Effects of Muscimol Inactivation of the Cerebellar Nuclei on Precision Grip

Joël Monzée, Trevor Drew, and Allan M. Smith
Centre de Recherche en Sciences Neurologiques, Département de Physiologie, Université de Montréal, Montreal H3C 3T8, Canada

Submitted 13 December 2002; accepted in final form 8 November 2003

Monzée, Joël, Trevor Drew, and Allan M. Smith. Effects of muscimol inactivation of the cerebellar nuclei on precision grip. J Neurophysiol 91: 1240–1249, 2004; 10.1152/jn.01124.2002. A single monkey was trained to perform a grasp, lift, and hold task in which a stationary hand-held object was sometimes subjected to brief, predictable force-pulse perturbations. The displacement, grip, and lifting forces were measured as well the three-dimensional forces and torques to quantify specific motor deficits after reversible inactivation of the cerebellar nuclei. A prior single-cell recording study in the same monkey provided the stereotaxic coordinates used to guide intranuclear injections of muscimol. In total, 34 penetrations were performed at 28 different loci throughout the cerebellar nuclei. On each penetration, two 1.0-μl injections of 5 μg/μl muscimol, were made 1.0 mm apart either within the nuclei or in the white matter just lateral or posterior to the dentate nucleus. Injections in the region corresponding to the external interpositus nucleus produced pronounced dynamic tremor and dysmetric movements of the ipsilateral arm when the animal performed unrestrained reaching and grasping movements. In contrast, no relatively short-latency (∼15–20 min.) deficits were observed after injection in the dentate nucleus, although some effects were observed after several hours. When tested in a primate chair with the forearm supported and restrained at the wrist and elbow, the monkey performed the lift and hold task without tremor or dysmetria. However, with the restraint removed, the forces and torques applied to the manipulandum were poorly controlled and erratic. The monkey’s arm was ataxic and a 5-Hz intention tremor was clearly visible. In addition, the animal was generally unable to compensate for the predictable perturbations and the anticipatory force increases were absent. However, overall the results suggest that reversible cerebellar nuclear inactivation with muscimol has little effect on isolated distal movements of the wrist and fingers.

INTRODUCTION

In a review of cerebellar function, Thach et al. (1992) noted that there has been no general consensus about the different functional roles played by each of the deep cerebellar nuclei in the adaptive coordination of movement. In a more recent study, Goodkin and Thach (2003) described different major deficits produced by muscimol microinjections into each of the cerebellar nuclei. They suggested that the fastigial nucleus played a special role controlling the proximal musculature involved in postural support (e.g., sitting, standing, etc.). Injections into the anterior and posterior interpositus caused marked tremor of the arm, whereas injections in and around the dentate nucleus were reported to cause poor coordination of reaching and pinching with the arm unrestrained but only slight increases in reaction time when the arm was supported at the wrist and elbow.

However, our recent study of single-cell activity in the cerebellar nuclei did not find digit-related neuronal activity in the dentate during performance of an over-trained task where the monkeys had to grasp, lift, and hold an object with a precision grip for a few seconds (Monzée and Smith 2004). Also, more recent studies in animal and humans have suggested that some parts of the dentate might play a role in the “cognitive” control of movement (see Schmahmann 1997 for review). It would seem, therefore, that questions remain about the function performed by the deep cerebellar nuclei especially with respect to the relationship between dentate activity and movements of the hand. The variety of motor tasks used to elicit neuronal activity or demonstrate deficits makes a comparison between studies difficult, and impairments in the control of shoulder musculature can produce instabilities in grasping and object manipulation by the distal limb.

Martin and colleagues (Cooper et al. 2000; Martin et al. 2000) recently examined the impact of inactivation of the deep cerebellar nuclei on multitjoint coordination in cats. These studies suggested that the anterior and posterior interpositus nuclei have an important function in controlling the limb trajectory in reaching and grasping movements. Although their injections included the dentate nucleus, they did not describe any specific deficits associated with injections in this nucleus. Mason et al. (1998) injected muscimol into the interpositus nuclei close to the dentate in monkeys; this caused a variety of deficits in arm and hand motor functions and especially impaired both reshaping hand movements and object manipulation. However, it was not clear from the observations of Thach et al. (1992) or Mason et al. (1998) whether the motor deficits seen in the hand actually originated in wrist and finger muscles or were the result of an ataxia in more proximal limb muscles because the hand movements were performed naturally without restraint or support for the upper arm. That is, if the shoulder and elbow muscles were affected by cerebellar inactivation, inadequate stabilization of these joints might have contributed to the appearance of impaired wrist and digit movements.

Based on the deficits seen after local anesthesia of the fingers, Johansson and Westling (Johansson and Westling 1984a; Westling and Johansson 1984) demonstrated that cutaneous feedback was of critical importance in coordinating the grasping and lifting forces involved in object manipulation. Hikosaka et al. (1985) and Brochier et al. (1999) found significant motor deficits in the precision handling of small objects after inactivation of the hand area of somatosensory cortex in monkeys. After these injections, the monkeys lost manual dexterity and the ability to correctly appose the thumb and index finger for grasping objects. Neuronal recordings in both the cerebellar cortex and in the anterior interpositus nucleus in monkeys performing a lift-and-hold task found strongly mod-
ulated unit activity related to hand movements (Dugas and Smith 1992; Espinoza and Smith 1990; Monzé and Smith 2004). Consequently, the purpose of the present study was to examine the effects of inactivating the cerebellar nuclei on the grasp, lift, and hold task in a monkey in which the intermediate and lateral cerebellar nuclei had been extensively mapped for single-cell recording and for which stereotaxic coordinates were well established (Monzé and Smith 2004). This study focused on grasping and lifting with the arm restrained and unrestrained to examine specific impairments of finger movements after cerebellar nuclear inactivation.

**Methods**

A single adolescent female monkey (*Macaca fuscata*) weighing 3.8 kg was used in this experiment. After extensive single-cell recording from the dentate and interposed nuclei (Monzé and Smith 2004), this monkey was subjected to a series of reversible inactivations by injection of muscimol into different regions of the deep cerebellar nuclei. The study was approved by the animal ethics committee of the Faculty of medicine of the Université de Montréal.

**Lift-and-hold task and other behavioral observations**

The principal task was the same lift-and-hold task used in the previous study (Monzé and Smith 2004) although a variety of additional systematic observations were conducted to assess the motor functions of single digits and movements about the wrist, elbow and shoulder. The monkey was trained to grasp, lift, and hold a metal tab between 15 and 35 mm above the starting position for 2.5 s. A 1.0-KHz tone indicated that the tab was correctly maintained within the position window. The monkey performed the task either with the right arm free or constrained by an arnrest supporting the forearm at the wrist and elbow and restricting movement at the shoulder and elbow. On perturbed trials, a 100-ms force-pulse was given 1.5 s after the onset of the tone. The magnitude of the force-pulse perturbation was adjusted to between 1.5 and 5.0 N to produce a downward displacement of the object, which if unopposed, would have prevented the animal from receiving the fruit juice reward. To obtain the reward, the monkey had to resist to the force pulse by increasing the grip force and stiffening the wrist to maintain the object within the limits of the position window and to prevent it from slipping from the grasp.

In addition to the maintained precision grip task, other observations were conducted to assess the muscle synergies with the arm unrestrained or with the whole body unrestrained, as reported in previous studies (Brochier et al. 1999; Hikosaka et al. 1985; Matsumura et al. 1991; Schieber and Poliakov 1998; Thach 1996). Briefly, the monkey was required to reach and grasp small pieces of fruit. These pieces of fruit were sometimes presented in a modified Köhler board (Brochier et al. 1999; Lawrence and Kuyper 1968) to examine the dexterity of independent finger movements. This behavior required the use of a two-fingered, precision grip to extract small pieces of fruit (3–8 mm cubes) from a circular well 2 cm wide and 2 cm deep, which would not allow the whole hand to penetrate. To observe bimanual coordination, pieces of banana or orange were sometimes given to the monkey unpeeled, and some of these observations were recorded with a video camera.

**Apparatus**

The apparatus used in this experiment is illustrated in Fig. 1 of the Monzé and Smith 2004. The apparatus was essentially as described in earlier studies, although it was recently modified to add high-resolution measurement of the pressure exerted by each finger and an additional lightweight (9.4 g) 6-axis force and torque sensor (ATI Industrial Automation, Garner, NC) was added to measure side to side (x axis), and up and down (y axis), and pushing and pulling (z axis) forces. The force traces were fed to an analog-to-digital converter with 16-bit precision at a conversion rate of 250 Hz and that was used to calculate the three torque components.

**Surgical preparation and preinjection recording procedures**

Because the monkey had already been prepared for single-neuron recording, no further surgery was necessary. The injection system, which was adapted to the cylinder implanted for single-cell recording, was described in an earlier paper (Brochier et al. 1999). A stainless steel microwire was used to identify the cerebellar nuclei from the white matter below the cerebellar cortex by recording the cellular discharge. On some occasions, the insulated microwire was also used to stimulate the cerebellar nuclei. Using the coordinates from the extensive mapping obtained during cell recording sessions as a reference, the deep cerebellar nuclei were systematically explored searching for regions with activity specifically modulated during performance of the precision grip task. Whenever possible, the regions were tested for the presence of receptive fields. This examination consisted of imposing movements on the shoulder, elbow, wrist, and fingers and tapping the muscle mass of the arm or the thenar eminence, and cutaneous fields were identified by stroking the skin with a camelhair brush or by applying air puffs. In addition, on some occasions microstimulation was also conducted to assist in relating the injected regions to the hand.

**Muscimol injections**

The muscimol injections were performed with the monkey seated in a primate chair with the head immobilized as during the cell recording sessions described in Monzé and Smith (2004). The injections were performed ipsilateral to the working right hand. The injection system, described in Brochier et al. (1999), was lengthened to reach the cerebellar target areas. Briefly, the muscimol was injected with a 5.0-μ Hamilton syringe connected by a polyethylene tubing to a 31-gauge inner canula inserted in a larger, 25-gauge, external canula, which had a beveled tip to penetrate the cortical dura mater and the tentorium.

The canula system was mounted on a Trent-Wells micropositioner used for single-unit recordings. Both the inner canula and the extremity of the microwire were kept inside the external canula until the tip was in the white matter beneath the cerebellar cortex. The external canula was immobilized ~3–4 mm above the cerebellar nuclei. From this point, the inner canula and the microwire were advanced into the nuclei. Using a 50-μ enamel insulated stainless steel filament, we were able to record multiecellular activity and to apply microstimulation to assist in the identification of the nuclear gray matter. The injections consisted of two 1.0-μl (5 pg/μl) injections of muscimol. A first injection was made ~2.0–3.0 mm beneath the dorsal edge of the nucleus. The immediate cessation of electrical activity recorded by the canula microwire was used verify the actual ejection of muscimol. After injection, the canula was kept in place for 5–10 min and then withdrawn ~1.0 mm where a second injection was performed after which the canula was withdrawn completely. When effects on motor performance were observed, they generally persisted for several hours but were absent the following day. The onset of muscimol inactivation is rapid within 1.0 mm around the injection site, but, after an hour, it probably diffuses >2–3 mm from the injection site (Martin and Ghez 1999). Muscimol injections were never performed at <48-h intervals. The depth of the penetration was determined partly from the earlier single-unit recordings performed prior to this study but also confirmed by the cellular activity recorded with the microwire. In this way, we were able to establish the lateral limit of the dentate nucleus and all subsequent injections could be stereotaxically related to this lateral coordinate.
Histological analysis

Because the injection canula occasionally blocked, the muscimol was mixed with a fluorescent dye to help ascertain the injected volume. Fast Green was routinely employed, but Texas Red was used in a few injections to verify from postmortem examination that the entire dentate and interposed nuclei had been subjected to muscimol inactivation. At the conclusion of the inactivation study, the animal was killed with an overdose of pentobarbital and perfused transcardially with 0.9% saline followed by 4% paraformaldehyde. The brain was immersed in a solution of 20% sucrose at 4°C for 24 h for cryoprotection before freezing at −80°C. The cerebellum was then cut into 40-μ frozen coronal sections on a cryostat. Alternate sections were stained with cresyl violet or prepared for the immunofluorescence of Texas Red.

RESULTS
General behavioral observations after muscimol injection

Overall, motor deficits after muscimol injection were observed in 26/34 sessions. Qualitative observations of the monkey’s movements were made both in the primate chair and in unrestrained conditions for every inactivation session. These muscimol injections produced deficits that were qualitatively different in the three zones representing the fastigial, interposed, and dentate nuclei. Injections in or near the fastigial nucleus produced impairment of axial and proximal muscles of the trunk and leg with consequent loss of equilibrium. The proximal joints of the ipsilateral hip and shoulder were affected by injections in the posterior interpositus nucleus corresponding to the most rostromedial part of the intermediate zone. At more caudal and lateral loci within the anterior interpositus nucleus, the shoulder and elbow were even more affected but not the leg. Major impairments in reaching to grasp pieces of food were seen although dexterous finger movements (e.g., peeling a banana) could be well executed if the proximal upper arm was stabilized against the trunk. That is, no clear ataxia was ever seen involving the intrinsic muscles of the hand. Although we did not objectively quantify the monkey’s ability to extract food using two fingers from the narrow wells of a Klüver board, the animal appeared able to perform fine finger movements adequately if the upper arm was sufficiently well braced against the body trunk. For lateral cerebellar injection sites, the dysmetria and dynamic tremor of the ipsilateral arm only became visible more than two hours after the muscimol injections.

Histological examination of injection sites

In stereotaxic coordinates, the explored region extended laterally from 2 to 10 mm from the midline and 2 to 8 mm posterior to the interaural line. The microwire recording helped to distinguish the lateral and posterior limits of the dentate nucleus from white matter. Examination of the histological sections (see Fig. 2 in Monzée and Smith 2004) showed the gliosis due to the passage of the injection canula within the cerebellar nuclei in a coronal section of the cerebellum stained with cresyl violet. Vertical tracks indicate the canula penetrations. Labeling with Texas Red was seen throughout the entire extent of the cerebellar nuclei, indicating that during the course of this study, the entire nuclear region of the cerebellum had been subjected to muscimol inactivation. A comparison of the stereotaxic coordinates derived from single-cell recording with those producing inactivation deficits indicated that the insertion of the more flexible injection canula systematically deviated 1–2 mm rostrally. Once this systematic deviation had been corrected, it became clear that the region which yielded the greatest concentration of task-related unit activity was also the same region producing the clearest inactivation deficits; the anterior interpositus nucleus.

Although the recording microwire used to record nuclear electrical activity did not reliably isolate single cells, multicellular activity could be recorded, and on some occasions, multunit receptive fields helped identify the somatotopy of the spinal input to a particular region. The cellular properties of the intermediate regions responded to the stretch or taping of the arm and hand muscles. In some cases, electrical stimulation evoked contractions in forearm arm muscles including digit flexion especially in the region corresponding to the anterior interpositus.

Figure 1 shows the muscimol injections sites. Only 28/34 sites are shown on the map because injections into the same site were sometimes repeated on separate occasions to confirm the original observations. Three zones were used to categorize the motor deficits described in this study. Generally, when we injected muscimol in the most medial sites (zone A) corresponding approximately to the fastigial nucleus, the inactivation was associated with ataxia in axial, trunk muscles, and the proximal muscles of the leg. Occasional involvement of the shoulder may have been due spread into the adjacent posterior interpositus. Injections made in the intermediate (zone B) zone had the most immediate and powerful effects on arm movements. In contrast, the effects on arm movements obtained from injections in the lateral border of the dentate (zone C) only appeared after an interval of ≥2 h.

Precision grip

The intermediate zone injections produced effects within 15–30 min after injection, whereas the more lateral injections required ≥2 h before the earliest signs of motor impairment appeared. In our opinion, the effects of these lateral injections arose from diffusion to the intermediate zone and specifically the anterior interpositus rather than by direct inactivation at the injection site. Similar but much less marked effects were also sometimes observed with medial injections possibly due to diffusion into the posterior interpositus. Diffusion into the anterior interpositus was thought to be unlikely because of its greater distance from the fastigial nucleus in the primate.

Precision grip task with the arm unrestrained or restrained

The most frequent error made by the monkey performing the lift and hold task was releasing the object before the required 2.5 s had elapsed. Occasional errors of overshooting the upper limit of the position window also occurred. In terms of general task performance, the monkey made more errors (62 vs. 80%, t-test, P < 0.001) overall with the arm unrestrained due to its inability to maintain steady grasping for the required 2.5-s duration. Table 1 shows the effect of muscimol injection on task performance expressed as the number of rewarded trials as a function of both the distance from the midline and whether the arm was restrained or unrestrained. It can be seen from
TABLE 1. Effect of muscimol injection on rewarded trials

<table>
<thead>
<tr>
<th>Injection Zones</th>
<th>A</th>
<th>B†</th>
<th>C‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral coordinates, mm</td>
<td>3.0</td>
<td>3.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Post injection duration, min</td>
<td>0</td>
<td>60</td>
<td>15–80</td>
</tr>
<tr>
<td>Number of injection sites (with task test)</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Arm unrestrained</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Number of trials (n)</td>
<td>43</td>
<td>137</td>
<td>402</td>
</tr>
<tr>
<td>Mean of rewarded trials, %</td>
<td>97</td>
<td>44</td>
<td>40 ± 20*</td>
</tr>
<tr>
<td>Arm restrained</td>
<td>—</td>
<td>21</td>
<td>268</td>
</tr>
<tr>
<td>Number of trials (n)</td>
<td>—</td>
<td>26</td>
<td>643</td>
</tr>
<tr>
<td>Mean of rewarded trials, %</td>
<td>—</td>
<td>77</td>
<td>71 ± 17*</td>
</tr>
</tbody>
</table>

Coordinates with a single observation could not be evaluated statistically. * Significant < 0.01; † pooled data in zone B: significant (P < 0.000); ‡ pooled data in zone C: significant (P < 0.042).

The 28/34 injection sites are mapped on the cerebellar nuclear contours as seen in a horizontal section. Three zones were used to categorize the motor deficits described in this study. Muscimol injections in the most medial sites (zone A) corresponding approximately to the fastigial nucleus, produced ataxia in axial trunk muscles and the proximal muscles of both the arm and leg. Injections made in the intermediate (zone B) zone had the quickest and most powerful effects on arm movements. Injections in the lateral zone (zone C) correspond to dentate nucleus and were not associated with any immediate motor deficits. Hatched lines indicate the separation among zones A–C. AIN, anterior interpositus nucleus; DN, dentate nucleus; FN, fastigial nucleus; PIN, posterior interpositus nucleus.

Table 1 that with the forearm restrained, task performance remained relatively good throughout. In contrast, with the arm unrestrained, the ability to obtain the fruit juice reward was impaired after zone B and C injections compared with zone A as indicated by t-test shown in Table 1. However, task performance was evaluated 30 min postinjection for zone B and >2 h postinjection for zone C. For injections in the medial zone, the monkey did not show as marked signs of dysmetria and dynamic tremor as with intermediate area injections. Figure 2 compares a single trial before and after a muscimol injection in the vicinity of the fastigial nucleus. A slight hypermetria can be seen in the load force trace but the deficits described in this study. Muscimol injections in the most medial sites (zone A) corresponding approximately to the fastigial nucleus, produced ataxia in axial trunk muscles and the proximal muscles of both the arm and leg. Injections made in the intermediate (zone B) zone had the quickest and most powerful effects on arm movements. Injections in the lateral zone (zone C) correspond to dentate nucleus and were not associated with any immediate motor deficits. Hatched lines indicate the separation among zones A–C. AIN, anterior interpositus nucleus; DN, dentate nucleus; FN, fastigial nucleus; PIN, posterior interpositus nucleus.

Figure 2 shows the task performance immediately after with the arm restrained and supported at the elbow and wrist. The 50-trial average prior to injection is represented by - - -; depict a single trial within 15 min after muscimol injection. The traces have been aligned on the reward (not shown). The x-axis force (horizontal plane) and the y- and z-axis torques all showed evidence of marked dynamic tremor that was most clearly visible in the pronation and supination direction. In general, the erratic force traces captured by the manipulandum were the result of ataxia arising from the elbow and the pronator and supinator muscles of the forearm. The slight overshoot in the displacement does not really represent hypermetria or tremor since these were successful trials in which the manipulandum was correctly lifted and held within the position window. More dysmetric movements were seen but these trials were unrewarded and are not shown. Similarly, the undershooting in the arm-restrained condition is not evidence of hypometria nor were any hypometric movements observed on the error trials either. Although these dysmetric force traces are presented as a single-trial example, they were in fact typical of injections in the region of the anterior interpositus nucleus, and these observations were both repeatable and reliable. Figure 3B shows the monkey’s performance of the task immediately after with the arm restrained and supported at the elbow and wrist. Under these conditions, the task was as well executed as before the muscimol injection.
In striking contrast to the performance shown in Fig. 3A, Fig. 3B shows no trace of dysmetria or dynamic tremor.

The dynamic tremor seen in the z-axis (pronator/supinator) torque trace was a reliable observation in all injections made in the anterior interpositus. Figure 4 shows z-axis torque on 10 trials from three separate injections made at ~4.5 mm lateral to the midline and an identical number of trials with the forearm restrained. The pronator-supinator tremor with the arm unrestrained was equally apparent regardless of whether the arm was first tested restrained or unrestrained. A fast Fourier analysis of z-axis torque for the 2.5-s holding period shown in Fig. 4 indicated a peak at a tremor frequency of ~5 Hz on each trial. The mean for the thirty trials shown in Fig. 4 was 4.9 ± 0.2 (SD) Hz. Figure 5 shows two attempts, with the arm unsupported, to lift and hold and compensate for the force-pulse perturbation with obvious dysmetria and tremor evident in the force traces.

**Predictable perturbations to the precision grip**

On 6/34 occasions when inactivation produced a significant arm ataxia, a predictable, 100-ms, force-pulse perturbation was tested during the static holding phase of the task. As described in Monzée and Smith (2004), the 100-ms force pulse occurred 1.5 s after the onset of the tone when the tab was held stationary within the position window. To obtain the reward, the monkey was required to increase the grip force and stiffen the wrist to avoid slip due to the downward force pulse. When the injection sites were in the region of the most medial cerebellar nucleus, the monkey’s task performance was rela-
**FIG. 3.** A: the effect of muscimol injection into the region of the anterior interposed nucleus (zone B in Fig. 1) on task performance is shown with the arm unsupported at the elbow and wrist. The dotted lines represent a 50-trial average prior to injection. The thicker black lines depict a single trial within 20 min after a muscimol injection. B: the task performance following immediately after the performance shown the Fig. 4A, with the arm restrained and supported at the elbow and wrist. The thin lines represent the 50-trial average prior to injection. The thick lines depict a single trial after muscimol injection with no trace of dysmetria or dynamic tremor.
tively unaffected with success ratio varying between 68 and 97% over several hundred trials. In contrast, for injection sites in the region of the anterior interposed nucleus, successful trials only comprised between 10 and 48% of the total trials. This observation was based on a smaller sample because of the difficulty in maintaining the animal's motivation in the face of repeated failure.

A single, successful trial in response to the perturbation with the arm unrestrained is shown in Fig. 6. The coordination between the grip and lifting forces is ataxic, the grip force is poorly maintained and tremor is evident in the y- and z-axis torque traces. In addition, an anticipatory increase in grip force just prior to the perturbation appears to be absent even though this was a successfully rewarded trial. Despite this absence, a reflex-like, triggered reaction is still visible in the grip force trace, although with this degree of arm ataxia, the monkey was generally reluctant to work with the perturbation.

**DISCUSSION**

In general, the results of cerebellar nuclear inactivation support the findings from single-cell recording (Monzée and Smith 2004) that the anterior interpositus nucleus shows a greater involvement in the performance of the lift-and-hold task than the dentate nucleus. The most unexpected observation from the inactivation injections was the failure to find ataxia in the distal finger muscles when the more proximal muscles had been stabilized and restrained.

**Effects of reversible inactivation of the deep cerebellar nuclei**

The present study generally agrees with results reported by Bracha et al. (1999), Martin and Ghez (1999), and Martin et al. (2000) in the cat and Goodkin and Thach (2003) and Mason et al. (1998) in the monkey that muscimol injections in area of interpositus produced the clearest effects on motor control. In the cat, Martin et al. (2000) found that although inactivation of the dentate nucleus slowed movement execution, it did not impair reaching and grasping. Mason et al. (1998) reported specific motor deficits in reaching and grasping associated with both the interpositus and dentate nuclei, but they did not really attempt to make muscimol injections limited to the dentate alone. Goodkin and Thach (2003) reported that dentate nucleus injections caused ataxic reaching and pinching with the arm free but only slight increases in reaction time when the arm was supported at the wrist and elbow. We were unable to demonstrate any motor impairment after muscimol injections from the dentate nuclei that could not be ascribed to diffusion into anterior interpositus. Observable effects from the dentate were only apparent after >2 h. This long delay suggested to us that the impairments were due to diffusion into the anterior interpositus and not due to a local inactivation of the dentate alone. Goodkin and Thach (2003) reported that dentate nucleus injections caused ataxic reaching and pinching with the arm free but only slight increases in reaction time when the arm was supported at the wrist and elbow. We were unable to demonstrate any motor impairment after muscimol injections from the dentate nuclei that could not be ascribed to diffusion into anterior interpositus. Observable effects from the dentate were only apparent after >2 h. This long delay suggested to us that the impairments were due to diffusion into the anterior interpositus and not due to a local inactivation of the dentate alone. However, activity in dentate neurons has been associated with the initiation of fast, ballistic movements (Chapman and Lamarre 1987), and our testing did not examine the possibility that the muscimol might have produced a slowness to initiate fast movements.

**Cerebellar ataxia**

Cerebellar ataxia comprises several different motor impairments arising from direct or indirect damage to the cerebellum that result in uncoordinated activity in groups of muscles usually spanning multiple joints. Ataxia may be further subdivided into symptoms of dysmetria and dynamic tremor, which are only evident when the affected muscles are voluntarily activated. Several recent studies (Bastian 1997; Bastian and Thach 1995; Bastian et al. 1996, 2000; Sainburg et al. 1995; Timman et al. 1999) have suggested that clinical ataxia is in part due to an inability to compensate for interaction torques generated by the rotation of one joint on the rotation of another during multiarticular movements. With prehension and in par-
ticular during isometric pinching, these interaction torques would be minimal or absent, and this may partly explain the absence of any effect of cerebellar inactivation specific to finger muscles.

Role of cerebellum in feedback and feedforward control

Some time ago, Allen and Tsukahara (1974) suggested that the lateral and intermediate subdivisions of the cerebellum reflect separate loop circuits with different functional roles. The lateral cerebellum (hemispheric cortex and dentate nucleus) was thought to be more involved with planning and preprogramming movements, whereas the intermediate cerebellum (paravermal cortex, and anterior and posterior interpositus nuclei) were said to be implicated in correcting and revising the motor commands during movement execution. However, nuclear recording in monkeys during a grasp-and-hold task did not support a strict nuclear segregation of the feedback and feedforward controls within the cerebellum. Instead, Monzée and Smith (2004) suggested that the anterior interpositus plays a more important role than the dentate nucleus in both the feedback and feedforward control over movements of the hand. In addition, recent anatomical tracing studies by Strick (Hoover and Strick 1999; Middleton and Strick 1997, 2001) using the retrograde transneuronal transport of herpes simplex virus reported that although a small part of the dentate nucleus projects to the hand area of the motor cortex, a substantial portion projects to prefrontal and posterior parietal areas, suggesting a role in more cognitive functions in addition to its involvement in motor control.

Role of the cerebellar nuclei in digit motor control

In contrast to the results of the present study, muscimol inactivation in the finger region of the motor cortex produced an inability to execute independent finger movements (Schieber and Poliakov 1998) and a substantial reduction in pinch force in the same lift-and-hold task (Brochier et al. 1999). Microinjections of muscimol into the hand region of the somatosensory cortex produced inappropriate grip force increases with a marked loss of manual dexterity task (Brochier et al. 1999). In general, muscimol injection into the cerebellar nuclei did not duplicate the specific impairments in hand muscle control induced by injections in cerebral cortex. Although single-cell recording in the anterior interpositus in the same monkey had previously found unit activity that appeared

FIG. 5. Two examples (A and B) of unsuccessful attempts to lift and hold with the arm unrestrained. Both examples show evidence of ataxia and tremor. Traces are aligned on grip onset.
strongly related to finger movements in the grasp-and-hold task (Monzée and Smith 2004), no pure grasp-related deficits were seen after anterior interpositus nucleus inactivation.

In the cat, Martin and collaborators (Cooper et al. 2000; Martin et al. 2000) reported muscimol inactivation of the anterior interpositus produced deficits in both reaching and prehension in cats trained to reach and grasp small cubes of meat. Among the impairments of limb movements they noted a difficulty with movements about the metacarpal-phalangeal joints related to feline prehension (Cooper et al. 2000). In contrast, we found no such deficits in the monkey when the forearm was supported and constrained at the wrist. However, the monkey, unlike the cat, has both intrinsic and extrinsic finger muscles and therefore has greater control and range of motion over the most distal interphalangeal joints. The paradoxical absence of a substantial deficit in prehension in the monkey compared with the cat may be due in part to the increased capacity of the motor cortex with its cortico-motoneuronal connections to compensate for the loss of cerebellar input.

It is interesting to compare the reported deficits in grasping with the effects of cerebellar lesions on ball throwing, which requires precisely timed hand opening (Hore et al. 2002; Timmann et al. 2001). Hand opening is essentially achieved by the forearm extensor digitorum communis, which is not an intrinsic hand muscle. Nevertheless, Mai and collaborators also reported isometric pinch force instability in patients with cerebellar lesions (Mai et al. 1988, 1989), but the pinch gauge transducer was held freely by the unsupported ataxic arm maintaining a normal position at the shoulder and the elbow flexed at 90°.

FIG. 6. The effect of a muscimol injection into the region of the anterior interposed nucleus on anticipatory responses to a predictable perturbation. The dashed lines represent a 50-trial average prior to injection with no perturbation. The thicker black lines depict a single trial within 20 min after a muscimol injection showing the reaction to the perturbation. Although a reflex-like response is seen in the grip force trace after the perturbation, the preparatory increase in grip force in anticipation of the perturbation is absent.
similar study of patients with cerebellar lesions performing a lift-and-hold task with the arm supported at the elbow, but not the wrist, was reported by Müller and Dichgans (1994), who also noted an irregular temporal pattern in the pinch force rate. It is therefore of some interest to know how patients with cerebellar lesions would behave with the forearm restrained at both the elbow and wrist. Bastian and Thach (1995) examined two patients with superior cerebellar artery infarcts who were asked to pinch and lift a coin with the forearm supported but with the wrist and fingers free to move. They reported marked deficits in both the positioning and timing of the index and thumb on the coin with frequent dropping. However, it is unclear how much pronator and supinator movements were restrained at the wrist. The reported deficit may have been due in part to a misalignment of the thumb and index causing an undesired torque on the coin and consequent loss of grasp stability. In contrast, the single degree of freedom allowed by our apparatus may have helped the monkey to grasp and lift in a way that a free-standing object with little inertia like a coin would not. Although we did not observe any substantial or consistent pronator-supinator torques after muscimol injection, this aspect deserves further study. Our results imply that the intrinsic finger muscles may be less affected by cerebellar damage than one might have expected from either the clinical literature or single-cell recording in trained monkeys.

ACKNOWLEDGMENTS

The technical assistance of L. Lessard, J. Jodoin, C. Gauthier, and C. Valiquest is gratefully acknowledged.

GRANTS

This research was supported by a grant to Groupe de Recherche en Sciences Neurologiques from the Canadian Institutes for Health Research Council and to the Groupe de Recherche sur le Système Nerveux Central from the Fonds pour la Formation des Chercheurs et l’Aide à la Recherche and the FRSQ–FCAR Santé program.

REFERENCES