Organization of Reaching and Grasping Movements in the Primate Cerebellar Nuclei as Revealed by Focal Muscimol Inactivations

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Mason, Carolyn R., Lee E. Miller, James F. Baker, and James C. Houk. Organization of reaching and grasping movements in the primate cerebellar nuclei as revealed by focal muscimol inactivations. J. Neurophysiol. 79: 537–554, 1998. Two monkeys were trained to point to targets and to retrieve fruit bits from a Klüver board, bottles, and tubes. Once proficient in the tasks, the macaques underwent aseptic surgical implantation of a recording chamber over the cerebellar nuclei on the side of their preferred hand. After recovery from surgery, a series of mapping penetrations were completed to identify task-related areas within the cerebellar nuclei. Muscimol (4–16 μg; 1–2 μg/μl) was pressure injected at different sites within the forelimb zone, and the resultant deficits were observed as the monkeys performed the behavioral tasks. Quantitative measures of task performance were supplemented by direct observation of live and videotaped performance. The locations of nuclear inactivation sites were reconstructed from marking lesions and tracks visible in histological sections. Injections placed in the cerebellar interpositus nucleus and adjacent regions of dentate caused a variety of deficits in forelimb function. A prominent anteroposterior specialization was apparent within the forelimb zone of this intermediate nuclear region. Injections into the anterior interpositus nucleus and adjacent dentate impaired preshaping of the hand and the manipulation of objects, whereas injections placed more posteriorly in posterior interpositus nucleus and adjacent dentate produced deficits in the aiming of reach and the stability of the arm. During anterior injections, the monkeys failed to adequately extend their fingers in preparation for target contact, as documented for >85% of the reaches in the pointing task of monkey J. Up to 38% of the fruit bits it attempted to retrieve from the Klüver board were dropped. In comparison, during posterior inactivations, 15% were dropped and during control conditions 3% were dropped. The monkeys made significantly greater pointing errors during posterior inactivations (11 times for monkey J and 4 times for monkey C) than during anterior inactivations (8 times for monkey J and 2 times for monkey C). We refer to the region producing hand deficits as the anterior hand zone and the region producing reaching deficits as the posterior reach zone. These results are discussed in relation to the problem of achieving spatiotemporal coordination in the large population of nuclear cells that participate in any given movement. The results do not favor the hypothesis that coordination is achieved through a selection of Purkinje cells along beams of parallel fibers. Instead, it is proposed that distal and proximal musculature is coordinated by the adaptive influences of climbing fiber input to Purkinje cells. We envision a relatively nonspecific recruitment of anterior and posterior nuclear cells due to positive feedback in the limb premotor network, which then is shaped into an appropriate spatiotemporal pattern of discharge through the inhibitory input from Purkinje cells.

INTRODUCTION

Experimental evidence from a variety of techniques has established a mediolateral organization of the primate cerebellum, dividing the cerebellar cortex and the underlying deep nuclei into three functional zones. The most medial zone consists of the fastigial nucleus and the overlying vermal cortex. This zone projects to the medial descending system, which mainly is involved in the control of posture and locomotion (Kuypers 1981). Monkeys with their fastigial nuclei removed (Carrea and Mettler 1947) or inactivated (Thach et al. 1992b) have difficulty sitting unsupported, standing, or walking.

The intermediate zone of the primate cerebellum, which is the subject of the present study, includes the anterior and posterior interpositus nucleus (NIA and NIP, respectively) and the paravermal cerebellar cortex that projects to these nuclear areas. Adjacent regions of the dentate nucleus exhibit similar properties (Goldberger and Growden 1973; Leiner et al. 1989; van Kan et al. 1993b), suggesting that they be included as part of the intermediate zone. Like NIA and NIP, these regions of dentate project to the magnocellular red nucleus (Kennedy et al. 1986) and to the primary motor cortex by way of ventrolateral thalamus (Middleton and Strick 1997). Through these projections to rubrospinal and corticospinal pathways, the intermediate zone is poised to control the independent use of the limb in reaching and grasping (Kuypers 1981). Lesions centered on the intermediate zone in monkeys result in impaired reaching and poor use of the digits (Growdon et al. 1967; Mackel 1987).

The lateral cerebellar zone consists of the cerebellar hemisphere and most of the dentate nucleus. Leiner, Leiner, and Dow (1989) noted that dentate is composed of a phylogenetically older dorsomedial division and a newer ventrolateral division, the latter increasing in size in parallel with the frontal lobe. The ventrolateral division projects to premotor and prefrontal areas and is thought to participate in higher motor and cognitive functions (Leiner et al. 1989; Middleton and Strick 1997; Rispal-Padel 1993). This major part of dentate can be considered the nuclear component of the lateral zone of the cerebellum, leaving dorsomedial dentate as part of the intermediate nuclear zone.

A variety of evidence supports the concept that each of these functional zones contains at least one map of the body musculature (Rispal-Padel 1993; Thach et al. 1992a,b). According to Thach’s analysis of these data, each of the cerebellar nuclei contains a complete map of body parts with the leg located anteriorly, the arm at intermediate sites, and the head located posteriorly. Thach and colleagues further proposed that the myotomes within a given body part are represented along mediolateral gradients in the cerebellum, which could allow parallel fibers to coordinate muscle synergies about proximal and distal joints.
Microelectrode recordings from the intermediate nuclear zone (Thach et. al. 1993; van Kan et al. 1993b) confirmed the presence of a leg representation anterior and an arm representation posterior within NIA and adjacent parts of dentate. Within NIP and adjacent dentate, many additional arm-related cells were found mixed with a few leg-related cells, and head-related units were found in the most posterior regions of NIP. In the forelimb regions of both NIA and NIP, the most intense unit activity was noted during multijoint movements as opposed to single-joint motion (van Kan et al. 1993b). Individual neurons were not specifically related to motion about individual joints (Thach et. al. 1993; van Kan et al. 1993b), suggesting that a finer representation of the forelimb may not be present in the intermediate nuclear zone. Subsequent studies stressed the importance of including a component of hand use for obtaining high-frequency discharge in both NIA and NIP (Gibson et al. 1996; van Kan et al. 1994).

None of the single-unit recording studies have addressed the variety of movements made by the fingers and wrist in their analyses of the topography of the interpositus and dorsomedial dentate. As a result, it would have been difficult to discover a finer representation within the forelimb zone. However, focal electrical stimulation within interpositus caused movements of single joints, suggesting the possibility of a finer representation of movements within the individual limb regions (Rispal-Padel et al. 1982, 1983). Within the arm zone, stimulation in the center of NIP produced shoulder movement, whereas stimulation of ventral NIA and dorsal NIP produced different kinds of finger and hand movement.

The present experiments were undertaken to clarify the organization of the intermediate nuclear zone, composed of NIA, NIP, and adjacent regions of dentate. In particular, we sought to determine if there is any specialization in function along the considerable anterior to posterior dimension of the intermediate forelimb zone. To address this issue, we first mapped the intermediate zone of the cerebellar nuclei with microelectrodes while the monkeys performed several forelimb motor tasks. We then used microinjections of muscimol at several physiologically identified sites to produce discrete reversible inactivations, and we assessed the resulting deficits in forelimb skills and in task performance. The results demonstrate a clear anteroposterior specialization of function within the forelimb representation of the intermediate zone. At sites in NIA and adjacent regions of dentate, muscimol produced deficits in hand shaping and manipulation, whereas injections more posteriorly, into NIP and adjacent regions of dentate, caused aiming errors and problems with arm stability. Our results also support a finer representation of function within the hand portion of the intermediate zone.

**METHODS**

**Behavioral task description**

Two male macaques were trained in a variety of behavioral tasks. The first animal, monkey C, was a Macaca fuscata weighing 5.5 kg. The second, monkey J, was a M. mulatta weighing 7.5 kg.

**POINTING TASK.** The equipment for the pointing task was a touch pad and target array. The touch pad was a capacitive proximity detector that was positioned by the monkey’s side at waist level. The monkey’s hand rested easily on it out of view. The target array consisted of a 6 × 6 grid of capacitive proximity detectors, each 2.5 × 2.5 cm. Embedded in each of the central 16 touch detectors was a green target light emitting diode (LED). This allowed reaching errors to be detected in all directions around a given LED (Fig. 1A). The target array was oriented vertically and positioned in front of the monkey at a comfortable reaching distance (Fig. 1B).

The trial began with the monkey contacting the touch pad for a random period of 1 ± 0.5 s (mean ± SD). A target LED then would turn on. The monkey was trained to touch the square containing the target LED and return to the touch pad (Fig. 1C). The target LED turned off when the monkey made contact with the target array or after the upper limits of the allotted response time (0.5 s for monkey C and 0.7 s for monkey J). Each monkey was rewarded on a variable schedule. For monkey C, a random number was generated between two and five inclusive. For monkey J, the number was between two and four inclusive. Each monkey had to have a series of correct touches equal to the random number to be rewarded with a drop of water or juice.

**BOTTLE TASK.** Various bottles were used to assess the monkey’s ability to aim correctly for the bottle and shape its hand properly for insertion into the bottle. The successful removal of the fruit bit from inside the bottle also gave an indication of how well the monkey was manipulating small objects. All the bottles were opaque except for the largest one. Opening sizes were 2, 3.2, 3.7, and 6.8 cm. The smaller openings required better aim and hand shaping than did the larger openings. The bottles typically were offered to the monkeys at a comfortable reaching distance in front of them. At times, bottles were held on the fringes of their work space.

**TUBE TASK.** Monkey C failed to retrieve fruit bits from the bottles during some inactivations, but the opaqueness of the bottles prevented observing the suspected impairment of hand function. Consequently, the tube task was introduced with monkey J to enable the investigator to observe the monkey’s hand function when the monkey’s view of its hand was obstructed. Each tube had a vertical face plate with an opening to the tube (Fig. 1D). The transparent tube extended away from the monkey perpendicular to the face plate. An opaque sliding door was positioned in slots 1.2 cm in front of the tube opening. The door was opened manually by the investigator sliding it laterally. An infrared diode and phototransistor detector were located above and below the opening between the door and the tube. The detector picked up three levels of signal. The lowest level indicated the door was closed. An intermediate level indicated the open door, and the highest level indicated when the sensor was occluded by the monkey’s limb. The monkey’s performance could be timed by the level changes. After a random interval of contact with the touch pad by the monkey, the door was opened and the monkey was given the opportunity to retrieve the fruit bit. If successful, the monkey placed the fruit bit in its mouth before returning to the touch pad (Fig. 1F).

Several different tube designs were used to emphasize different aspects of reaching and hand function. The smallest tube opening (3.2 cm diam) emphasized aiming and proper shaping of the hand for entry but severely restricted hand function in the 3.2-cm diam tube. The other opening size (5.8 cm diam) was more forgiving of aiming deficits and poor hand shape during entry, emphasizing the monkey’s function in the larger tube (7 cm diam) beyond the opening. One tube had a shelf located on the right side of the tube, 8.5 cm beyond the opening, midway up the tube (Fig. 1E). The shelf, 1.5 cm deep and 2.5 cm long, was out of sight of the monkey. With practice, the monkey was quite skilled at removing the fruit bit from the shelf. This tube design enabled us to observe both reaching and hand deficits. The monkey needed to be able to hold the forelimb steady to use the precision grasp to pick up the fruit bit. If the monkey knocked the fruit bit off the shelf, it needed to be able to find the bit and pick it up. The monkey’s search...
Electrophysiological recordings techniques could be monitored. A third tube had no shelf but a screw and nut partially imbedded in dental cement on cardboard inserted on the bottom of the tube to test the monkey’s ability to distinguish and to retrieve the fruit bit from amid the confounders. Observations of the hand deficits of monkey C suggested it was not able to make use of cutaneous inputs.

Surgery

After training, the monkeys underwent surgery for implantation of a recording chamber and head holder. Under halothane anesthesia and aseptic conditions, a stainless steel recording chamber was placed over the parietal lobe ipsilateral to the trained limb in stereotaxic alignment with the deep cerebellar nuclei, ~8 mm posterior and 3 or 4 mm lateral. The chamber of first monkey was vertical in the sagittal and frontal planes. The angle of penetration of the second monkey slanted 5° anteriorly and 5° medially. All hardware was anchored with bone screws and dental cement. Both monkeys were treated with the prophylactic antibiotic cefazolin (Ke¯ex 35 mg/kg im) before and after surgery. Monkeys received buprenorphine hydrochloride (Buprenex: 0.01 mg/kg im) for pain control for 2–3 days after surgery. For all behavioral tasks, the monkeys sat in a primate chair with their heads fixed.

Electrophysiological recordings

A series of mapping penetrations was made to identify the subdivisions of the cerebellar nuclei on the basis of their single and multunit activity. This tentative identification was histologically confirmed later after the animal had been sacrificed. We recorded neural activity with epoxy-coated tungsten microelectrodes mounted in a modified Narashige microdrive while the monkey performed the pointing task described earlier. Electrode penetrations passed through parietal cortex and into the cerebellar cortex, which was identified on the basis of the characteristic Purkinje cell and granular layer activity (van Kan et al. 1993a). Upon exiting the cerebellar cortex, the electrode would pass through 1–2 mm of relatively quiet white matter with only an occasional fiber potential. Penetration of the nucleus would result in a sudden increase in activity. Single units had burst firing rates that could reach 200-400 spikes/s and spike amplitudes ≈1 mV. The relation between neural activity and the monkey’s behavior was determined, and, if an isolated unit was well related to the tasks, one or more data files were recorded.

As in a previous study from this laboratory (van Kan et al. 1993b), the interpositus nucleus and adjacent regions of dentate were recognized readily by the presence of neural activity related to voluntary movements of the forelimb. In addition, we found that recordings from posterior sites typically evoked activity during the transport phase of the pointing task as illustrated in Fig. 2A, whereas anterior recordings were better related to contact with the target array (Fig. 2B) and other activities that used the hand (illustrated later). These recording were an invaluable aid to the placement of muscimol injections.

Muscimol inactivations

Several weeks to months after the mapping penetrations, muscimol was injected at various nuclear locations through a cannula mounted on the microdrive. The doses and volumes are listed in Table 1. For monkey C, doses were typically 4 μg (range 2–4 μg) diluted in volumes of 1-2 μl. For monkey J, the doses ranged from 4 to 12 μg diluted in 2 μl except for the largest dose, which inadvertently involved 6 μl. If no effect was observed after ~30 min, a second injection was given in some cases either at the same or a more ventral site. In Table 1, time of deficit onset is given from the time of the first injection. In the final inactivations (J9.5, J10, and J10.5), the cannula had an indwelling fine wire electrode
1 μg of radio-labeled muscimol in 1 μl saline resulted in a radioactivity profile that dropped off steeply to background levels ~1 mm from the injection site, when measured 10 min postinjection. At later times, the peak concentration was diminished appreciably, whereas the spread was only slightly expanded, presumably due to strong receptor binding and powerful uptake mechanisms for this long-acting γ-aminobutyric acid (GABA) agonist. The spread of hypometabolism as measured in the cerebral cortex was considerably greater; this was attributed to neuronal interaction in local circuits rather than to drug diffusion.

The larger injections used in the present study might spread further than 1 mm. Myers (1966) measured dye diffusion and found that a 2-μl volume spread 2.4 mm from the injection site, whereas 4 μl spread up to 3.7 mm. Although the strong binding of muscimol should limit diffusion to shorter distances, our larger injections should nevertheless spread a few millimeters, which would explain why the 6-μl volume inadvertently given inactivation J7.5b inactivated both anterior and posterior portions of the forelimb zone, thus explaining the mixed hand and reach deficits. However, the 2 μl used for most injections probably were much more confined, which accounts for the very different hand deficits observed with inactivations that were only 1 mm apart in the anteroposterior dimension. The unique hand deficits observed at J5.5, J6.5, and J7.5 suggest that the 2-μl injections of muscimol remained functionally in a very localized region.

Data collection

Various signals related to the monkey’s task performance, were collected on PDP 11/73 and Macintosh IIcx computers. If a single unit had been well isolated, output pulses from the discriminator were low-pass filtered (10-ms time constant) to provide a signal proportional to the unit’s firing rate. The pointing task-related signals included touch pad contact, target LEDs, and target array contact. During the performance of the tube task, the phototransistor detector signal was also collected. The same behavioral data were collected during control and inactivation sessions, and performance also was videotaped to allow direct assessment of the movements and any skill deficits. Control data for monkey C was collected immediately preceding each inactivation. Instead, control data for monkey J was collected on other days when inactivations that allowed the monitoring of multiunit activity, which disappeared after injection of the muscimol.

The extent of muscimol spread from an injection site has been estimated autoradiographically by Martin (1991). An injection of

![Image of two nuclear neurons recorded while monkey J performed the pointing task.](http://jn.physiology.org/)

### Table 1. Summary of inactivations in monkeys C and J

<table>
<thead>
<tr>
<th>Inactivation No.</th>
<th>Dose, μg</th>
<th>Volume, μl</th>
<th>Delay, min</th>
<th>Reaching Deficits</th>
<th>Hand Deficits</th>
<th>Hindlimb Deficit</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Aiming</td>
<td>Stability</td>
<td>Preshaping</td>
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<td>Monkey C</td>
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<tr>
<td>C4.5</td>
<td>4</td>
<td>2</td>
<td>39</td>
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<td></td>
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<tr>
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<td>2</td>
<td>33</td>
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<tr>
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<td>17</td>
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<td>33</td>
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<td>C8.0b</td>
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<td>2</td>
<td>35</td>
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<tr>
<td>C9.5</td>
<td>4</td>
<td>2</td>
<td>74</td>
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<tr>
<td>C10a</td>
<td>2 + 2</td>
<td>1 + 1</td>
<td>64</td>
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<tr>
<td>C10b</td>
<td>4</td>
<td>2</td>
<td>35</td>
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<tr>
<td>Monkey J</td>
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<tr>
<td>J5.5</td>
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<tr>
<td>J9.5</td>
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<td>2</td>
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<tr>
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<td>8</td>
<td>2</td>
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<tr>
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<td>8</td>
<td>2</td>
<td>1</td>
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* Cases in which deficits were observed.
were not attempted. For various reasons, the monkeys did not necessarily perform all of the tasks during each inactivation.

**Analyses**

Our first analyses focused on measures of goal achievement, for example, the accuracy of pointing or the success at removing fruit from the tube. Often, during inactivations, the monkeys could complete the task in a manner that was rewarded even though they employed different strategies than under control conditions. In these cases, the measures of goal achievement did not reflect the impairments the monkeys exhibited or the compensations the monkeys used to accomplish the goals. Other measures were introduced to examine the changed strategies and to determine if there was a site dependence of the different impairments observed during the inactivations. These measures focused on how the monkey performed the tasks. Analyses used both computer and videotaped records of monkey behavior. When possible, the Mann-Whitney U test was used to compute the significance of differences between conditions.

**POINTING TASK.** A measure of a goal achievement was the accuracy of the monkey’s pointing. For each reach, a distance error was calculated by subtracting the initial row and column touched from the target row and column. The resulting two numbers were squared and then averaged. The square root of that sum was defined as the distance error for that reach. Two other measures were implemented to document the manner in which the monkeys accomplished the pointing. One was the number of different rows the monkey touched as well as the number of rows touched simultaneously during a given trial. The other was the sequence of contacts the monkey made on the target array. Problems with hand stability or shape resulted in an atypical patterns of contact. A count of the number of rows touched gave an indication of how steady the monkey could hold its limb during the point. The number of rows contacted simultaneously gave an indication of the monkey’s hand shape. If the monkey was pointing with its fingertips, it would touch fewer rows simultaneously than if its fingers were flexed either at the initiation of contact or as the contact continued. Another way to address stability and hand shaping was to look at the sequence of contacts the monkey made during its contact with the target array. The contact sequence was determined by the rows touched sequentially from the monkey’s first contact with target array until the monkey removed its hand for the return to the touch pad. The contact sequence indicated if the monkey was touching with its fingers and sliding down the surface of the target array or if the hand was making contact with multiple adjacent or nonadjacent rows at once indicating the hand was flattening against the surface of the target array.

Another measure of hand-shaping deficits was determined from the videotape recordings. A count was made of the number of times the fingers were not fully extended at the moment of contact with the target array in the first 20 reaches.

**BOTTLE TASK.** Monkey C had the two smaller bottles and sometimes the largest bottle presented to it in each inactivation. Monkey J was presented the three larger bottles. From the video tapes, the number of attempts required by each monkey to insert its hand into the bottles was counted. The first approach was counted as one and each retreat and reapproach incremented the count. The count continued until the monkey successfully inserted its hand into the bottle or gave up.

**TUBE TASK.** The transparent tube allowed videotaping the hand movements, and the detector in the entryway allowed timing of hand insertion and removal. If the monkey were having a problem with aim, we might expect a prolongation of the time needed for the reaching component of the task but not necessarily of the time spent in the tube picking up the fruit. The prolongation of either time period should be accompanied by videotaped documentation of deficits. Measures of the monkey’s performance could be made from the videotape.

Two time periods were calculated for each attempt to remove the fruit bit from the tube. The first time period was the reaching time defined as the time from the monkey’s lift off from the touch pad to the occlusion of the sensors at the tube opening (Fig. 1F). The second time period, manipulation time, was the time the monkey’s hand was in the tube feeling for and picking up the fruit. Its hand and forearm occluded the sensors while the hand was in the tube (Fig. 1F). To measure day-to-day variability, control trials were collected on four different days during a 2-mo period and the times averaged. Neither time period addressed how the monkey performed the task or what deficit was impeding the monkey’s performance.

To address how the monkey performed the tube task, we watched the videotapes, monitoring its performance. Its typical manner of performance was noted during control conditions. The types of deviations the monkey exhibited during inactivations were identified. The number of occurrences of acts such as failure to retrieve the bit on the first attempt or dropping the fruit bit were counted in the various conditions. The counts then were compared. These counts complemented the timing information.

**Histology and reconstruction.**

Marking lesions were made after completion of all the inactivations several days before the animals were perfused. In addition, electrolytic marking lesions were made after data collection in inactivations J9.5, J10, and J10.5 using the fine wire electrode in the cannula.

An overdose of pentobarbital sodium was given to each monkey before perfusion with normal saline followed by 4% paraformaldehyde through the aorta. The brains were removed and placed in 4% paraformaldehyde/20% sucrose solution until sectioning. Brains were frozen and sectioned at 50 μm in the frontal plane. Slices encompassing the cerebellar nuclei were mounted and alternate slices were stained with thionine or luxol blue. Tracings of the outlines of the cerebellar nuclei were made using a projection microscope. Electrode paths, recording sites, and inactivation locations were reconstructed on the tracings with the aid of the marking lesions and stereotactic coordinates.

A three-dimensional (3-D) model of monkey J’s cerebellum and brain stem was constructed on a Silicon Graphics Workstation. Every second slide was projected onto a bitpad (WACOM SD-412E Digitizer, Wacom), and the boundaries of the brain stem, cerebellum, cerebellar nuclei, and the fourth ventricle were traced manually. The locations of the marking lesions and inactivation sites were marked in the appropriate slide tracings. The sections then were aligned using the external boundaries of the tissue and the shape of the fourth ventricle as cues. After alignment, an anterior-posterior coordinate was assigned to each section (He et al. 1995). The 3-D model then could be viewed from different angles with different degrees of transparency. Figure 8 is a horizontal view of this model illustrating the A–P and M–L coordinates of the cerebellar nuclei. The injection sites for monkey J, a left-handed animal, are shown on the left.

Comparison with the tracings of the cerebellar nuclei for monkey C indicated that the A–P extent and general shape of the interpos-
Results

Muscimol injections were placed at discrete cerebellar nuclear sites in a forelimb region that had been identified by microelectrode mapping (cf. METHODS). The variety of behavioral deficits that resulted were classified as predominant problems in forelimb reaching, hand use or, in one case, use of the hindlimb (Table 1). Despite severe impairment of reaching or hand motor control that was apparent to the investigator and in the video tapes, both monkeys often could complete the behavioral tasks with only modest degradation of performance. The monkeys could make adjustments in their movements that minimized the effects of their deficits on task performance. For example, the hand could grip an object to stabilize a poorly controlled arm, or repeated reaches by a well-controlled arm could compensate for an imprecisely shaped hand. Careful observation of live and videotaped task behavior was required to establish the exact nature of the disability produced at a particular inactivation site. After briefly categorizing the observed deficits, results are presented in the context of the four tasks.

Deficits of forelimb reaching were of two types, subcategorized as aiming and stabilization deficits. Aiming refers to the monkey’s ability to place its hand on the target object without the need for obvious corrective movements. When their aim was impaired, the monkeys compensated by over-shooting the target if the task allowed it, or, if not allowed, by aiming above the target object, and then descending rapidly to it. Stabilization refers to the monkey’s ability to maintain its hand at the desired location long enough for it to complete the desired task, such as retrieving raisins from a Kluver board slot.

Deficits in hand use also could be broken into two subcategories, inappropriate preshaping of the hand in preparation for contact with an object and poorly coordinated manipulation of an object. Each task required some preshaping of the hand, whether for forming the hand to touch a target square with the middle finger tip or for insertion into a bottle. The monkey with a preshaping deficit typically failed to extend its fingers in anticipation of contact with the target array or to extend and adduct its fingers for insertion into a bottle or tube opening. Manipulation refers to the monkey’s ability to use its fingers in a coordinated fashion to grasp and manipulate objects. Deficits of manipulation were observed most frequently as failure to use its thumb or fingers in isolation when the monkey was trying to retrieve fruit bits from the Kluver board, bottle or tubes.

A hindlimb deficit was observed in the most anterior inactivation in monkey C. This animal was very skilled in grasping the electrical cable supplying its touch pad with its toes and using the hindlimb to bring the cable up to where it could grab it with its hands. During this inactivation, the monkey could not grasp the cable with its toes on the inactivated side but had no difficulty with the contralateral side. In monkey J, we explored several sites posterior to the anticipated caudal border of the cerebellar nuclei and later confirmed to be located in the cerebellar cortex (not included in Table 1). At several of these sites, the monkey exhibited a head tilt to the side of inactivation when the head holder was removed but remained able to track moving targets with its eyes and head. Reaching deficits also were observed at some of these posterior cerebellar cortical sites.

In the following sections, we report on the monkeys’ behavior during the four different tasks described earlier. Analyses of the deficits were noted during the cerebellar nuclear inactivations and during later videotape viewing. When possible, the behavioral deficits observed on videotape were quantified using the behavioral markers from computer files collected simultaneously with the videotape during the inactivations. In Table 1, each inactivation is referred to by a letter denoting the monkey and a number indicating the posterior stereotaxic coordinate.

Pointing task

The pointing task included two components, reaching and hand use. In the course of the mapping recordings (METHODS), we encountered single units in the deep nuclei having discharge patterns that were related to the transport phase of the reach (Fig. 1A) or to the contact with the target array (Fig. 1B). Injections of muscimol into the nuclei caused performance deficits which also could be related to one of these two components of the pointing task. Muscimol-induced deficits during the reaching component included both decreased accuracy and instability of the limb. Less obvious, perhaps because the task did not include manipulation of an object, were deficits in the hand-use component. These mainly resulted from abnormal hand shape and digit extension as the monkey attempted to touch the lighted target square.

We will consider first those deficits that were related to the reaching component. The accuracy of the reach is clearly of fundamental importance. During control conditions, both monkeys were quite accurate in their attempts to touch the lighted target square. Figure 3A includes data from 100 trials collected during a single control session with monkey J. It indicates that despite the rapidity of the movements, in 95% of the reaches, the initial contact with the array included only the single correct square (error = 0). In only 5% of the trials, did the monkey touch an adjacent square along with the intended one (error = 0.5). Similar data from this monkey are shown in Fig. 3B a few minutes after muscimol injection J10.5. The touch was correct only 53% of the time, missing by an entire square in 8% of 62 trials, and the difference between this and the control was highly significant (P < 0.0001). One-half hour after the injection, aiming appeared to be even more impaired as was confirmed by collecting an additional 60 trials of the pointing task. Lumping all 122 trials, the mean error was 0.53 ± 0.58 squares (Table 2).

Video recordings revealed that the trajectory of the limb also was disrupted by the muscimol injections. During inactivations C9.5, C10a, and C10b, monkey C would throw its arm high so that the hand would sweep down the surface of the target array from top toward the bottom if reaching for an upper target or throw its arm up from below if reaching for a lower target. Monkey J showed similar behavior during
FIG. 3. Monkey J’s accuracy and contact sequence during control condition and inactivation J10.5. A: this graph shows the distance error during a control session expressed as percentage of reaches. In 95% of the reaches, monkey J was on target (error = 0). In 5% of the trials, monkey J touched both the correct square and the square immediately adjacent simultaneously (error = 0.5). B: during inactivation J10.5, only 53% of the reaches were on target, 39% hit both the correct square and the adjacent square, and 8% of the reaches were off an entire square. N, number of reaches in A and B. C: traces taken from a series of digitized video frames during a reach in inactivation J10.5. D and E: representations of the contact sequence of monkey J during a reach to a target in row 2. D: monkey made an initial contact in row 2 followed by row 3. Sequence was reversed as the monkey removed its fingers from the target array. Monkey touched 2 rows simultaneously and a total of 2 rows during this reach. E: during inactivation J10.5, the monkey first made contact in row 2. Its fingers then slid up touch row 1 before sliding down to rows 3 and 4 before removing its fingers from the target array. Sequence of rows document the slide or sweep of the fingers down the surface of the target array. Monkey touched no more than 2 rows simultaneously during this reach and touched a total of 4 rows. F: this graph compares the number of rows the monkey contacted simultaneously and the total rows touched in each reach during a control session, during inactivation J10.5 and during J6.5b. During inactivation J10.5, the monkey touched significantly more rows than during the control session. During inactivation J6.5b, the monkey touched significantly more rows simultaneously as well as more total rows.

inactivations J9.5 and J10.5 and, to some extent, inactivation J10. Figure 3C depicts traces taken from a series of digitized video frames during inactivation J10.5. Note that the monkey’s fingers remained extended and the palm never touched the target array surface as it slid. The change in trajectory from a relatively straight one from touch pad to target under control conditions to a high arcing throw in some inactivations may have been a strategy adopted by the monkeys to compensate for the decreased stability proximally that prevented a more controlled reach for and contact with the target array. We studied this sweep quantitatively by documenting the sequence of array contacts.

Figure 3D shows this information for a control trial in which monkey J reached toward a target in row 2. Initial contact was made in row 2, followed by row 3. As the hand was removed from the array, the sequence was reversed, the finger was first removed from row 3, followed by row 2. The monkey never touched more than two rows simultaneously or in total. This sequence of contacts, which was typical of the control condition, is summarized in Fig. 3F.

However, during inactivation J10.5, monkey J initially touched row 2, but then slid up to row 1, then down to rows 3 and 4 before removing its hand from the surface of the target array (Fig. 3E). Although it touched at most only two rows simultaneously, it touched a total of four rows during the trial (Fig. 3F). The number of rows touched simultaneously was the same as control ($P = 0.4411$), but the total number of rows was significantly different ($P < 0.0001$). This pattern is consistent with a well-shaped hand,
Inactivations: The bottle task included two components, reaching and average of the controls using the Mann-Whitney and finger extension during pointing task performance by monkey J.

### Table 2. Distance errors and atypical metacarpophalangeal and finger extension during pointing task performance by monkey J

<table>
<thead>
<tr>
<th>Sessions</th>
<th>Number of Reaches</th>
<th>Squares</th>
<th>P Value*</th>
<th>Digit Extension Deficit, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>66</td>
<td>0.01 ± 0.09</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>100</td>
<td>0.03 ± 0.12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>100</td>
<td>0.10 ± 0.21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>50</td>
<td>0.03 ± 0.12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>100</td>
<td>0.05 ± 0.14</td>
<td>0</td>
</tr>
<tr>
<td>Average</td>
<td>416</td>
<td>0.05 ± 0.15</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactivations</th>
<th>Number of Reaches</th>
<th>Squares</th>
<th>P Value*</th>
<th>Digit Extension Deficit, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>J5.5</td>
<td>56</td>
<td>0.49 ± 0.41</td>
<td>&lt;0.0001</td>
<td>85</td>
</tr>
<tr>
<td>J6.5b</td>
<td>51</td>
<td>0.1 ± 0.25</td>
<td>0.4137</td>
<td>100</td>
</tr>
<tr>
<td>J7.5a</td>
<td>90</td>
<td>0.48 ± 0.51</td>
<td>&lt;0.0001</td>
<td>100</td>
</tr>
<tr>
<td>J7.5b</td>
<td>197</td>
<td>0.38 ± 0.46</td>
<td>&lt;0.0001</td>
<td>95</td>
</tr>
<tr>
<td>J9.5</td>
<td>40</td>
<td>0.60 ± 0.4</td>
<td>&lt;0.0001</td>
<td>35</td>
</tr>
<tr>
<td>J10</td>
<td>72</td>
<td>0.66 ± 0.37</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td>J10.5</td>
<td>122</td>
<td>0.53 ± 0.58</td>
<td>&lt;0.0001</td>
<td>15</td>
</tr>
<tr>
<td>Average</td>
<td>234</td>
<td>0.57 ± 0.49</td>
<td>&lt;0.0001</td>
<td>18.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. * Each inactivation was compared with the average of the controls using the Mann-Whitney U test.

but very unstable arm, such that the hand was sliding up and down the target array.

During control recordings, the relatively small contact surface of the hand was accomplished by extending the fingers with slight flexion of the metacarpophalangeal joints. Contact with the target array typically was made first with the distal pad of the middle finger followed at times by contact with the fourth or second finger.

This normal pattern of hand use was disrupted in inactivations C6.5, C7.5, C8b, J5.5, J6.5b, and J7.5a. Often the monkey’s fingers were flexed abnormally when initial contact was made and would subsequently flatten against the target array. Upon return to the touch pad, the hand would hang over its edge. The monkeys made no attempt to correct either hand posture. Figure 4A illustrates the normal finger extension as the finger contacted the target array. Figure 4B shows the lack of digit extension at the time of contact that resulted from inactivation J6.5b.

We summarized this effect by counting the frequency with which this abnormal hand posture was noted in the video recordings of monkey J performing the pointing task (Table 2). In inactivations J6.5b and J7.5a, hand posture during 100% of the trials was abnormal. In J5.5, the hand posture was abnormal in 85% of the trials. In inactivations J9.5, J10, and J10.5, hand posture was occasionally abnormal at the time of contact (35, 5, and 15%, respectively), but the monkey immediately corrected it. This indicated that the capacity for hand control was not affected but rather the initiation of this mechanism was delayed on occasional trials. The categorization scheme used in Table 1 does not treat this problem as a fundamental hand-shape deficit.

As a further means of quantification, we again considered the number and sequence of target array contacts. Unlike inactivation J10.5, in which the number of simultaneously touched rows remained small, for inactivations such as J5.5 or J6.5b, the monkey tended to contact squares in a greater than normal number of rows. Figure 4C illustrates this effect for inactivation J6.5b. Monkey J first made contact correctly in row 2. However, while contact was maintained in row 2, the monkey also touched squares in row 4 and later in rows 3 and 5, as the hand continued to flatten. During this inactivation, the monkey touched squares in significantly more rows than during control, or injection J10.5 (Fig. 3F; P < 0.0001). However, the aiming errors (determined by the site of initial contact) for this inactivation did not differ from control (Fig. 4D; n = 51; P = 0.4137).

**Bottle task**

The bottle task included two components, reaching and properly preshaping of the monkey’s hand for insertion into the bottle. During control conditions, the monkeys could insert their hands on the first attempt as is shown for monkey C in Fig. 5A. During inactivation C10b, monkey C had its hand properly shaped for entry into the bottle but required many attempts (Fig. 5B). The tracings in Fig. 5D depict three such successive attempts. In the first and third attempt, the monkey’s hand went over the bottle. On its second at-
Organism of Reach and Grasp in Cerebellum

Figure 6

A pinch grasp successfully 73% of the time. It always re-
A series of elbow "flexions and extensions would complete

Tube task

A

B

C

D1

2

3

Figure 5. Number of attempts to enter the bottle with a 3.2 cm opening
during control conditions, inactivation C10b and inactivation C8b. A: under
control conditions, monkey C inserted its hand into the bottle on the first
try 4 times it was presented the bottle. B: during inactivation C10b,
monkey C's aim was impaired hindering successful insertion of its hand into
the bottle. Only completed presentations are depicted. C: during inactivation
C8b, monkey C had little difficulty aiming its hand properly. A finger caught
on the rim of the bottle in the 4th presentation requiring the second attempt
to insert its hand. D: traces taken from digitized video of 3 successive attempts
by monkey C to insert its hand into the bottle during inactivation C10b. In D, J and J, its right hand went over the top of the bottle opening.
In D2, its hand went off the left side of the bottle. Monkey curled its fingers
after passing the opening.

The hand went off to the left of the bottle with the
fingers curling as the hand passed by the bottle opening.
Monkey J exhibited similar aiming problems during inactiva-
tions J9.5, J10 and J10.5. Monkey J also exhibited stability
problems. During inactivations J9.5, J10, and J10.5, if the
monkey managed to get its hand on the side of the bottle,
it would try to pull its hand back to the opening. In most
instances, the hand would fall off the bottle and tremor would
ensue.

During some inactivations, the monkeys failed to adduct
their fingers adequately for insertion into the bottles. They
appeared oblivious to the obstruction created by one or more
fingers caught on the rim. Aim was not a problem as is shown
for inactivation C8b in Fig. 5C. In monkey J, improper hand
shape interfered with entry into the bottle in ~70% of the
trials in inactivations J5.5, J6.5a, and J6.5b.

Tube task

The tube task stressed aim but also required proper hand
shaping for entry into the tube and good stability and
manipulation skills once in the tube. Under control condi-
tions, monkey J was observed, both live and on videotape,
retrieving the fruit bits in very stereotypical manners for
each tube used. For example, during control trials with the
smallest tube, the monkey retrieved the fruit bit by flexing
its fingers to slide the fruit toward the end of the tube where
it would catch it between the finger pads and dorsum of the
thumb, dropping <5% of the fruit. If using the tube with
the shelf, the monkey removed the fruit from the shelf using
a pinch grasp successfully 73% of the time. It always re-
covered fruit that had dropped to the bottom of the tube.
Figure 6A graphically presents the reaching and manipula-
tion times during one control session with the tube with a

shelf. The mean reach time (0.23 ± 0.05 s, △) and the mean
manipulation time (1.18 ± 0.38 s, ▲) are close to the average
of all the control sessions for this tube (reach time 0.26 ±
0.03 s; manipulation time 1.23 ± 0.62 s).

Figure 6B shows a neuron exhibiting a similar pattern of activity
as did the neuron shown in Fig. 2B during the pointing task
with a decrease in activity during the reach and a burst of
activity about the time of target array contact. Figure 6D
shows a single trace of this neuron’s activity recorded while
the monkey was retrieving the fruit bit from the shelf. It had
an increase in firing that began prior to the insertion of the
hand into the tube. This increase was maintained as the
monkey picked up the fruit bit and returned it to its mouth.
Activity diminished once the monkey’s hand had returned
to the touch pad. An example of neuronal activity near sites
in which muscimol injection produced reaching deficits is
illustrated in Fig 6F showing a sharp burst of activity during
the reach to the tube but little increase above baseline while
the hand was in the tube. This is consistent with the reaching
activity of this nuclear neuron during the pointing task shown
in Fig. 2A.

Monkey J exhibited analogous deficits during performance
of the tube tasks as it did in its performance of other tasks.
The impaired aim and instability observed in inactivations
J9.5, J10, and J10.5 in the pointing and bottle tasks also
were observed during the tube task. During inactivation
J10.5, monkey J took significantly longer to reach the tube
(0.34 ± 0.14 s, P = 0.006) and to remove the fruit from
the tube with the shelf (2.07 ± 1.01 s, P = 0.0015) than
during control conditions (Fig. 6E). The monkey’s hand
was shaped properly for insertion to the tube, but the finger-
tips often hit above the doorway. Up and down correcting
movements would ensue until the monkey successfully in-
serted its hand, prolonging the reach time. The monkey
appeared able to compensate for aiming impairments as indi-
icated by the decreased reaching time after the first two trials.
The time would increase again if the monkey was distracted
between trials (see trial 9 in Fig. 6E). Similar patterns of
decreases in reach times were noted in inactivations J9.5
and J10. Instability of the forelimb prolonged manipulation
time. The monkey could not hold the limb still long enough
to use a pinch grasp and instead would grab at the fruit bit
by flexing the fingers against the thumb at the end of the
shelf. In the 69% of the trials in which the fruit dropped to
the tube floor, the monkey could retrieve it successfully
without obvious need for visual cues. The same instability
of the limb was observed when the monkey withdrew its
hand from the smallest tube. The forelimb would suddenly
drop dislodging the fruit from the end of the tube in inactiva-
tions J7.5b, J10, and J10.5.

Hand deficits also were observed during the tube task.
Inadequate extension of the metacarpophalangeal joints
resulted in the dorsum of the fingers hitting the face plate of
the tubes. Rather than reshape its hand, monkey J raised its
hand until the fingers entered the tube by flexing its elbow.
A series of elbow flexions and extensions would complete
the insertion. The impaired preshaping of the hand signifi-
cantly increased the reach time above control in inactivation
J6.5b (0.29 ± 0.04, P = 0.0112; Fig. 6C). Once in the tube,
manipulation time was prolonged significantly (3.73 ± 1.58 s, P < 0.0001; Fig. 6C). The monkey attempted to remove the fruit from the shelf using only flexion of the four lateral fingers without the assistance of the thumb and was successful in 25% of the trials. In the remaining trials, after the monkey knocked the fruit to the tube floor, it would sweep the fruit forward, frequently moving its forelimb to the side to allow for visual assessment of the fruit location. It appeared unable to locate the fruit bit by feel, leaving the fruit behind when the fruit bit was not visible on the floor of the tube. The monkey used the back of the face plate to stabilize the fruit so it could scoop the fruit up with its fingers without thumb assistance. The monkey’s inability to use its thumb during inactivation J6.5b also was observed during removal of the fruit from the smallest tube. The monkey dropped >47% of the fruit bits as it withdrew its hand from the tube because the thumb was not in the proper position to catch the bit.

The monkey exhibited other manipulation deficits during inactivations J6.5a and J7.5b when attempting to retrieve the fruit bit placed in the midst of a screw and nut partially embedded in dental acrylic on the tube floor. The monkey would claw indiscriminately at the objects on the floor and appeared unable to detect the fruit bit by cutaneous cues. If the bit was in view, the monkey would use a clawing grasp to retrieve it.

FIG. 6. Graphic representation of reaching and manipulation times during the tube task and single unit recordings. A: under control condition depicted, monkey J took an average of 0.23 ± 0.05 s to lift its hand off its touch pad and reach the tube opening (reaching time, D, and left vertical axis) and an average of 1.18 ± 0.38 s to retrieve the fruit bit from the shelf and exit the tube (manipulation time, m, and right vertical axis). C: reaching times (mean 0.29 ± 0.04 s) and manipulation times (mean 3.73 ± 1.58 s) during inactivation J6.5b. B and D: recording of a single unit in the vicinity of inactivation J6.5b. B is the ensemble average of single-unit activity while the monkey performed the pointing task. Activity is centered on contact with the target array. Unit burst just before target contact. D is a single trace of the same unit during the tube task. Activity of the unit increases just before the removal of its hand from its touch pad. Activity continues during the reach and is maintained while the hand is in the tube and the fruit brought to the monkey’s mouth. E: reaching times (mean 0.34 ± 0.14 s) and manipulation times (mean 2.07 ± 1.01 s) during inactivation J10.5. F: single trace of activity during the tube task showing a burst of activity during the reach and return to baseline levels during manipulation time. This unit was shown during the pointing task in Fig. 2A and was in the vicinity of inactivation J10.5.
The monkey reached the tubes faster in inactivations J5.5 and J6.5a and significantly slower in inactivations J9.5 and J10. In inactivations J6.5b, J7.5b, and J10.5, the change in reach time was not consistent across the tubes. In all inactivations in which the monkey performed the tube task, it had a prolonged manipulation time.

Kluver board

The Kluver board task has three phases. During the first phase, the transport phase, the monkey must aim for the slots as well as prepare its hand for the removal of the fruit bit. During the second or removal phase, the monkey must hold its hand steady and use its thumb and forefinger in a coordinated manner to remove the fruit bit from the slot. The remaining lateral fingers should be held quiescent out of the way. In the third phase, the monkey must maintain its grip of the fruit bit until it brings its hand to the mouth and then let go. Under control conditions, both monkeys accomplished all three phases skillfully. During inactivations, the monkeys’ performance of the Kluver board task could be hindered by reaching or hand deficits.

Inactivations that caused reaching deficits during the performance of the pointing task and tube task also caused reaching deficits during performance of the Kluver board task. Both monkeys were observed to hit lateral to a slot and then slide over so that their forefinger entered the slot (inactivations C9.5, C10a, C10b, J7.5b, J9.5, and J10.5). Once in the slot, instability of the forelimb frequently caused monkey C’s hand to jerk abruptly out of the slot as it tried to grasp the fruit bit. The monkey then would attempt to land in another slot. Another approach used by monkey C during inactivation C10.5 was to bring the hand out to above the desired slot in the upper row of the board, hover, and then drop quickly to the board. In inactivation J10, the monkey would get its finger in the slot only to pivot around the finger preventing any grasping function of the fingers. In inactivation J9.5, it would exhibit pivoting around the finger in the slot until it rested the heel or hypothenar eminence of the hand on the board. Both monkeys used a pinch grasp to retrieve the fruit bits if they could maintain their fingers in the slot long enough.

A consistency across tasks was likewise observed in those inactivations that caused hand deficits. Both monkeys could place their hands on the slots but couldn’t use their fingers skillfully to retrieve the fruit bits (Table 4). All fingers might be flexed in unison (inactivations C6.5, C8a, and C8b) or one finger used in isolation either to dig (inactivation C8a) or as a hook with all joints immobile except for wrist pronation and supination (inactivation J7.5a). The thumb was frequently not used as the monkeys tried to catch the fruit between finger and palm (inactivation C9a), between fingers and palm (inactivations C6.5, C8a, C8b, J6.5a, and J7.5b) or with a fist (inactivation J7.5a).

Correlation of deficits with inactivation sites

The reconstructed locations of the nuclear inactivation sites in monkey J are illustrated on a set of tracings from frontal sections through the dentate and interpositus nuclei in Fig. 7. Each inactivation site produced a distinctive set of deficits as judged by the quantitative measures of task performance summarized in Tables 2–4 along with careful observation of live and videotaped movements. The inactivations located at the more anterior sites caused different types of hand deficits, marked in Fig. 7 (×), whereas inactivations at more posterior sites caused deficits in reaching (○). The filled circle indicates a site of mixed hand and reaching deficits and the filled square is the site of a marking lesion.

To gain a better appreciation of the spatial organization of the forelimb region, we reconstructed monkey J’s cerebellar nuclei in three dimensions (cf. METHODS). Figure 8 shows a horizontal view of the 3-D reconstruction with the locations of monkey J’s inactivations sites on the left and the approximate locations of monkey C’s inactivations sites on the right, coded as in Fig. 7. The open square anterior in the right NIA indicates the site of a foot deficit whereas the remainder of the sites, extending more than one-half centimeter in the anteroposterior dimension, produced different types of hand and reach deficits. Inactivations causing hand deficits were located in or near the NIA or adjacent dentate nucleus, in a region we refer to as the anterior hand zone (AHZ). Sites that caused reaching deficits were located more posteriorly in the NIP or adjacent dentate nucleus, in a region we refer to as the posterior reaching zone (PRZ).

Direct observation of the live and videotaped arm movements the animal made as it performed the various behav-
TABLE 3. Distance errors during pointing task performance by monkey C

<table>
<thead>
<tr>
<th>Sessions</th>
<th>Number of Reaches</th>
<th>Squares</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre C6.5</td>
<td>112</td>
<td>0.07 ± 0.19</td>
<td>0.0007</td>
</tr>
<tr>
<td>Pre C7.5</td>
<td>74</td>
<td>0.16 ± 0.23</td>
<td>0.0317</td>
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<tr>
<td>Pre C8.0a</td>
<td>100</td>
<td>0.22 ± 0.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pre C8.0b</td>
<td>100</td>
<td>0.18 ± 0.29</td>
<td>&lt;0.0001</td>
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<tr>
<td>Pre C9.5</td>
<td>96</td>
<td>0.17 ± 0.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pre C10a</td>
<td>102</td>
<td>0.21 ± 0.27</td>
<td>&lt;0.0001</td>
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<tr>
<td>Pre C10b</td>
<td>83</td>
<td>0.17 ± 0.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average</td>
<td>667</td>
<td>0.17 ± 0.27</td>
<td></td>
</tr>
</tbody>
</table>

Inactivations

| C6.5  | 108 | 0.31 ± 0.36 | 0.0007 |
| C7.5  | 100 | 0.26 ± 0.34 | 0.0317 |
| C8.0a | 113 | 0.48 ± 0.43 | <0.0001 |
| C8.0b | 125 | 0.55 ± 0.44 | <0.0001 |
| Average| 446 | 0.41 ± 0.46 | <0.0001 |
| C9.5  | 288 | 0.79 ± 0.53 | <0.0001 |
| C10a  | 150 | 0.52 ± 0.56 | <0.0001 |
| C10b  | 169 | 0.56 ± 0.64 | <0.0001 |
| Average| 607 | 0.66 ± 0.58 | <0.0001 |

Values ± SD. * Each inactivation was compared with the average of the controls using the Mann-Whitney U test.

Several types of hand deficit were observed at different inactivation sites along the anteroposterior dimension. At the most anterior site (J5.5) for monkey J, the monkey could not make isolated finger movements when retrieving fruit from the Kluver board slots or from the tubes. When the monkey tried entering its hand into the tubes, the hand was aimed appropriately, as judged by third metacarpal position, for entrance into the tube, but the flexed metacarpal joints resulted in the collision of the dorsum of the fingers with the bottom of the tube opening. At the time of contact with the target array in the pointing task, the metacarpophalangeal and interphalangeal joints often were flexed so that contact was made with the dorsum of the distal phalanx instead of the finger pad of its middle finger resulting in a distance error of approximately one-half a square (0.49 ± 0.41). This error was significantly greater than the average of the control cases (Table 2) and was not due to any problems in reaching. Instead, it was caused by a hand-shaping deficit. Slightly posterior to inactivation J5.5 are inactivations J6.5a and J6.5b, located between NIA and dentate. The consistent finding in both of these cases was that the thumb remained adducted and was not used in any of the tasks. As a consequence, the monkey’s ability to retrieve fruit bits from the Kluver board slots (Table 4) or the tubes was considerably impaired. The larger dose used in inactivation J6.5b (Table 1) also impaired finger extension before contact with the target array (Table 3). However, in this case, the distance error during the pointing task was not significantly different than in control reaches. This injection also prolonged manipulation times in the tube task (Fig. 5C). The videotapes revealed that the poor performance reflected the monkey’s inability to use its thumb. Moving further posterior, inactivation J7.5a was located in the dentate nucleus and inactivation J7.5b was located in the NIA. Inactivation J7.5a resulted in inadequate finger extension during the pointing task (Table 2) such that the monkey was contacting the target array with its dorsal interphalangeal joints or the dorsal distal phalanx, again resulting in a distance error significantly greater than...
control. The large dose and injection volume used for inactivation $J7.5b$ resulted in both hand and reaching deficits.

Monkey C exhibited similar hand deficits during AHZ inactivations. During inactivation $C6.5$, hand shape at contact with the target array in the pointing task was not as stereotyped as in the preinactivation control. Contact was frequently made with the dorsum of the fingers resulting in a distance error significantly greater than the average control reaches (Table 3). Its hand would continue to flatten against the target array surface. When attempting to remove raisins from the Kluver board slots, all of its fingers would flex in unison. (The Kluver board was not presented to this monkey in a systematic manner so it was not possible to calculate a meaningful percentage of fruit dropped.) During inactivation $C7.5$, contact with the target array often occurred with the fingers splayed with each finger in various degrees of extension again resulting in a greater distance error than in the control reaches (Table 3). The lack of finger adduction resulted in the monkey catching one or more of its fingers on the bottle rim when attempting to insert its hand into the bottle to retrieve the fruit. During inactivations $C8.0a$ and $C8.0b$, the monkey again inadequately preshaped its hand for the task at hand. In the pointing task, the fingers were flexed so that contact was made with the dorsal middle phalanx or dorsal distal interphalangeal joint. The inadequate preshaping was most evident when the monkey attempted to retrieve a raisin from the investigator’s hand. The monkey’s hand remained closed during the approach to the raisin. It opened after contact with the investigator’s fingers but was not used effectively to grasp the raisin. In summary, inactivation sites located in the AHZ resulted in several types of hand deficits, whereas the aiming and stability of the arm was not appreciably affected. In contrast, inactivations in the PRZ resulted in reaching deficits. Inactivations $J9.5$ and $J10$ were located in the NIP and inactivation $J10.5$ was located on the medial border of the dentate. During inactivations $J9.5$ and $J10$, the monkey’s distance error in the pointing task was greater than the control average (Table 2) in the absence of any problem with hand shape, thus documenting an aiming problem. When attempting to remove fruit from the Kluver board slots, the monkey had difficulty landing in its desired slot, frequently hitting the surface of the board lateral to or below the slot and sliding in the board’s surface until its finger dropped into a slot whereupon the raisin was easily grasped. Furthermore, it effectively used a pinch grasp to remove the fruit bit if it could rest the heel of its hand or its forearm on the board to provide stability. Oscillations of the limb sometimes caused the finger to exit the slot abruptly, dislodging the fruit in the process. The monkey could not place its hand in the proper position to catch the fruit fast enough to prevent the fruit from dropping (Table 4). The aiming and stability problems caused by inactivation $J10.5$ were shown in Fig. 3, $B$ and $F$, during the pointing task and in Fig. 5$E$ during the tube task. The distance error was substantial in the pointing task ($0.53 \pm 0.58$ squares), and in the tube task the hand was shaped for entry but initially hit the face plate above the tube opening with its fingertips. Monkey J exhibited the same aiming and stability deficits when removing fruit bits from the Kluver board slots in inactivation $J10.5$ as it did in inactivations $J9.5$ and $J10$. In contrast to the digit-extension deficit and subsequent flattening of the hand on the target array observed during AHZ inactivations, during the PRZ inactivations, the monkey immediately corrected the inadequate digit extension, suggesting an awareness of hand contact that appeared to be lacking in the AHZ inactivations. The finger-extension deficit may have been caused by an incoordination of the timing between the transport of the limb and the shaping of the hand.

Monkey C exhibited similar aim and stability deficits during PRZ inactivations. During inactivation $C9.5$, its finger extension was normal at contact with the target array yet its distance error was significantly greater than control (Table 3). The monkey’s hand slid down the surface of the target array appearing to fall to the start pad. When attempting to take a raisin from the investigator’s palm, the monkey’s hand was shaped properly for the grasp during the approach to the raisin but landed beyond the raisin. The monkey then used its fingers to “walk” its hand over to the raisin to successfully grasp it. During both inactivation $C10a$ and $C10b$, the monkey tended to throw its arm toward the target array sweeping down its surface. The distance errors were significantly greater than during the control average (Table 3). In both inactivations, the monkey could use a pinch grasp to remove fruit bits from the Kluver board slots if it could slide its fingers into the slot and maintain them there.

In summary, inactivations in the PRZ impacted the monkeys’ abilities to move their hands to desired locations in space and to stabilize their arms. For both monkeys, the average PRZ inactivations’ distance errors were significantly greater than the average AHZ inactivations’ distance errors ($P < 0.0001$) consistent with an aiming problem. While there were some impairments in hand use, these occurred in situations where the monkeys had trouble stabilizing their arms. As isolated manipulative instruments, the hands were well coordinated.

**DISCUSSION**

A variety of deficits in forelimb function resulted when the GABA agonist muscimol was injected at discrete sites in the cerebellar interpositus nucleus and adjacent regions of dentate. The impairments produced by 15 inactivations in two monkeys revealed a prominent anteroposterior specialization of function within the forelimb region of the intermediate cerebellum (Fig. 8). The more anterior injections, into caudal NIA and adjacent dentate, produced various deficits in hand shaping and manipulation, whereas injections more posteriorly in NIP and adjacent dentate impaired the aiming of reach and the stability of the arm. We refer to the region producing hand deficits as the anterior hand zone (AHZ) and the region producing reaching deficits as the posterior reach zone (PRZ).

**Skill deficits and compensations**

The muscimol injections into the cerebellar nuclei described in this paper resulted in profound deficits, although this was not always apparent from an analysis of task success measures. Both monkeys could, to a large degree, complete the tasks required of them in spite of the deficits caused by muscimol inactivations. The deficits became most apparent...
Comparison with previous lesion studies

Large irreversible lesions of the intermediate and lateral cerebellum in monkeys generally resulted in the full constellation of reaching and hand deficits seen in the present study (Botterell and Fulton 1938; Growdon et al. 1967; Gilman et al. 1976). Electrolytic lesions destroying just the interpos-
inactivation affects movement about the elbow in a tracking task. Cooling of the lateral dentate resulted in hypermetric movements or the overshooting of the target, whereas cooling of the lateral interpositus, both anterior and posterior and also the medial dentate, resulted in hypometric movements. Both the hypermetric and the hypometric movements should result in aiming deficits in a less restrained task. Hand movements were not tested. In baboons trained to perform a pointing task, Beaubaton and Trouche (1982) noted impaired aiming with an increased dispersion of the movements during dentate cooling. The probe placement and the isotherms from the cooling appear to cover all of the dentate except for the medial anterior and most caudal parts. These results are consistent with our finding of impaired aim during muscimol inactivation of PRZ. Their isotherms suggest a sparing of AHZ, and they did not report any hand deficits.

Focal injections of muscimol produce relatively small inactivations (cf. METHODS) as compared with cooling probes. Furthermore, the injection site can be varied from day to day and inactivation protocols can be alternated with microelectrode recordings to compare activity and deficit maps. Using these methods, Thach and colleagues (1992b) found sites in interpositus where units discharged in a wrist tracking task and where inactivation caused terminal oscillations in tracking movements together with reach deficits during free form movements. The authors do not show any histology, but these impairments suggest sites in NIP. The fact that they found no sites of hand impairment in interpositus suggests that the forelimb zone of NIA was not explored. In dentate, the units showed discharge patterns similar to interpositus units for visually cued wrist movements, whereas they were less responsive when the same movements were self-paced or proprioceptively cued. Muscimol inactivation produced both reach and hand deficits depending on the site, but the lack of histological localization diminishes the value of these findings. In an earlier paper (Mink and Thach 1991), three inactivation sites in posterior dentate are shown, each of which resulted in reach deficits. The most medial of these is within PRZ, where we consistently observed reach deficits. The most lateral site at this posterior location may be in the zone identified by Middleton and Strick (1997) as projecting to the ventral premotor area; units here are selectively involved in visually cued arm movement. As noted earlier, visual-triggering specificity is a summary feature of Thach’s dentate unit sample (Thach et al. 1992a,b). It would be helpful to know the anteroposterior coordinates of the dentate sites producing hand deficits (Thach et al. 1992b) to determine if they were within the AHZ.

The injections placed in the PRZ probably inactivated cells in the eye movement region that exists in NIP and adjacent dentate (van Kan et al. 1993b). We were not equipped to measure eye movements quantitatively, but we tested qualitatively for deficits in eye control that might account for reaching errors. In no case did the monkey show any signs of nystagmus, and its eyes followed the movement of fruit bits with no obvious impairments. On this basis, it seems unlikely that the visible deficits in reaching produced by PRZ inactivations resulted from problems in eye movement control, but this possibility cannot be excluded.

The variety of hand-skill deficits we observed at different sites within the AHZ suggests that further studies combining inactivation and single-unit observations would be worthwhile, particularly if the sites are located histologically. Correlating such results with connectivity to other motor areas may serve to define how muscle synergies extend through the motor system. As an example of the suggested analysis, consider the connectivity and function of sites within the central region of NIA (J 5.5 and J7.5b in Fig. 7). As reviewed earlier, this zone projects densely to the hand region of red nucleus where units have been studied in a finger task that required the monkey to press switches with individual digits (Houk et al. 1988). A large fraction of the units discharged intensely for several different individual digit movements, which led to the conclusion that the activity was related to stabilizing unused digits in an extended position when an individual digit needed to be flexed. A lesion of the motor cortex did not diminish the intensity of rubral discharge, but individual digit motion was now impaired and discharge occurred preferentially during grouped extension (and in some cases flexion) of all of the fingers. This fits well with the deficit in hand shaping and finger extension at site J7.5b. At the same site, unit discharge showed a complex temporal pattern compatible with the finger extensor activity required in three phases of the tube task (Fig. 6): as the hand was lifted from the touch-pad (but not during the transport phase of the reach), as the hand was being shaped for entry into the tube, and while digits 3-5 were being stabilized in extension to allow the thumb and index fingers to manipulate and grasp a food object. Further anterior in NIA (J5.5), the deficit was probably also one of hand shaping, although it presented as a pinch grasp failure. Evidently, the pinch grasp became ineffective because the animal lost its normal capacity to stabilize the unused digits by flexing them against the palm of the hand. Moving to the next stage of processing, other studies have demonstrated preferential linkages between rubral neurons and the extrinsic extensors and flexors of the fingers (Miller et al. 1993; Sinkjaer et al. 1995). In combination, these various results begin to specify how synergistic extension and flexion of the fingers, and perhaps other synergies that help to shape the hand, may be represented through an interconnected portion of the cerebello-rubro-spinal pathway. If similar analyses were available for other synergies, one could begin to define the distributed synergy maps comprising a muscle-based coordinate system for controlling voluntary movements of the arm (Miller and Houk 1995; Miller et al. 1993).

Coordination of forelimb movements

It is accepted widely that coordination of movement is one of the main functions of the cerebellum (Ito 1984). Some authors have stressed the coordination of temporal patterns in motor commands so as to achieve smooth movements with accurate endpoints (e.g., Hore et al. 1991), whereas others have stressed the coordination of spatial patterns of muscle activity to achieve synergistic control of multijoint movements (e.g., Thach et al. 1992a). It is likely that both views are correct and that the overall function of the cerebellum is to ensure spatiotemporal coordination in the large population of nuclear cells that participate in any given movement. The microinjections of muscimol used in
the present study would be expected to inactivate select foci
within this population thus disrupting the spatial aspect of
coordination, which is precisely what we observed. When
we inactivated anterior foci, we disrupted different hand
components of arm coordination, leaving reach components
intact. Our interpretation is that we blocked elements of the
population that send commands to distal forelimb muscles.
In contrast, when we inactivated posterior foci, we disrupted
predominantly reach components of forelimb coordination
presumably by blocking elements of the population that send
commands to proximal arm muscles.

The apparent failure of single unit mapping studies (Thach
et al. 1982, 1993; van Kan et al. 1993b) to reveal a site
specificity as clear as that seen with muscimol inactivation
may be a reflection of how the cerebellum normally performs
coordination. Discrete regions of the cerebellar nuclei are
not activated in isolation; instead, large populations of neu-
rons fire in combination (Fortier et al. 1989; Thach et al.
1993; van Kan et al. 1993b). Although virtually all of the
intermediate nuclear cells seem to require a hand component
in the task to ensure high rates of discharge (Gibson et al.
1996; van Kan et al. 1994), this does not mean that all of
these cells have a hand control function. Instead, it probably
reflects some involvement of hand shaping, gripping, and
manipulation, along with aiming and stabilization of reach,
in those voluntary tasks that engage the intermediate cerebel-
ulum. The perhaps highly specific contribution of any given
neuron to task performance may be obscured by the rela-
tively large number of cells participating in the movements,
unless more detailed correlations with specific skills or spe-
cific muscle activity patterns are attempted.

A model that relates the unique circuitry of parallel fibers
(PFs) to the spatial coordination problem has been proposed
by Thach, Goodkin, and Keating (1992a). According to this
model, coordination of muscle groups relies on beams of
active PFs exciting sets of Purkinje cells (PCs) in coronal
planes, which then regulate activity in corresponding sets of
nuclear cells that lie along a mediolateral axis. Their model
assumes that, within each nuclear zone, distal muscles are
innervated by medially located nuclear cells and proximal
muscles are innervated by laterally located nuclear cells.
They propose that a particular beam of PFs would become
active, and this would recruit a set of PCs controlling nuclear
cells along a mediolateral axis, thus coordinating the contrac-
tions of distal and proximal limb muscles. Our finding that
nuclear zones controlling distal and proximal muscles are
arranged along an anteroposterior axis does not support this
model.

The proposal that beams of PF activity coordinate distal
and proximal muscles is motivated by the synchronized re-
sponses of PFs evoked with electrical stimulation. However,
in awake behaving animals, mossy fiber inputs to the cerebel-
rum are not activated synchronously as would be required
to instantiate PF beams; instead, they are activated asynchro-
nously in graded patterns of repetitive discharge (van Kan
et al. 1993a). On the basis of known properties of granule
cells (D’Angelo et al. 1995), such mossy fiber inputs would
produce asynchronous patterns of activity in PFs rather than
the synchronous beams required in the Thach et al. (1992a)
model.

Are there other mechanisms that might be used to coordi-
nate anteroposterior sets of cerebellar nuclear cells? One
obvious possibility is the spread of positive feedback in the
limb premotor network (Houk et al. 1993). This network is
composed of recurrent connections from the intermediate
zone of nuclear cells to magnocellular red nucleus and, via
a ventral thalamic relay, to primary motor cortex. Collaterals
of rubrospinal and corticospinal fibers then innervate precer-
bellar neurons in the lateral reticular and pontine nuclei,
and these sources of mossy fiber input send collaterals to
innervate the intermediate nuclear cells to close the positive
feedback loop. The buildup of positive feedback in this net-
work appears to be responsible for recruiting the large popu-
lation of rubral and motor cortical cells that are needed to
activate the many muscles in the limb that participate in a
voluntary movement (Houk et al. 1993).

The spread of recurrent activity in the limb premotor net-
work would ensure that cells in AHZ and PRZ are recruited
as a coordinated population. Inhibition mediated by PCs in
paravermal zones of the cerebellar cortex then would have
the task of shaping this recurrent activity into a spatiotempo-
ral pattern that is appropriate for controlling the hand while
guiding the arm to its intended target. The cerebellar cortex
is organized into functional modules called olivocerebellar
complexes (Oscarsson 1980). Anteroposterior bands of PCs
are innervated by climbing fibers (CFs) that originate from
discrete sites within the inferior olivary nucleus (Voogd
and Bigaré 1980). These bands of PCs then converge upon small
clusters of nuclear cells, the same clusters innervated by
collaterals of the CFs (Oscarsson 1980; Voogd and Bigaré
1980). In several models of the cerebellum, these olivocere-
bellar complexes are considered as adaptive networks for
regulating motor commands in the cerebellar nuclei (cf.
Houk et al. 1996).

Different zones of the cerebellar nuclei participate in dif-
ferent olivocerebellar complexes in primates (Voogd et al.
1987), in a pattern that parallels other mammalian species
(Voogd and Bigaré 1980). NIA is innervated by anteroposter-
fior bands of PCs, designated C1 and C3, which receive
their CF input from the rostral portion of the dorsal accessory
olive (rDAO). In contrast, NIP is innervated by the anter-
oposterior band of PCs designated C2 which receives its CF
input from the rostral portion of the medial accessory olive
(rMAO). The organizational features that distinguish rDAO
and rMAO have been studied most extensively in the cat.
Bidirectional transport of a neuroanatomic tracer (wheat germ-
laglutin–horse radish peroxidase; WGA–HRP) demon-
strated that rDAO connections with NIA are organized soma-
topically with the hindlimb represented anterior and medi-
ally and the forelimb represented posterior and laterally
(Gibson et al. 1987), and a fine representation within fore-
limb NIA also has been demonstrated (Troto et al. 1990).
The low-threshold tactile receptive fields of rDAO neurons
emphasize the distal limb, whereas the predominantly pro-
prrioceptive receptive fields of rMAO include many cells
related to shoulder rotation (Gellman et al. 1983, 1985).

The above properties, if present also in the monkey, could
help to explain the anteroposterior gradient of limb represen-
tation we delineated with muscimol injections. Distal cuta-
neous signals transmitted from rDAO might provide a basis
for sensing deficits in hand shaping and manipulation. Proxi-
mal proprioceptive signals transmitted from rMAO might,
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instead, provide a basis for sensing aiming and stabilization problems. Through the training influences of their respective CFs, PCs in the C1–C3 or C2 bands each would learn to recognize patterns in their parallel fiber input array that allow them to fire or pause so as to shape the spatiotemporal pattern of nuclear cell activity appropriately. In this manner, the C1 and C3 bands of PCs would learn to regulate their nuclear targets in AHZ so as to coordinate hand movements, and the C2 PCs would learn to regulate their targets in PRZ so as to coordinate the reach. The coordination of reaching and grasping by these combined regulations would be an extension of the cooperativity demonstrated to result when many cerebellar modules function simultaneously in the control of a simulated two-link arm (Berthier et al. 1993).

In conclusion, we have used microinjections of muscimol into regions of the interpositus and adjacent regions of the dentate nucleus to demonstrate an anteroposterior specialization in the forelimb representation of the cerebellar nuclei. The results demonstrate that hand skills such as preparatory shaping and manipulation are represented anteriorly, whereas reaching skills such as aiming and stabilization of the arm are represented posteriorly. Within the anterior zone there is a finer representation of specific components of skilled hand use. These different functions appear to be consistent with the differential organization of climbing fiber input to the two forelimb zones, which may serve to shape the spatiotemporal pattern of nuclear cell activity so as to insure coordination between reaching and manipulation. Knowledge of the somatotopic relationships in the intermediate nuclear zone should facilitate the assessment of these and other potential mechanisms for coordination.

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