucleus.

Discussion

Basic Response Pattern of Dentate Neurons

There is a remarkable similarity in the alternating sequences of excitations and inhibitions that are reported here and also found in the cat cerebellar cortex (Allen et al., 1974; Sasaki et al., 1975), cat interpositus (Eccles et al., 1974a, 1974c; Allen et al., in preparation), cat dentate (Allen and Ohno, in preparation), and monkey interpositus (Allen et al., 1976, 1977). The dentate neurons in Cebus monkey respond to electrical stimulation of cerebral cortex with E_1 at a mean latency of 8.4 msec, I_1 at 10.7 msec, E_2 at 19.7 msec, I_2 at 25.4 msec, E_3 at 33.1 msec, and I_3 at 36.6 msec. The neural connections mediating these responses are assumed to be the same as those found in the lateral cerebellum of the cat where there is an early mossy fiber input carried by the ponto-cerebellar fibers and a later climbing fiber input carried by the olivo-cerebellar fibers (Allen and Ohno, in preparation). E_1 would be mediated by the weak action of collaterals of ponto-cerebellar mossy fibers onto dentate neurons. I_1 represents the inhibitory action of Purkyne cells activated by the early mossy fiber input to the cerebellar cortex. The excitatory collaterals of the climbing fibers can contribute to E_2. In recordings from Purkyně cells of the

paramedian lobule in the present experiments, it was found that the climbing fiber responses have a latency of 19.5 msec (S.D., 2.5 msec), consistent with this possibility (not shown). However, from intracellular recordings of dentate neurons in these experiments (not shown) we found that hyperpolarizing and depolarizing potentials corresponding to I_1, E_2, I_2, and E_3 could be reversed in every case by injection of hyperpolarizing current through the recording electrode. This indicates that I_1 and I_2 are IPSPs induced by mossy fiber and climbing fiber activation of Purkyně cells respectively, and that E_2 and E_3 are disinhibitions (Wilson and Burgess, 1962) resulting at least partly from the subsequent basket cell or indirect Golgi cell induced silencing of Purkyně cell activity. I_3, which occurs in about half of the neurons, apparently represents an IPSP through a polysynaptic pathway.

The similarity in response pattern of cells in the deep cerebellar nuclei between animals of different species and between the lateral and intermediate nuclei of the same cerebellum attest to the remarkable constancy in cytoarchitecture throughout the cerebellar cortex in different animals (Eccles et al., 1967). Although the response components observed in the cat interpositus are the same as those observed in the monkey dentate, there is a considerable increase (average 37%) in the latencies of each of the components in the monkey as compared to the cat (Allen et al., in preparation). Correspondingly, there is an increase in the average latency of the climbing fiber response in the monkey cerebellar cortex (19.5 msec) over that found in the pars intermedia of the cat (15.4 msec) for stimulation of the sensorimotor cortex (Allen et al., 1974). This latency increase may be due to a decreased conduction velocity, greater conduction distance or a combination of these factors. It seems doubtful that there is any difference in the number of intervening synapses since the response characteristics remain so similar.

All of the responses observed in monkey dentate and interpositus can be explained without involving the interneurons within these cerebellar nuclei (Chan-Palay, 1973). However, these interneurons may make secondary contributions to the responses of the nuclear projection neurons and their role should be considered more carefully in future experiments.

Integration of Cerebral Inputs

The results of this study confirm that dentate neurons receive inputs from regions widely distributed over the cerebral cortex, especially from those areas involved in the control of movement. It is of particular interest to compare the integration of cortical inputs by dentate and by interpositus neurons in the monkey (Allen et al., 1977). Dentate neurons receive the heaviest projection from the premotor and supplementary motor regions of area 6 while weaker but nonetheless significant inputs come from the sensorimotor and frontal cortex. Seventy-six percent of all dentate cells receive input from some part of area 6 while only 42% respond to stimulation of the hand or foot regions of the sensorimotor cortex. By contrast, in the interpositus nuclei 56% of the cells respond to area 6 and 85% to the sensorimotor area. The inputs from the

peripheral nerves are likewise strikingly different: 53% of interpositus neurons respond to stimulation of the peripheral nerves while only 6% of dentate neurons do. Within the sensorimotor cortex the motor cortex provides a stronger input than the somatosensory cortex to both interpositus (82% vs 57%) and to dentate (32% vs 20%). These differences in the frequencies of input are enhanced by the observation that the less frequent inputs are also generally weaker. Thus, the strongest inputs to dentate neurons in decreasing order are PM, SMA, frontal, MI, and SI, while the strongest inputs to interpositus are MI, SI, nerves, PM, and SMA. Clearly the lateral cerebellum tends to integrate inputs from the cortical association areas in the frontal lobe whereas the intermediate zone integrates inputs chiefly from the primary sensorimotor cortex and peripheral nerves. These results are in accord with previous studies using evoked potentials in the monkey and cat (Dow, 1942; Hampson, 1949; Snider and Eldred, 1951; Jansen, 1957).

It is surprising that no or very few neurons in dentate or interpositus responded to stimulation of parietal, temporal, prefrontal, insular, orbital, or secondary visual cortex. Frontal, parietal, temporal, and occipital cortices have been described as projecting to the pons in monkey (Sunderland, 1940; Nyby and Jansen, 1951). Evoked potential studies have suggested that these areas are capable of activating the cortex of the lateral cerebellum (Dow, 1942; Sasaki et al., 1975). Furthermore, prefrontal, orbital, and insular are homologous to areas that activate dentate neurons in the cat (Kaada, 1960; Allen and Ohno, in preparation). Recently, orbital cortex has been shown not to project to the pons in the marmoset (Leichnetz and Astruc, 1975). However, there remains a discrepancy between the anatomy and physiology for the other cerebral areas.

Not all regions of the basal and mesial cortex were tested in the present experiments. However, we believe that the only one which remains a serious candidate is the secondary somatosensory area (SII). Due to a technical error in the present experiments, the possibility of a projection from SII was not adequately examined. Based upon studies in the cat where SII was shown to be a strong input to dentate (Allen and Ohno, in preparation) and in the squirrel monkey where it was shown to influence pontine neurons (Rügg et al., 1975), SII must still be considered a potential input to the primate dentate nucleus. Another question that remains to be studied is whether there are bilateral inputs to dentate. The results obtained in the cat suggest this possibility (Allen and Ohno, in preparation).

The premotor, supplementary motor, and sensorimotor cortices project topographically onto different regions of the dentate nucleus. The neurons in the anterior portion of the nucleus tend to receive inputs from SMA, medial PM, and hindlimb areas of MI and SI, while the neurons in the posterior dentate receive inputs from lateral PM and forelimb areas of MI and SI. This topographical arrangement is especially clear in the large ventral pole of the nucleus but does not appear to hold for the dorsal poles. A similar topography was also found in the interpositus nuclei (Allen et al., 1977) where the HL cells receive their input from area 6 chiefly from SMA and medial PM and are located in the anterior-medial part of the nucleus while FL interpositus cells receive lateral PM input and are located in the posterior-lateral regions. This

suggests a rostral-caudal organization in these deep cerebellar nuclei corresponding to a hindlimb-forelimb sequence. However, the somatotopy is rather crude and shows considerable overlap as can be seen from Figure 10 and the interpositus results (Allen et al., 1977, Fig. 6). A similar somatotopy has been suggested from studies of the cerebellofugal fibers in the monkey (Flumerfelt et al., 1973; G.B. Stanton, personal communication; Chan-Palay, 1977).

Function of the Lateral Cerebellum

The lateral cerebellum performs its function based primarily upon information from areas that are functionally "pre-motor" (PM, SMA and Frontal) and secondarily upon information from MI and SI, but with no requirement for direct peripheral sensory information. By combining the evidence derived from electrophysiological studies with clinical studies, it has been proposed that the lateral cerebellum, in cooperation with area 6 and frontal cortex, is involved in the pre-programming of movement, whereas the intermediate zone of the cerebellum in conjunction with sensorimotor cortex and nerves performs an up-dating of the skilled movement as it begins and throughout its course (Evarts and Thach, 1969; Allen and Tsukahara, 1974).

Additional evidence has been obtained recently from experiments in chronic monkeys trained to execute specific movements. Thach (1970, 1975) has shown that 82% of dentate cells change their firing rate before a learned arm movement as compared to 42% of interpositus cells. Nevertheless, there was considerable overlap in the distributions of the timing. Robertson and Grimm (1975a) found that 80% of dentate cells discharged in relation to a sequential arm movement task although alterations in the limb trajectories produced little change in the discharge profiles of the dentate cells, which seemed to indicate that the dentate cells were involved in computing some general higher-order function or strategy rather than the precise specification of the muscle commands. In contrast, some interpositus cells were more closely linked to the flexion or extension phases of arm movement and discharged in relation to the length of time of flexion and extension (Robertson and Grimm, 1975b). These are found predominantly in the dorsolateral region of the posterior interpositus nucleus, the same region in which forelimb cells were found in our studies (Allen et al., 1977).

Strick (1976) has recently reported the results of recordings made in alert monkeys while they were performing an instruction paradigm (Evarts and Tanji, 1976) which dissociated the direction of the required movement from the direction of a triggering perturbation. He found that interpositus neurons discharged in relation to the direction of the externally imposed perturbation, whereas dentate cells responded at a longer latency and in relation to the direction of the required movement rather than to the direction of perturbation. This suggests that the interpositus cells are discharging in response to the sensory disturbance, while the dentate discharge is associated with the pre-programmed movement triggered by the perturbation.

The present study suggests that some neurons in dentate should be preferentially involved in the pre-programming of forelimb movements while others should be more concerned with hindlimb movements. Thus far, no attempts have been made in chronic monkeys to determine if separate populations of dentate neurons are linked to forelimb and hindlimb movements. Because the dentate neurons with forelimb and hindlimb involvement receive inputs from different regions within cortical area 6 with suspected different functions, it seems possible that forelimb and hindlimb movements may be regulated in different ways by the dentate nucleus. A similar conclusion was drawn for interpositus nucleus based upon the source of its afferent input (Allen et al., 1977).

Independent evidence suggests that the dentate coordinates the distal and proximal musculature in producing a smooth movement. Dentate nucleus contributes importantly to the regulation of movements of the distal musculature as shown by the fact that in patients with lesions restricted to the lateral cerebellum and nucleus dentatus, there are disturbances in writing and in the ability to follow a rhythmic pattern accurately with the fingers (Dow, 1969).

Recently, it has been shown in the macaque that the dentate projects secondarily to the PM cortex (medial) in addition to the MI cortex (primarily lateral) (Sasaki et al., 1976). The role of the dentate projections to PM is not clear. From clinical studies, it is known that area 6 influences posture via extrapyramidal pathways (Lance, 1970). In addition to this possible route for dentate influences, it has recently been demonstrated that there is a dentato-reticulo-spinal pathway through which the lateral cerebellum can directly influence axial and proximal muscles (Bantli and Bloedel, 1976; Schultz et al., 1976). Thus, it appears that the lateral cerebellum and area 6 have the ability to modify the posture upon which the skilled movement, involving the distal musculature, must be superimposed.

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