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Integration of Cerebral and Peripheral Inputs by Interpositus Neurons in Monkey

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Summary. The patterns of convergence of cerebral and peripheral nerve inputs onto interpositus neurons were studied in cebus monkeys. The strongest inputs to interpositus neurons are from motor and somatosensory cortex, with weaker inputs from peripheral nerves and cerebral area 6. The neurons in the anterior portion of interpositus receive cerebral and peripheral inputs primarily representing the hindlimb, while inputs to neurons in the posterior division represent forelimb or mixed forelimb and hindlimb. The hindlimb neurons integrate signals principally from motor cortex, somatosensory cortex, nerves, supplementary motor and medial premotor areas, while forelimb neurons receive inputs from motor, somatosensory, lateral premotor cortical areas and nerves. The results from this study are compared with those from studies of interpositus and dentate neurons in cat and monkey in order to determine the role of n. interpositus in movement. It is suggested that the inputs integrated by interpositus neurons are consistent with a role in up-dating skilled movements.

Key words: Cerebro-cerebellar – Interpositus – Monkey

Introduction

The role of the cerebellum in the initiation and control of movement has been a subject of much interest in recent years. Several lines of evidence derived from anatomical and physiological studies have led to the concept of a differential role of the cerebellum (Evarts and Thach, 1969; Allen and Tsukahara, 1974). According to this hypothesis, the cerebellar hemispheres, which project to the dentate nucleus, are involved in the preprograming of

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movements, while the intermediate zone projecting to the interpositus nuclei is concerned with up-dating of an on-going movement. Physiological and anatomical data supporting this hypothesis show that the inputs to the intermediate zone are derived chiefly from the primary motor and somatosensory cortical areas and from peripheral spinal and brainstem pathways while the cerebellar hemispheres receive projections from wide areas of association and primary cerebral cortex with very little peripheral inputs (Dow, 1942; Jansen, 1957; Grant, 1962; Matsushita and Ikeda, 1970; Allen and Ohno, 1973; Allen et al., 1974b, c). Two of the output nuclei of the cerebellum, dentate and interpositus, project back to motor cortex via the ventrolateral thalamus, and interpositus projects to the spinal cord via the red nucleus. Electrophysiological recordings from behaving monkeys have shown that while the motor cortical cells begin to discharge up to 100 msec prior to a movement (Evarts, 1966; 1972), the discharge of dentate neurons related to the movement begins slightly earlier than that of motor cortex cells (Thach, 1970, 1975) and the discharge of interpositus neurons follows the activity of motor cortex (Thach, 1970). However, there is considerable variability and overlap in these latency distributions. This suggests that the interpositus neurons are involved in the correction of on-going movements via peripheral feedback and motor cortex corollary discharge while dentate neurons are involved in an earlier stage of the movement, relying principally upon information from nonprimary cerebral areas.

In cats, it has been shown recently that Purkyně cells in pars intermedia of the anterior lobe and interpositus neurons receive input mainly from primary cortical areas and from peripheral nerves (Allen, Azzena and Ohno, 1972, 1974b, in preparation; Eccles et al., 1974a, b, c). The majority of interpositus cells respond to stimulation of either forelimb or hindlimb nerves and their somatotopically related areas in motor and somatosensory cortex. Only a few cells could be excited from nonprimary cortical areas. Compared to the cat, primates are much more capable of performing well-coordinated fine distal movements. This is paralleled by the great expansion of the frontal lobe as well as by the enlargement of the lateral cerebellum. It would be of special interest for the concept of the cerebellar role in movement to see how in monkeys the neuronal structures active in movement are linked together. In the present investigation we have recorded the responses of interpositus cells in cebus monkeys to electrical stimulation of contralateral primary and nonprimary cortical areas as well as ipsi- and contralateral fore- and hindlimb nerves. They were found to integrate inputs from primary cortical areas and peripheral nerves in a somatotopical manner and, to a lesser extent, from area 6 in a similar topographical pattern. A preliminary account of part of these results has previously been given (Allen et al., 1976).

Methods

Preparation. The experiments were performed on 16 male, adult capuchin monkeys (Cebus apella), weighing 1.5–2.0 kg. The animals were anaesthetized with nitrous oxide (60–80%, in oxygen), with additional administration of halothane (0.2–0.5%) during the surgical preparation. They were

mounted in a stereotaxic frame in the prone position. During recording, the animals were immobilized with Flaxedil and artificially ventilated. Expiratory CO_2-concentration (3–4%) as well as blood pressure were continuously monitored, and the experiment was discontinued whenever the mean blood pressure could not be maintained above 90 mm Hg, even by infusing small amounts of Aramine. Body temperature was controlled between 37 and 38° C. A craniotomy was performed over the right frontal and parietal cerebral cortex and the left cerebellum.

Stimulation. Single insulated steel insect needles with tips exposed 0.3 mm were inserted into 8–13 cortical sites:

1 each into the precentral gyrus (MI) where surface stimulation yielded the strongest response in finger movements (hand area) and toe movements (foot area), and in various other intermediate areas representing more proximal muscles.

1 each into the postcentral gyrus (SI) in corresponding hand and foot areas as subsequently verified with evoked responses by nerve stimulation.

1–3 electrodes into the medial wall of area 6 (supplementary motor area, SMA), one at 12.8 ± 0.7 mm anterior to the central sulcus, with the other electrodes being successively 5 mm more anterior.

3 electrodes in a medio-lateral array into the dorsolateral convexity of area 6 (premotor cortex, PM) 8.4 ± 0.6, 14.5 ± 0.7, 20.6 ± 0.6 mm lateral to the midline along the convexity and 14.3 ± 1.8, 11.7 ± 1.6, 9.7 ± 0.9 mm anterior to the central sulcus respectively.

The exposed cortical surface was covered by a low-melting point paraffin. A large indifferent electrode was placed on the temporal muscles. Each cortical site was stimulated monopolarly with paired cathodal pulses of 0.1 msec duration, 1.3 msec interval and 1.0 mA amplitude. For antidromic activation of interpositus neurons, the right red nucleus was stimulated bipolarly through needle electrodes inserted stereotaxically (Manocha et al., 1968). The sciatic as well as the common radial and the ulnar nerves of the left and sometimes right extremities were placed upon bipolar electrodes and stimulated with paired shocks, 0.1 msec duration, 2.0 msec interval, 5–10 times threshold. Proper nerve functioning throughout the experiment was assured by recording evoked responses in SI to nerve stimulation after completion of each electrode track.

Recording and Data Analysis. Glass microelectrodes (2 M NaCl, 3–4 MΩ) were driven in a horizontal plane into left nucleus interpositus. Brain pulsation was prevented by covering the cerebellar cortex with 4% agar and, when necessary, by performing a pneumothorax. Extracellular action potentials were recorded and amplified using conventional techniques and photographed from an oscilloscope. Post-stimulus time histograms (PSTHs) and their cumulative frequency distributions (CFDs) were computed with a Fabri-Tek 1062 with 64 repetitions and a bin width of 0.5 msec. The CFD was obtained from the PSTH by adding to every memory address the contents of all preceding addresses. After completion of a successful penetration, the microelectrode was cut and the shaft left in the cerebellum for later reconstruction of the track. At the end of each experiment, the animal was sacrified with an overdose of Nembutal and perfused with 0.9% NaCl solution, followed by 10% formalin. The exact location of all stimulation sites was checked after the experiment in 60 μm thick frozen sections. A three-dimensional reconstruction of the nucleus incorporating all data from the 16 animals (see Fig. 6) was achieved by aligning the different cerebella according to the ventral and dorsal poles of dentate nucleus.

Results

Basic Response Patterns

From a total of several hundred neurons, 139 interpositus neurons were selected in which responses to stimulation of all cortical and peripheral sites were tested and whose localization was verified histologically. All recordings were from cell bodies and 81% of these cells were identified as projection neurons by antidromic activation from ipsilateral red nucleus.

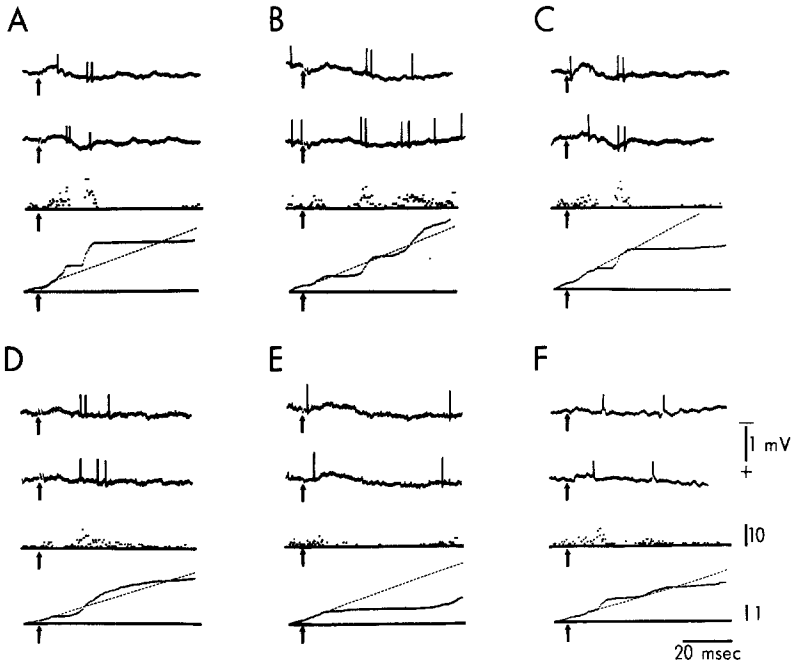

Fig. 1A–F. Response patterns of 6 interpositus neurons to stimulation of cerebral cortex and nerves. The top pair of traces are specimen records. The third row is the PSTH constructed from 64 responses. The bottom row is the CFD obtained by integrating the PSTH. The dashed line is extrapolated from the spontaneous discharge rate. All cerebral stimulating sites were contralateral to the recording electrode. **A** Stimulation of lateral precentral gyrus. **B** Stimulation of medial precentral gyrus. **C** Stimulation of lateral precentral gyrus. **D** Stimulation of lateral precentral gyrus. **E** Stimulation of medial precentral gyrus. **F** Stimulation of ipsilateral radial nerve. The time scale of 20 msec applies to all records. The calibration of 1 mV applies to the specimen records, 10 counts to the PSTH and 1 count added per stimulus to the CFD

The responses of interpositus neurons to electrical stimulation of cerebral cortex usually consisted of a combination of excitatory and inhibitory components. Figure 1A and B show the four or five basic components that constitute the typical response patterns. In Figure 1A, the response started with early excitation at 6.5 msec, followed by inhibition at 15.5 msec, another excitation at 23.0 msec, and an inhibition at 29.0 msec. The neuron of Figure 1B responded with a weak early excitation at 5.5 msec, inhibition at 10.5 msec, stronger excitation at 26.0 msec, another inhibition at 31.5 msec, and a third excitation at 45.0 msec.

The majority of responses, however, were not composed of all five components. In Figure 1C, the earliest response was an inhibition at 14.5 msec, which was followed by excitation at 21.5 msec and inhibition at 28.0 msec. The response of Figure 1D consisted only of early inhibition at 7.0 msec and subsequent excitation at 18.0 msec, followed by later weak inhibition. Numerous responses were encountered which simply displayed

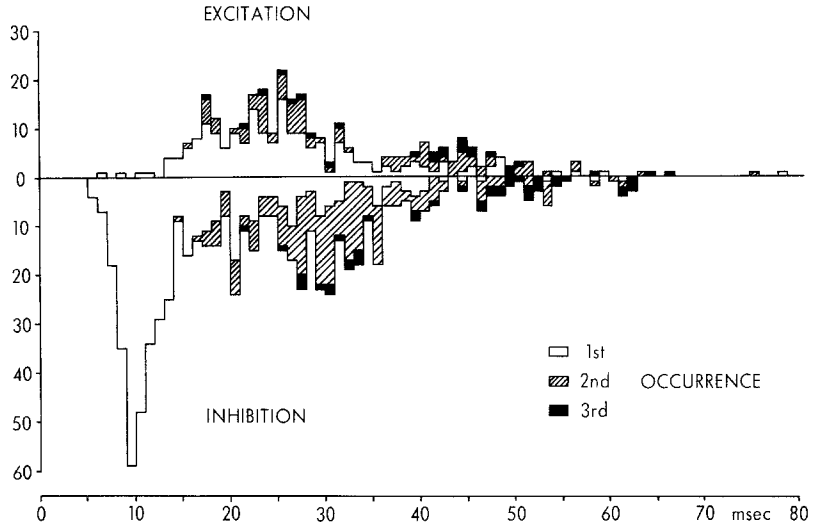

Fig. 2. Latency histogram of excitatory and inhibitory components of responses to cortical stimulation recorded from interpositus neurons. The components are marked differently according to the order in which they occurred in a given response. The first, second and third occurrences do not necessarily correspond to E_1, E_2, E_3 or I_1, I_2, I_3 respectively as defined later in the text

inhibition of shorter or longer duration arising at different latencies (Fig. 1E). Responses to electrical stimulation of peripheral nerves showed similar sequences of excitation and inhibition. In Figure 1F, stimulation of ipsilateral radial nerve elicited an excitation at 13.0 msec and an inhibition at 17.5 msec, followed by a later inhibition at 43.0 msec.

The latencies of the excitatory and inhibitory components of all responses to cortical stimulation are shown in the histogram of Figure 2. The components are marked differently according to whether they were the first, second or third occurrence of excitation or inhibition within a response. Since a response usually consisted of more than one component and a cell responded to more than one stimulation site, the number of components in the histogram surpasses the number of cells recorded. Trace responses are not included in this histogram, but they were taken into account in determining the order of a given component. The main excitation is distributed between 13.0 and 35.0 msec. In a few cases this excitation is preceded by a trace of earlier excitation as shown in Figure 1A and B. A later peak of excitation starts at 36.0 msec and generally consists of second or third excitation. A strong early inhibition occurs mainly between 7.0 and 14.0 msec. Most of the remaining inhibition is distributed between 15.0 and 42.0 msec. Within this distribution, inhibition at longer latencies is comprised of progressively higher order occurrences. The distribution of the second inhibition is displaced slightly toward longer latencies than the distribution for the main excitation.

For the following analysis the different response components are defined by their latencies in the following way: E_1 is an early, generally weak excitation

with a latency to cortical stimulation between 5.0 and 12.0 msec and not preceded by inhibition. E_2 is the main excitation arising between 13.0 msec and 35.0 msec. E_3 is the late excitation with latencies greater than 36.0 msec. Inhibition I_1 occurs between 7.0 and 14.0 msec. I_2 has a latency between 15.0 and 42.0 msec and I_3 is any inhibition later than 43.0 msec. It will be concluded in the Discussion section, in analogy to findings in the cat (Allen et al., 1972), that E_1 and I_1 are due, respectively, to early collateral activity of mossy fibers and the Purkyně cell inhibition mediated by them. E_2 is due to climbing fiber and late mossy fiber collaterals as well as to disinhibition due to basket cell inhibition and Golgi cell disfacilitation of Purkyně cells. I_2 is a Purkyně cell inhibition following climbing and late mossy fiber action. E_3 again is caused by disinhibition. I_3 is probably mediated through a polysynaptic pathway.

For a given neuron, the observed response pattern depended upon factors such as site of stimulation, strength of stimulation, and number of shocks in the stimulating train. However, when all neurons were taken together, no correlation was found between site of stimulation and response pattern. The latencies of responses evoked from the different cortical sites were very close. In particular, the mean latencies for I_1 evoked from hindlimb and forelimb motor and somatosensory cortex as well as supplementary motor cortex and premotor cortex were within a range of 1.8 msec. Intensity (1 mA) and number of shocks (2; 1.3 msec interval) were chosen so as to activate the mossy fiber and climbing fiber pathways mediating these responses, as shown in the cat (Allen et al., 1974a; Allen, Azzena and Ohno, in preparation) and as verified in the present experiments.

Total Input to a Single Interpositus Neuron

An example of the responses of an interpositus neuron to stimulation of all cortical and peripheral sites is shown in Figure 3. A stimulus to the medial part of motor cortex (A), at a point where flexion of all contralateral toes was elicited by surface stimulation, induced an early inhibition I_1 at 9.5 msec latency, followed by excitation E_2 at 27.5 msec, weak late inhibition I_2 at 35 msec and E_3 at 44.0 msec. A similar response pattern was evoked from the corresponding medial part of the primary somatosensory cortex (E) with early inhibition I_1 at 12.0 msec, E_2 at 29.0 msec and E_3 at 45.0 msec. Stimulation of a motor cortical area giving rise to a more proximal hindlimb movement (B) resulted only in a long lasting inhibition with a latency of 10.0 msec. Stimuli delivered to the more lateral portions of motor and somatosensory cortex did not evoke any change in activity of this neuron (C, D, F). Stimulation of the supplementary motor area (SMA) evoked an early excitation E_1 at 5.5 msec, followed by I_1 at 10.5 msec, E_2 at 26.0 msec, I_2 at 31.5 msec and E_3 at 45.0 msec (G). Also, from the medial part of premotor cortex a response was elicited with I_1 at 13.5 msec, E_2 at 21.0 msec, I_2 at 31.5 msec and E_3 at 45.0 msec (H), while no responses were elicited by stimulation of the more lateral premotor cortex (I, J). From the ipsilateral sciatic nerve an early

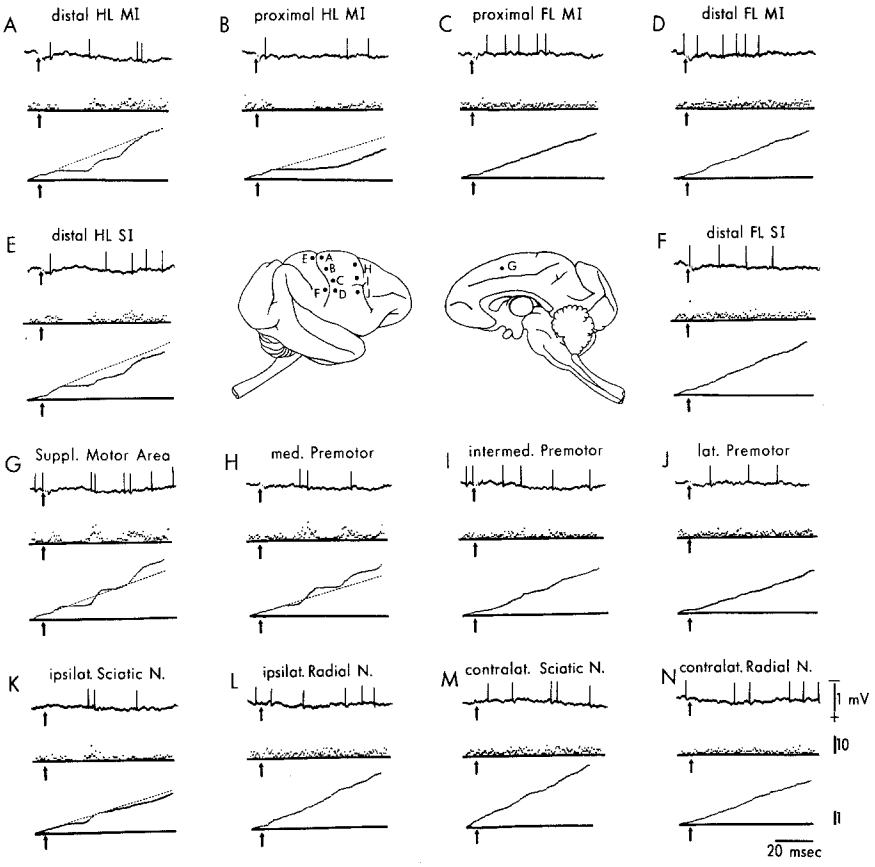

Fig. 3A–N. Responses of an interpositus neuron to stimulation of contralateral cerebral cortical areas and ipsi- and contralateral nerves. Inset shows the cortical stimulation sites from which the responses A–J were elicited. The motor cortex electrodes were inserted where surface stimulation resulted in flexion movements of toes **A**, knee **B**, elbow **C** and fingers **D**. *HL*, hindlimb; *FL*, forelimb; *MI*, primary motor cortex; *SI*, primary somatosensory cortex. **G–J** represent area 6 stimulating sites in supplementary motor area and premotor cortex. The time scale of 20 msec applies to all records. The calibration of 1 mV applies to the specimen records, 10 counts to the PSTH and 1 count added per stimulus to the CFD

inhibition was evoked at 13.0 msec, followed by excitation at 22.0 msec and inhibition at 32.5 msec (K). This neuron did not respond to stimulation of either the contralateral sciatic nerve (M) or the radial nerves on either side (L, N). In summary, this cell received a somatotopically pure hindlimb input from primary cortical areas and the peripheral nerve with an additional response to SMA and the medial part of premotor cortex.

Besides neurons related to the hindlimb as shown in Figure 3, there were also cells somatotopically related to only the forelimb. Both types of somatotopically pure cells comprised 56% of all interpositus neurons recorded. They did not always respond to all three of the somatotopically related inputs

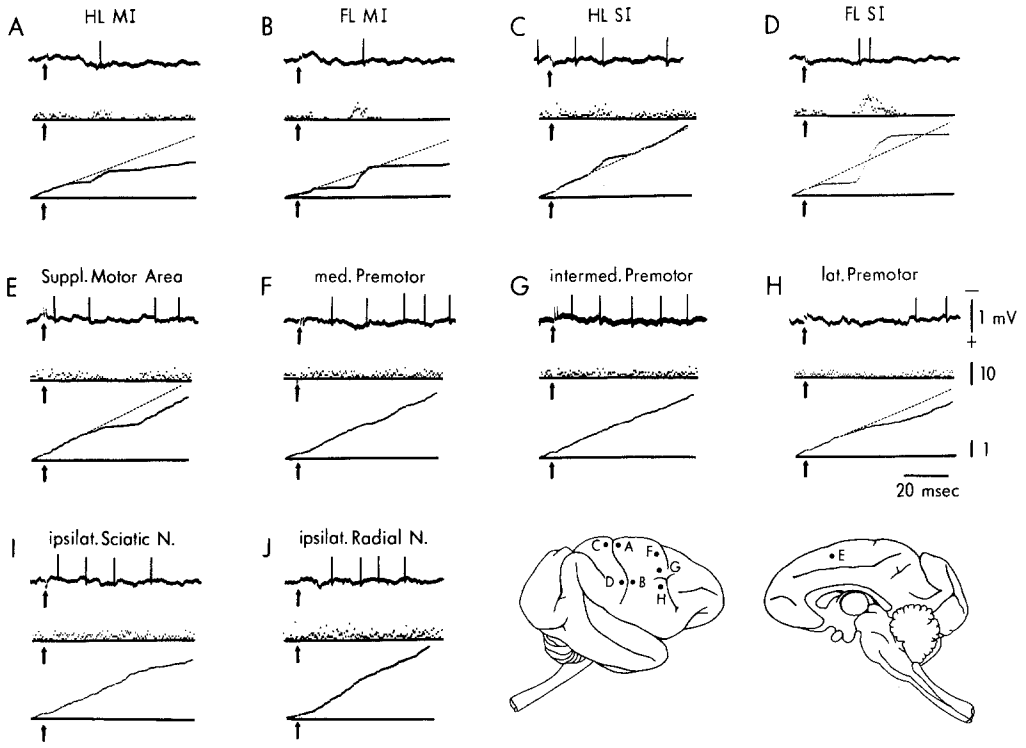

Fig. 4A–J. Responses of an interpositus neuron to stimulation of contralateral cerebral cortical areas and ipsilateral nerves. **A–H** Responses to cortical sites as shown in inset. Conventions and abbreviations same as in Figure 3. Each of the motor and somatosensory cortical areas represent the distal limb. The time scale of 20 msec applies to all records. The calibration of 1 mV applies to the specimen records, 10 counts to the PSTH and 1 count added per stimulus to the CFD

(primary motor cortex, MI; primary somatosensory cortex, SI; nerves), but often to only one or two of these inputs.

Twenty-nine percent of all neurons received a somatotopically mixed input, an example of which is shown in Figure 4. This neuron responded to stimulation of both forelimb and hindlimb motor cortex as well as the corresponding areas of somatosensory cortex (A, B, C, D). It also was activated by supplementary motor area and lateral premotor cortex (E, H). In this particular neuron, however, stimulation of peripheral nerves did not produce any response (I, J). In most cases, a "mixed" neuron did not respond to all four primary cortical stimulation sites and all ipsilateral peripheral nerves. In only three out of our 139 interpositus neurons did the nerve input not follow the same somatotopy as the cerebral cortex and thereby cause the cell to be classified as "mixed".

Interpositus neurons tended to be activated more frequently by primary areas than by nonprimary areas or by nerves. 82% were driven by motor cortex and 57% by somatosensory cortex, while 85% were activated by one or

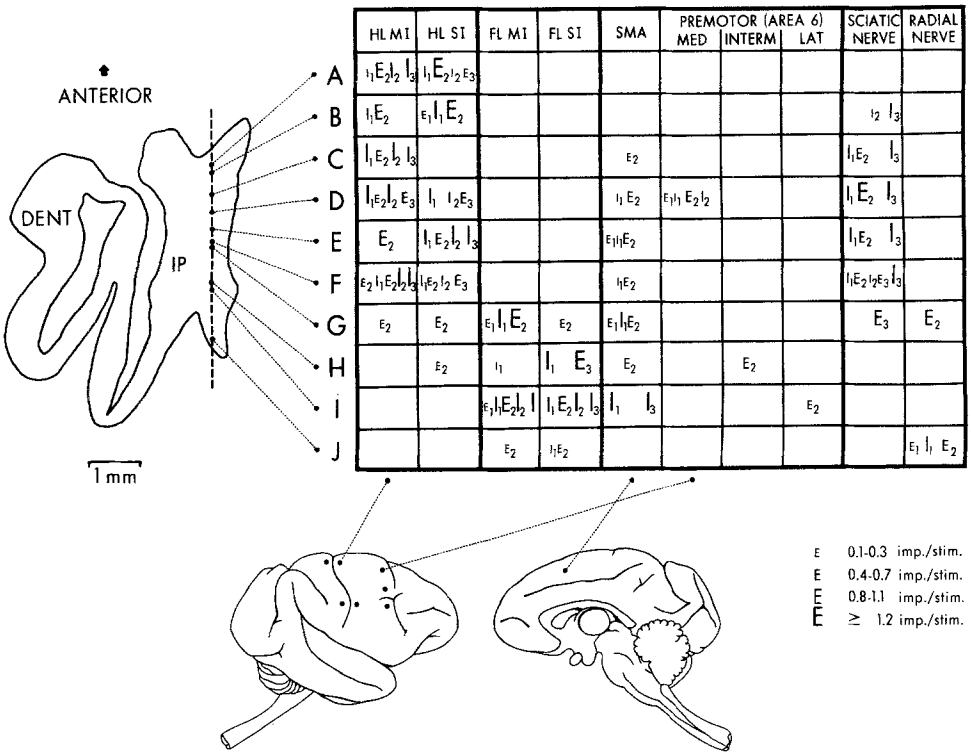

Fig. 5A–J. The responses of ten neurons sampled along one track through left nucleus interpositus in a horizontal plane. Neurons were recorded by advancing the electrode from **J** to **A.** E_1 to E_3 and I_1 to I_3 are the different phases of excitation and inhibition, respectively, as defined in the text. The size of the letters corresponds to the number of impulses added (E) or subtracted (I) per stimulus as shown in the inset. Conventions and abbreviations same as in Figure 3. SMA, supplementary motor area (medial part of area 6); Premotor area (lateral part of area 6), stimulated at medial, intermediate and lateral positions

both of these areas. Of the 15% which did not respond to stimulation of primary motor or somatosensory cortex, one third (7 units) could not be activated by any of the nerve or cortical stimuli employed. In contrast, stimulation of supplementary motor area or premotor cortex led to a response in only 32% and 42%, respectively, of all neurons, with 56% responding to one or both of these areas. 53% of interpositus neurons were driven by peripheral nerves.

Somatotopy within Nucleus Interpositus

In most histological sections, a division of the nucleus into an anterior and a posterior part is evident; this is even more apparent in the macaque (Courville and Cooper, 1970) and leads to the appearance of two distinct nuclei in

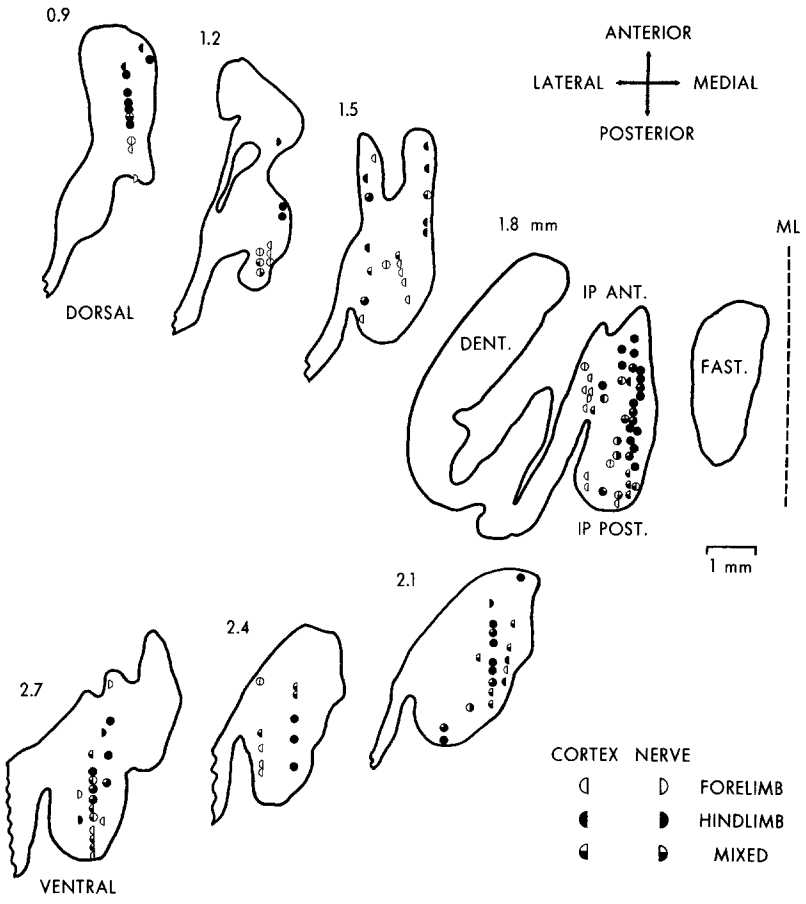

Fig. 6. Three-dimensional reconstruction of nucleus interpositus showing all neurons responding to primary motor or somatosensory cortex or nerves or both. The location of all neurons from all experiments was projected onto the appropriate section in a model nucleus. The sections were aligned according to their relative distance from the dorsal pole of dentate. The absolute distance from the dorsal end of dentate in the model nucleus is indicated with each section (0.9–2.7 mm). It was essential for the reconstruction that all of our neurons showed negative or negative-positive spikes and could be easily held for one hour or more, indicating that the recordings were taken from the somata. Trace responses were eliminated in computations for Figs. 6–8

humans, nuclei emboliformis and globosus. Since all penetrations were made in a horizontal plane, it was possible to sample both the posterior and anterior subdivisions in most electrode tracks. Figure 5 shows a typical track. The first cells encountered (I, J) received input from areas of motor cortex (MI) and somatosensory cortex (SI) representing the forelimb. Neuron J also had a forelimb nerve input. Upon advancing the electrode into more anterior portions of the nucleus, neurons were encountered that were driven by cortical areas representing the hindlimb (Fig. 5A–F). Cells B to F also received nerve inputs from the hindlimb. In the transition zone, cells G and H had

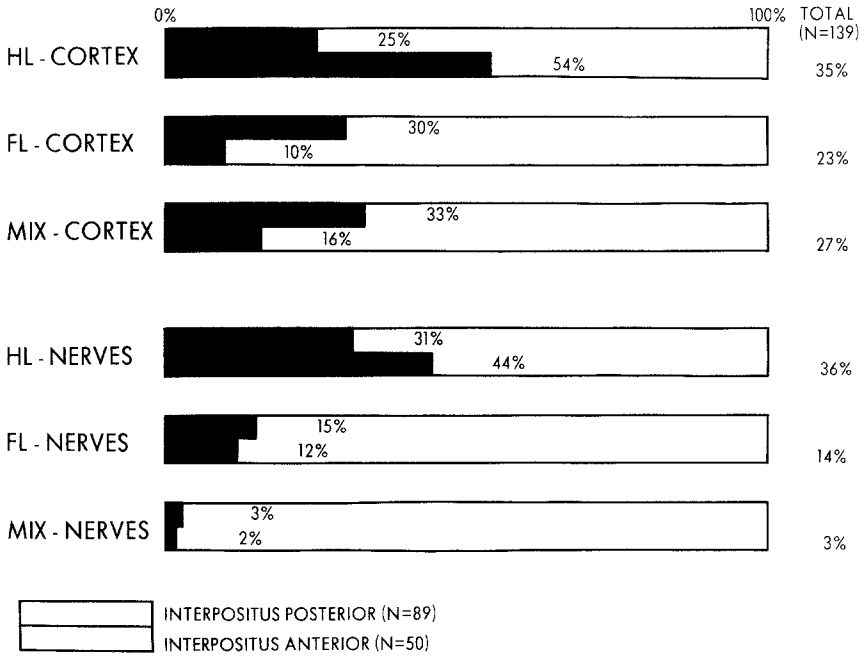

Fig. 7. Percentages of interpositus neurons in posterior and anterior divisions receiving inputs from primary cortical areas and nerves. Considering separately the cortical and nerve inputs, these bar histograms show the number of neurons responding to hindlimb inputs only (*HL*), forelimb inputs only (*FL*) and to both hindlimb and forelimb inputs (*MIX*). Cortical inputs were from contralateral primary motor and/or somatosensory cortex, nerve inputs from ipsilateral sciatic (hindlimb) and radial or ulnar nerve (forelimb)

somatotopically mixed cortical as well as nerve input. In this track, most cells could also be activated by stimulating SMA and a very few (D, H, I) responded to stimulation of premotor area.

The fine somatotopic projection pattern to interpositus nucleus as seen in Figure 5 was substantiated in a three-dimensional reconstruction (Fig. 6). Here, the results from all experiments were plotted on typical horizontal sections through the nucleus. The cells along each track were located on the horizontal section chosen according to the dorso-ventral position and nuclear morphology. Neurons receiving input from hindlimb nerves (closed, right half circles) or hindlimb areas of the primary cerebral cortex (closed, left half circles) were situated chiefly in the anterior medial part of the nucleus, whereas neurons related to forelimb nerves (open, right half circles) or cortex (open, left half circles) were found predominantly in the posterior-lateral part of the nucleus. Neurons of mixed input (half-filled circles) occurred most frequently in the posterior nucleus. It can be seen that a somatotopic differentiation was not apparent along the dorso-ventral axis of the nucleus.

A statistical analysis of the somatotopy of nerve and cortical inputs to interpositus neurons in the anterior and posterior subdivisions substantiated

the above described organization. As shown in Figure 7, hindlimb cortical areas and hindlimb nerves project more frequently to anterior interpositus neurons, whereas stimulation of forelimb and mixed cortical input activates neurons in posterior interpositus more frequently. Cells receiving input from forelimb or from both forelimb and hindlimb nerves, i.e., "mixed" nerve input, are relatively rare, but evenly distributed throughout the nucleus. As was stated above, nerve somatotopy followed cerebral somatotopy in every case but three. Therefore, the conjoint cerebral and nerve somatotopy follows essentially the same pattern as for cortex alone. Although not shown in Figure 7, there were no major differences in the frequencies of inputs from either MI or SI to the three somatotopically related groups of interpositus neurons, i.e., hindlimb, forelimb and mixed.

Differentiating the Input from Nonprimary Cortex

The cortical area 6 can be subdivided into supplementary motor area (medial wall) and the premotor area (dorsolateral convexity) (see Jones and Powell, 1970; Wiesendanger et al., 1973). The supplementary motor area was stimulated with 1–3 electrodes in an anterior-posterior array and the premotor area at three points in a lateral-medial line. The anterior and posterior subdivisions of interpositus receive equal input from the medial premotor area (24%), whereas the intermediate and lateral parts of premotor area activate more cells in the posterior subnucleus (20% and 26%, respectively) than in the anterior (8% and 12%, respectively).

A more distinct pattern emerges when interpositus neurons of different forelimb/hindlimb somatotopy are compared in terms of their inputs from area 6 (Fig. 8). Cells designated as forelimb neurons by their input from primary cortical areas and nerves receive a much greater projection from PM (55%) than from SMA (15%), whereas hindlimb cells receive about an equal number of SMA (35%) and PM (27%) inputs (Fig. 8A). A topographic projection within the premotor area itself to interpositus can be seen from Fig. 8B. Forelimb neurons tend to respond to stimulation of lateral premotor cortex (45%) more than intermediate (15%) or medial (18%) while hindlimb cells respond more often to medial premotor cortex (24%) than to intermediate (6%) or lateral premotor (2%). Thus, "hindlimb" cells receive their major afferents of secondary cortical origin from supplementary motor area and the medial part of premotor cortex, whereas, "forelimb" cells have secondary cortical input mainly from lateral premotor cortex.

Peripheral nerves and area 6 converge differently onto forelimb and hindlimb related interpositus neurons (Fig. 8C). "Hindlimb" cells were mostly driven by nerves with or without additional input from area 6 (37% and 33%, respectively), and only 10% were activated by area 6 stimulation alone. The largest proportion of forelimb related neurons, however, were driven by area 6 alone (39%), fewer by area 6 and nerves (24%), and the smallest percentage received input from nerves alone (12%). "Mixed" cells showed a somewhat intermediate convergence pattern (Fig. 8C). Thus, forelimb cells tend to

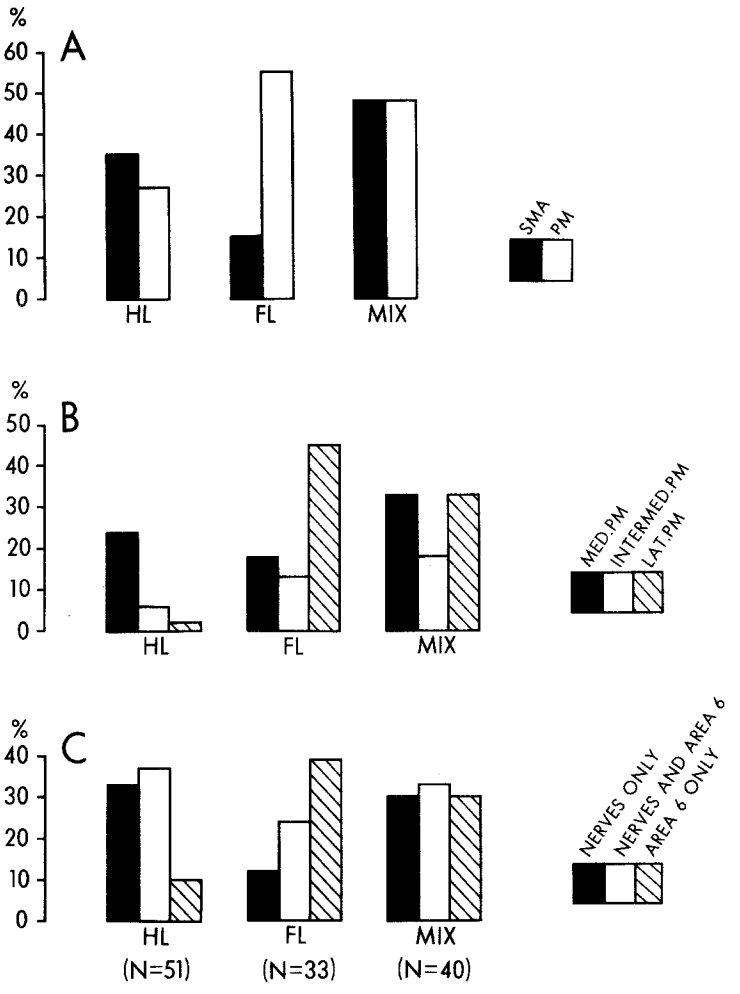

Fig. 8A–C. Input from area 6 to cells of different somatotopy. The somatotopy of the individual neuron was established by its inputs from primary motor and somatosensory cortex and peripheral nerves. **A** The projection of supplementary motor area (*SMA*) and premotor cortex (*PM*) onto cells having hindlimb (*HL*), forelimb (*FL*) or mixed (*MIX*) somatotopy. **B** The input from three different stimulation points in premotor cortex (medial – intermediate – lateral) to interpositus cells of different somatotopy. **C** The percentages of responses to nerve and area 6 (SMA and/or PM) stimulation seen in interpositus neurons of different somatotopy

receive their secondary input more from area 6 than from peripheral nerves, whereas the opposite obtains for hindlimb cells.

Other areas of the cerebral cortex were stimulated in a few monkeys to test for the possibility of projections to interpositus nucleus: the secondary somatosensory area (SII) of the posterior superior temporal gyrus (Woolsey, 1958); areas 5 and 7 of the parietal lobe lying on both sides of the intraparietal

sulcus; and the frontal lobe immediately anterior to the arcuate sulcus and lying on both sides of the principal sulcus (area 9 of Brodmann (1909), areas 9d, 9c and 9a/6aβ of Vogt and Vogt (1919) and areas 46 and 8B of Walker (1940)). Of the 41 cells in 6 monkeys examined for inputs from SII, only 1 responded (2%). Parietal and frontal inputs were studied in 21 neurons in 2 monkeys, with no responses.

Discussion

Response Pattern of Interpositus Neurons

The typical response of an interpositus neuron to cerebral cortical stimulation consisted of sequences of excitation and inhibition. In the cat, different conduction velocities of neurons along the cerebro-cerebellar pathway as well as cerebellar network properties provide the underlying mechanisms (Allen, Azzena and Ohno, in preparation). The early excitation E_1 has been attributed to activation by mossy fiber collaterals of the fast cortico-reticulo-cerebellar and, to a lesser extent, the fast cortico-ponto-cerebellar pathways. The subsequent inhibition I_1 is caused by Purkyně cells (Ito et al., 1970) which are activated by early mossy fiber inputs through lateral reticular and pontine nuclei. E_2 was suggested to result from several factors: excitation from collaterals of climbing fibers of inferior olivary origin and later mossy fibers mainly of lateral reticular origin, and disinhibition due to the direct action of basket cells and the indirect action of Golgi cells on the Purkyně cells (Eccles et al., 1967; Allen and Ohno, in preparation). I_2 is due to the influence of Purkyně cells activated by climbing and late mossy fibers. E_3 presumably results from disinhibition mediated by slow mossy fiber and climbing fiber input. The different latencies of E_1 and E_2 result from the fact that the pontine and LRN fibers contributing to E_1 are excited monosynaptically by the fast conducting pyramidal tract fibers, while the climbing fibers contributing to E_2 are excited polysynaptically by the slow PT fibers (Kitai et al., 1969; Allen et al., 1974a). Late mossy fibers contributing to E_2 are presumably excited polysynaptically.

Although these details have been worked out mainly in cats, there is reason to believe that similar mechanisms underlie the observed response patterns in primate interpositus neurons. The two groups of pyramidal tract fibers in cat, which mediate the cerebro-cerebellar connections, have conduction velocities of 5–17 m/sec and 18–72 m/sec (Kitai et al., 1969). Although, to our knowledge, similar studies have not been carried out in primates, there also seem to be two classes of pyramidal tract neurons, conducting with about 14 m/sec and 59 m/sec (Patton and Amassian, 1960). Therefore, the conduction velocities of the two groups of pyramidal tract neurons concerned with cerebro-cerebellar connections are very similar in the two species. Although the brain of a cebus monkey is considerably larger than that of a cat, the pathways from motor cortex and area 6 to the cerebellum are of similar length, due to the fact, that these cortical areas are located at different anterior-posterior positions in the two animals. The fact that the latency values

for the components E_1, I_1, E_2, I_2, E_3 were higher in this study on primates than in the previous report on cats suggests that there exists in each fiber population a larger amount of slower conducting elements in primates. For example, E_2, with a latency range from 13.0 msec to 35.0 msec, and I_2, with values from 15.0 msec to 42.0 msec, occur remarkably later and more dispersed in time than in the cat, where the values were 9.5–16.0 msec for E_2 and 16.0–28.0 msec for I_2 (Allen, Azzena and Ohno, in preparation).

Integration of Cerebral and Peripheral Inputs

This study has shown that the most frequent and strongest inputs to interpositus neurons are from MI and SI, with weaker inputs arising from peripheral nerves. Of the higher order cortical areas, responses could only be obtained from area 6. The neurons located in the anterior portion of interpositus tend to integrate primary cortical and peripheral inputs representing the hindlimb, whereas neurons in the posterior part are primarily related to the forelimb. Neurons receiving both hindlimb and forelimb information also tend to lie in the posterior nucleus. The HL neurons integrate signals principally from MI (96%), SI (65%), nerves (70%), SMA (35%) and medial PM (24%) in performing their function. By contrast, the FL neurons integrate signals from MI (94%), SI (59%), lateral PM (45%) and nerves (36%). Thus, it is clear that the cerebral projections to interpositus from area 6 follow the same medial-lateral topography as from areas 4 and 1–2–3: the medial regions of area 6 (SMA and medial PM) influence the same interpositus neurons as medial motor and somatosensory cortex, whereas another set of neurons are activated by the lateral zones of PM, motor and somatosensory cortex. This cannot be explained by spread of stimulating current from area 6 to motor cortex. The area 6 electrodes were 7–13 mm posterior to the electrodes placed in the optimal points in the motor cortex, which is considerably more than the 2.0 mm effective spread found for a stimulus strength of 1 mA (Ranck, 1975). Histological observations, designed to examine the cytoarchitecture, confirmed that the premotor and SMA electrodes were in area 6 (see also Bucy, 1935; von Bonin, 1938; Rosabal, 1967). It is also unlikely that area 6 influences interpositus neurons through a relay in areas 4 and 1–2–3 without significant direct projections from area 6 to the brain stem pre-cerebellar nuclei. No significant differences were observed for latencies of responses evoked from primary cortex and area 6, as would be necessary. In addition, neurons responded to stimulation of area 6 that did not respond to areas 4 or 1–2–3. Both anatomical and electrophysiological studies have shown that area 6 projects directly to the pontine nuclei in monkey (Nyby and Jansen, 1951; Rüegg et al., 1975). In the companion study to this one, area 6 was shown to project to dentate in cases where it was clear that there was no MI or SI input (Allen, Gilbert and Yin, in preparation).

There is a distinct difference between interpositus and dentate neurons in terms of the inputs that they integrate and the topography of the projections (Allen, Gilbert and Yin, in preparation). The most frequent and strongest

inputs to dentate neurons are area 6 (PM, 64%; SMA, 50%) with additional inputs from MI (32%) and SI (20%) but almost nothing from peripheral nerves (6%). Although a clear somatotopy of MI and SI inputs to dentate was not apparent, the topography of area 6 inputs was comparable in the two nuclei: SMA and medial PM tended to project to more rostral regions while lateral PM projected to more caudal regions.

Function of the Intermediate Cerebellum

By combining the knowledge derived from electrophysiological studies on cerebellar nuclei with clinical studies and recordings from chronic monkeys, it has been proposed that the lateral cerebellum is involved in the preprograming of movement, whereas, the intermediate zone of the cerebellum performs an up-dating of the skilled movement as it begins and throughout its course (Evarts and Thach, 1969; Allen and Tsukahara, 1974). The results of the present study suggest that there is a clear tendency for topography along the input pathways to interpositus. Thus, the somatotopical organization may be functionally important for the performance of the intermediate cerebellum. Recent anatomical evidence suggests that there is a corresponding somatotopy along the pathway from interpositus to motor cortex, a prerequisite for the hypothesized loop operation. In the rhesus monkey, G.B. Stanton (personal communication) has found that rostral and caudal anterior interpositus project to the zones in VL thalamus considered to project to the hindlimb and forelimb areas of the motor cortex, respectively.

In ascending the phylogenetic scale from cat to monkey to man, there is an increase in the size of dentate nucleus with respect to interpositus that parallels the increasing ability to perform fine skilled movements. From cat to man, the number of cells in interpositus only increases by a factor of 3, but dentate increases from smaller than interpositus to 10 times as large (Allen and Tsukahara, 1974). The dentate nucleus develops in parallel with and receives its primary input from the frontal association cortex which is considered to have an important role in planning a movement (Deecke et al., 1969; Kubota and Niki, 1971; Ingvar and Schwartz, 1974). Thus, in ascending the phylogenetic scale, there is a shift toward dentate's function – apparently preprograming – and less emphasis on interpositus' function – up-dating of movement. The apparent shift in emphasis of the cerebellar nuclei toward preprograming is not only expressed by the relative decrease of interpositus but also by the increasing inputs from non-primary cortical areas and weaker inputs from peripheral nerves to this nucleus. With better preprograming, an up-dating of movement using peripheral input may become less necessary. Incorporation of information about the next phase of movement by inputs from area 6 may then make an important contribution to the control of complex, sequential movements. This shift is greatest for the FL interpositus neurons of monkey (Fig. 8C) which coincides well with the fact that in primates the greatest skills in performing fine movements become evident in the forelimb. Further insight into the role of the pars intermedia in movement

control will require an understanding of the contributions made by the area 6 inputs. It will be crucial to use anatomical and electrophysiological techniques to determine the input and output relations of area 6, and chronic recording techniques in behaving animals to determine the function of area 6 neurons in relation to movement.

Mixed units. What is the significance of the units with cerebral and/or peripheral inputs representing both forelimb and hindlimb? In the cebus monkey, the zone of mixed FL/HL cells does not lie principally between the FL and HL populations, but rather tends to overlap the forelimb population. It is worth noting that the percentage of mixed FL/HL neurons in interpositus does not decrease drastically in ascending the phylogenetic scale from cat to monkey, although the somatotopy along sensorimotor pathways becomes sharper and the ability for independent skilled movements of a single limb increases. Thus, it seems more likely that the mixed FL/HL cells are a separate population with a specific function. These neurons could perform a function requiring the integration of both FL and HL inputs. Because of the wider body representation, it is conceivable that these neurons provide information necessary for the regulation of more proximal muscle groups (Eccles et al., 1975).

Comparison with Recordings in Chronic Monkeys

Thach (1970) found that in rhesus monkeys performing a quick wrist flexion or extension in response to a light signal, interpositus neurons initiated their discharge as early as 70 msec before the movement to as late as 70 msec after the movement onset. The afferent connections of primate interpositus shown in this study may provide some insight into the underlying mechanisms. Discharges beginning after the movement may be initiated by activity in peripheral afferents, or by input from neurons in the somatosensory cortex which are active after the movement occurs (Evarts, 1972). Interpositus discharges before the movement may be due to the action of cerebro-cerebellar pathways from the motor cortex, whose neurons are active up to 80 msec before the movement begins (Evarts, 1966, 1972). This activity may also be caused in part by inputs from premotor and supplementary motor areas.

Robertson and Grimm (1975; personal communication) found in squirrel monkeys performing a sequential button-pushing task with the forelimb that there are two types of large, presumably projection neurons in interpositus – those discharging or silencing tonically throughout the movement, and those discharging phasically during either the extension or flexion components of the movement. The neurons with the tonic discharge pattern for this forearm movement are uniformly distributed throughout the nucleus. For the neurons discharging phasically during the movement, only those related to flexion are found in the posterior nucleus, while neurons related to flexion or extension are found in the anterior nucleus. Since those studies were performed on a closely-related species, the results are surprising because from the present

study it would have been anticipated that only the activity of posterior neurons would be closely correlated with the forelimb movements.

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