Impaired Reaching and Grasping After Focal Inactivation of Globus Pallidus Pars Interna in the Monkey

KIRSTIN K. WENGER, KRISTINA L. MUSCH, AND JONATHAN W. MINK

Department of Neurology and Program in Physical Therapy, Washington University School of Medicine; and St. Louis Children's Hospital, St. Louis, Missouri 63110

Wenger, Kristin K., Krystina L. Musch, and Jonathan W. Mink. Impaired reaching and grasping after focal inactivation of globus pallidus pars interna in the monkey. J. Neurophysiol. 82: 2049–2060, 1999. The purpose of this study was to test the hypothesis that the basal ganglia output from globus pallidus pars interna (GPI) contributes to inhibition of competing motor patterns to prevent them from interfering with a volitional movement. To test this hypothesis, the kinematics of a natural reach, grasp, and retrieval task were measured in the monkey before and after focal inactivation in GPI with the GABA<sub>A</sub> agonist muscimol. Two rhesus monkeys were trained to reach in a parasagittal plane to grasp a 1-cm cube of apple and retrieve it. Reflective markers were applied to the shoulder, elbow, wrist, and index finger. Movements were videotaped at 60 fields/s, digitized, and analyzed off-line. In each session the monkey performed 12–15 reaches before and 12–15 reaches after injection of 0.5 µl of 8.8 mM muscimol. Muscimol was injected into 22 separate locations in the “arm” area of GPI. Inactivation of the GPI with muscimol produced movement deficits in a reach-grasp-retrieve task that can be summarized as follows: 1) decreased peak wrist velocity during the reach to target; 2) decreased elbow and shoulder angular velocities, with elbow angular velocity relatively more impaired than shoulder angular velocity; resulting in 3) higher maximum vertical wrist and index finger positions at the apex of the reach; 4) prolonged latency from the end of the reach to the completion of grasp; and 5) less impairment of retrieval than reach, with inactivation at the majority of sites causing no impairment and some actually speeding up retrieval despite slow reaching. The results of this study show that reaching movements are impaired in a specific way after focal inactivation of GPI in previously normal monkeys. The slowing of the reach with normal (or fast) retrieval suggests that there is difficulty inhibiting the posture holding mechanisms that were active before the reach, but that assist the retrieval. The nature of the impairment supports the hypothesis that GPI lesions disrupt the ability to inhibit competing motor mechanisms to prevent them from interfering with desired voluntary movement.

INTRODUCTION

It is generally agreed that the basal ganglia play a role in the control of movement. However, the specific contribution of the basal ganglia to normal movement remains controversial. Inactivation or ablation of basal ganglia output neurons for limb movement in globus pallidus pars interna (GPI) has been used to study the contribution of basal ganglia circuits to an otherwise intact motor system. Although many previous studies have described clear and consistent deficits after GPI lesions, others have revealed little or no effect on movement (see DeLong and Georgopoulos 1981; Mink 1996a for review). Discrepancy among findings has been attributed to factors such as lesion placement, lack of quantitative behavioral measures, or task differences. An additional confounding factor is the observation that lesions of the GPi can improve movement in Parkinson’s disease (Baron et al. 1996; Lang et al. 1997).

The most consistent finding in primates after GPi lesion is slowing of movement, muscular co-contraction, and a flexor positional bias (DeLong and Coyle 1979; Hore and Vilis 1980; Inase et al. 1996; Mink and Thach 1991). In concordance with known properties of GPi discharge during movement, we have hypothesized that the basal ganglia output acts during voluntary movement to inhibit potentially competing motor patterns (Mink 1996a; Mink and Thach 1993; Thach et al. 1993). During any given movement, the desired movement must be planned and executed, but also a multitude of potentially competing motor mechanisms must be inhibited to prevent them from interfering with the desired movement. It follows that removal of GPi output would lead to unwanted competition resulting in slowness of movement, muscular co-contraction, and abnormal postures.

The purpose of this study was to test the general hypothesis that the GPi output contributes to inhibition of competing motor patterns in monkeys performing a natural reach and grasp task before and after reversible inactivation of GPi neurons. For the primate sitting upright, the typical posture is one of flexed arms, legs, and neck. In that posture, tonic neck, vestibular, and other postural mechanisms favor flexion (Denny-Brown 1967; Magnus 1924; Mink 1996a). Movement of any limb out of the initial position requires selective inhibition of those postural mechanisms, for that limb only, in addition to activation of mechanisms involved in producing the desired movement. Inability to inhibit those posture-holding mechanisms for the moving limb would be expected to slow movement and to bias movement toward that initial flexed posture. We hypothesized specifically that GPi inactivation in the monkey would result in an impairment in moving a limb out of the initial posture, but little or no impairment in returning the limb to the initial posture.

To test this hypothesis, two monkeys were studied while they performed a reaching task before and after GPi inactivation with the GABA<sub>A</sub> agonist muscimol. The task consisted of a reach-grasp-retrieval sequence in which the monkey’s target (and reward) was an apple bit. The monkeys, already familiar with the experimenter and with sitting in a primate chair, readily learned this task over the course of only five training sessions. No limits on reaction time, movement time, or reach
Subjects and apparatus

METHODS

Subjects and apparatus

Two male rhesus monkeys (monkeys T and L) weighing 7–10 kg were trained to sit in a primate chair and reach for a bit of apple. The monkeys were restrained only by a collar-like aluminum plate attached to the chair into which they inserted their necks. The monkeys were conditioned to sit upright in the chair with their legs flexed, upper arms vertical, elbows flexed 80–90°, and each hand lightly grasping the top of a 1-in. diam pole (Fig. 1). A apple bit, ~1 cm³, was presented on the end of a small flexible stick (mounted on a fixed pole) at shoulder height in front of the right shoulder and at a distance such that it was aligned with the metacarpal-phalangeal joint with the arm outstretched. The straight path distance of the wrist from the starting position to the target was ~24 cm for monkey T and 28 cm for monkey L. The apple bit was presented as a target only if the monkey assumed the required initial posture. Once the apple bit was attached to the stick, the monkey could reach with the right arm to grasp, retrieve, and eat the apple bit. If the monkey began to reach with the left arm, he was prevented from obtaining the apple bit. The monkeys had been trained previously to perform a wrist movement task similar to those described by Mink and Thach (1991).

Localization of GPi and injection protocol

Surgery was performed in a stereotaxic frame under general anesthesia with Isoflurane. Using sterile technique, the scalp, the left temporalis muscle, and the peristeum were reflected. Six stainless steel screws were inserted through the outer table of the skull and covered with methyl methacrylate. The exposed skull was also covered with methyl methacrylate, and bolts were imbedded in the acrylic to allow fixation of the head during recording. After the animal recovered and the behavior returned to baseline, a second procedure was performed to place a 20 × 20 mm square Lucite chamber centered over the left GPi at 50° from vertical in the coronal plane [stereotaxic coordinates A12.0, L9.0, H6.0 (Snider and Lee 1961)]. The animal was given analgesia with buprenorphine and acetaminophen after each procedure.

The borders of GPi were localized with single-unit recording during a wrist movement task and with microstimulation. The animal was seated in a primate chair with attached wrist manipulandum as described by Mink and Thach (1991), and the head was held by bolts attached to the acrylic cap. Multiple penetrations were made at 1-mm intervals while recording neuronal discharge patterns at rest and during wrist movement (Mink 1996b). GPi was identified by the characteristic high-frequency tonic discharge rate of neurons in this structure (DeLong 1971). The adjacent internal capsule was identified by fiber activity characteristic of fibers and with microstimulation. The optic tract was identified by change in discharge evoked by light. Injection sites were chosen to be at sites within GPi where neurons discharged in relation to right upper extremity movements and a minimum of 1 mm from the dorsolateral border to avoid spread of muscimol into GPes.

Before injection, a series of 12–15 reaches was performed by the monkey, and data were collected as described below. A 10-μl syringe with a 24-gauge needle was filled with 8.8 mM (1 μg/μl) muscimol (Sigma). In some sessions, a tungsten microelectrode (impedence 300 kΩ to 1 MΩ) was attached to the syringe needle with the electrode tip extending ~300 μm beyond the needle tip. The head was held, and the syringe was attached to a microdrive and the Lucite chamber. After the monkey performed a series of wrist movements (Mink 1996b), the syringe was lowered to the predetermined target coordinates. A total of 0.5 μl of muscimol was injected in 0.1–0.2 μl increments over a 5-min period. The monkey performed a series of wrist movement tasks again, the injection needle was withdrawn, and a second series of 12–15 reaches was performed 30–45 min after the muscimol injection was completed. At least 2 days elapsed between injections to assure that there was no residual effect of muscimol. In four sessions, 0.5 μl of saline was injected as a control for nonspecific effects of injection.

Data collection and kinematic analysis

To identify the index finger, wrist, elbow, and shoulder joints for video-based motion analysis, bright white circular markers, 1.5 cm diam, were painted on the skin overlaying the acromion (shoulder), lateral epicondyl (elbow), and extensor aspect of the wrist. The tip of the right index finger was also painted white. The white markers were outlined in black to increase the contrast. The subjects were videotaped at 60 fields per second. The video camera recorded the movements in the sagittal plane and was zoomed-in to provide the largest image possible. Marker positions were tracked and digitized using a Peak Performance Motion Measurement System, and the data were smoothed using a fourth-order Butterworth filter at 6 Hz. Angular displacements were calculated from the marker positions; angular and linear displacement data were numerically differentiated to calculate velocity and acceleration. The joint angle conventions used for data analyses were as follows: 1) for the elbow, 180° was defined as full extension (arm and forearm in line) and decreasing angle was referred to as flexion; and 2) for the shoulder, 180° was defined with the arm...
vertical at the monkey’s side and decreasing angle was referred to as flexion.

For analysis, the movement was broken into three phases: 1) reach to target, 2) grasp of target, 3) retrieval of target. Using custom software, the following events were defined and marked: 1) “Start of movement” (reach or retrieval) was defined as the time and position at which the tangential wrist velocity exceeded 10% of its peak; 2) “End of movement” (reach or retrieval) was the time and position at which the wrist velocity dropped below 10% of the peak or (in a few trials) when the tangential velocity reached a minimum prior to a subsequent corrective movement; 3) “Grasp” was defined as the time at which the hand closed around the apple cube target. Kinematic data for the reach and retrieval phases were analyzed from start of movement to end of movement, before any corrective movements. Endpoint error was the distance between the tip of the index finger and the target in horizontal (X) and vertical (Y) dimensions at the end of the first phase of the movement.

Data were analyzed from 10 trials before injection and 10 trials after injection. The 1st 10 trials in which the monkey satisfied the above specified criteria (i.e., waiting for the target to be in position before beginning reach, reaching with right arm) were chosen for analysis. For comparisons between control and muscimol within each injection, the kinematic data were analyzed using unpaired t-tests. If the peak tangential wrist velocity after muscimol injection was significantly different from control, the data were included for further analysis across injections using paired t-tests. Unless otherwise indicated, the results are expressed as means ± SD.

**Histology**

To verify the accuracy of localization using physiological methods, the brain of one monkey was processed for histology. After being given a lethal dose of pentobarbital sodium, the monkey was perfused transcardially with normal saline followed by 4% paraformaldehyde.

The brain was removed, fixed for 4 wk, and subsequently saturated with 4% paraformaldehyde in a 40% sucrose solution. The brain was blocked in the coronal plane, frozen, cut in 50-μm sections with a microtome, and stained with thionin. Evaluation of the stained sections in comparison with the physiologically identified landmarks revealed that the physiological mapping was accurate to within 0.5 mm. The injection locations from the second monkey were based on physiological mapping.

**RESULTS**

The normal reach in our paradigm consisted of a slightly curved wrist path that was made by flexing the shoulder and slightly flexing and then extending the elbow (Fig. 2). As the apple bit target was reached, the monkey grasped the target and then retrieved the apple bit to his mouth by flexing the elbow and extending the shoulder. As described in METHODS, the sequence was divided into three phases for analysis: 1) Reach to target, 2) Grasp of target, and 3) Retrieval. Figure 2 shows wrist position, and elbow and shoulder angles over the course of a typical reach. In the normal state, both the reach to target and retrieval were performed with a single movement, i.e., with no corrective sub-movements.

Muscimol was injected at a total of 22 sites in the GPi of 2 monkeys: 10 in monkey T, 12 in monkey L. Using peak tangential wrist velocity during the reach to target phase as the dependent variable, significant deficits (P < 0.05, t-test) were seen after injection into nine sites in monkey T and six sites in monkey L (Tables 1 and 2).

**Slowing of reach to target after GPi inactivation**

Inactivation in GPi caused slowing of peak wrist velocity during the reach at the majority of injection sites. Average peak wrist velocities for the effective injection sites are shown in Table 1. When averaged across injections, peak tangential wrist velocity was decreased to a similar degree in the two monkeys (Fig. 3). In monkey T, peak wrist velocity decreased from 87 to 74 cm/s (t = 8.76, P < 0.001) and in monkey L, peak wrist velocity decreased from 100 cm/s to 85 cm/s (t = 4.55, P < 0.01). Accompanying the decreased peak tangential wrist velocity was a prolongation of movement time from 435 to 562 ms (t = −4.53, P < 0.01) in monkey T and from 440 to 528 ms (t = −2.92, P < 0.05) in monkey L. Correlation between injection number and preinjection (control) wrist velocity in each monkey was not significant (monkey T, r = 0.42; monkey L, r = −0.59), hence the deficits were not due to injury caused by repeated penetrations.

Injections that produced slowing of peak wrist velocity during the reach also decreased elbow and shoulder angular velocities. In both monkeys, the percentage decrease of elbow angular velocity was significantly greater than the percentage decrease of shoulder angular velocity. Average peak elbow and shoulder angular velocities for the effective injection sites are shown in Table 2. In monkey T, elbow angular velocity decreased from 263 to 182 deg/s (t = 14.58, P < 0.001), and shoulder angular velocity decreased from 330 to 273 deg/s (t = 6.91, P < 0.001). The percentage elbow angular velocity decrease (29.4%) was greater than the shoulder angular velocity decrease (16.9%; t = 9.06, P < 0.001). In monkey L, elbow angular velocity decreased from 296 to 240 deg/s (t = 10.41, P < 0.001), and shoulder angular velocity decreased from 302 to 253 deg/s (t = 8.24, P < 0.001). The elbow angular velocity decrease (19.3%) was greater than the shoulder angular velocity decrease (16.4%; t = 3.97, P < 0.05).

Slow reaching due to GPi inactivation was accompanied by an increase in the maximum vertical wrist position during the reach. During the normal reach to target, the monkey’s wrist typically followed a curvilinear path in which the wrist acquired its maximum vertical position when the target was grasped. After GPi inactivation, the monkey tended to follow a more curved wrist path in which the maximum vertical position of the wrist was greater than the final vertical position and occurred before the target was grasped. In monkey T, the mean maximum vertical wrist position increased from 2.9 cm below target to 2.3 cm below target (t = 3.21, P < 0.05). In monkey L, maximum vertical wrist position increased from 1.1 cm below target to 0.8 cm below target (t = 4.78, P < 0.01).

**Reach endpoint accuracy**

Gpi inactivation caused slight yet consistent impairment of index finger endpoint accuracy in the vertical (Y) direction but not in the horizontal (X) direction (Fig. 4). When averaged across injections, the Y endpoint of the index finger was increased to a similar degree in the two monkeys. In monkey T, the Y endpoint increased from 0.7 ± 0.17 cm above the target to 1.3 ± 0.46 cm above the target (t = −4.18, P < 0.01) and in monkey L, the Y endpoint increased from 0.9 ± 0.27 cm above target to 1.2 ± 0.31 cm above target but did not reach significance. These results are comparable to those shown.
above for maximum vertical wrist position during the reach and reflect a slight impairment of the reach path.

Retrieval phase of movement

For injections that caused slowing of the reach to target, retrieval speed was normal after most injections (n = 11), but was slow after others (n = 4). We grouped the data into two categories for further analysis: injections causing slow reach but normal retrieval, and injections causing slow reach and slow retrieval (Fig. 5).

Injections causing slow reach but normal retrieval

Inactivation in GPi did not cause slowing of peak tangential wrist velocity during the retrieval of the apple bit target for five injections in monkey T and for six injections in monkey L. In fact, the velocity of retrieval was slightly faster on average after muscimol injection in monkey L. Figure 2 shows the kinematics for a injection with slow reaching but normal retrieval. Individual graphs are as follows: wrist position (A and G), tangential wrist velocity (D and J), elbow angle (E and H), elbow angular velocity (E and K), shoulder angle (C and I), and shoulder angular velocity (F and L). Data are shown for the last 5 of 10 trials analyzed in each condition. •••, data before injection of muscimol; —, data after injection. For the position traces, the target is located at (0,0). Data are time-aligned on the start of wrist movement and displayed from start to end of movement (see METHODS). In B, the time between the 2 arrows delimits (for control trials) initial elbow flexion. After muscimol, there is decreased wrist velocity, elbow angular velocity, and shoulder angular velocity during the reach, but no impairment during the retrieval.

Injections causing slow reach and slow retrieval

Inactivation in GPi caused slowing of mean peak wrist velocity during the retrieval phase at four injection sites in monkey T, but none in monkey L. Figure 6 shows the kinematics for an injection that caused slow reaching and slow retrieval. Mean peak wrist velocity was decreased from 100 ± 12 cm/s to 106 ± 9 cm/s after muscimol (t = −2.94, P < 0.05). Injections that produced no slowing of tangential wrist velocity during retrieval likewise did not cause significant slowing of elbow or shoulder angular velocities in either monkey.
TABLE 1.  Peak wrist velocity and movement time before and after GPi inactivation with muscimol

<table>
<thead>
<tr>
<th>Injection</th>
<th>Control</th>
<th>Muscimol</th>
<th>% Change</th>
<th>Control</th>
<th>Muscimol</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>92 ± 4</td>
<td>79 ± 4*</td>
<td>−14.8</td>
<td>402 ± 30</td>
<td>468 ± 34</td>
<td>14.2</td>
</tr>
<tr>
<td>5</td>
<td>79 ± 7</td>
<td>62 ± 9*</td>
<td>−21.3</td>
<td>485 ± 40</td>
<td>688 ± 156</td>
<td>29.6</td>
</tr>
<tr>
<td>7</td>
<td>77 ± 5</td>
<td>54 ± 9*</td>
<td>−30.0</td>
<td>482 ± 34</td>
<td>720 ± 153</td>
<td>33.1</td>
</tr>
<tr>
<td>9</td>
<td>88 ± 10</td>
<td>76 ± 7†</td>
<td>−12.7</td>
<td>448 ± 24</td>
<td>535 ± 53</td>
<td>16.2</td>
</tr>
<tr>
<td>10</td>
<td>87 ± 3</td>
<td>79 ± 8†</td>
<td>−10.1</td>
<td>420 ± 38</td>
<td>492 ± 113</td>
<td>14.5</td>
</tr>
<tr>
<td>12‡</td>
<td>92 ± 5</td>
<td>82 ± 7*</td>
<td>−11.6</td>
<td>390 ± 22</td>
<td>535 ± 74</td>
<td>27.1</td>
</tr>
<tr>
<td>13‡</td>
<td>92 ± 9</td>
<td>79 ± 10†</td>
<td>−14.0</td>
<td>457 ± 74</td>
<td>495 ± 45</td>
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<tr>
<td>14‡</td>
<td>86 ± 4</td>
<td>69 ± 6*</td>
<td>−20.3</td>
<td>430 ± 22</td>
<td>683 ± 60</td>
<td>37.1</td>
</tr>
<tr>
<td>15‡</td>
<td>91 ± 5</td>
<td>82 ± 5*</td>
<td>−9.6</td>
<td>397 ± 13</td>
<td>443 ± 23</td>
<td>10.5</td>
</tr>
<tr>
<td>Mean</td>
<td>87 ± 6</td>
<td>74 ± 10*</td>
<td>−16.0</td>
<td>434 ± 36</td>
<td>562 ± 106</td>
<td>21.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injection</th>
<th>Control</th>
<th>Muscimol</th>
<th>% Change</th>
<th>Control</th>
<th>Muscimol</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>96 ± 14</td>
<td>84 ± 9§</td>
<td>−12.8</td>
<td>433 ± 36</td>
<td>577 ± 85</td>
<td>24.9</td>
</tr>
<tr>
<td>9</td>
<td>103 ± 5</td>
<td>74 ± 12*</td>
<td>−27.9</td>
<td>460 ± 28</td>
<td>513 ± 137</td>
<td>10.4</td>
</tr>
<tr>
<td>12</td>
<td>93 ± 4</td>
<td>77 ± 7*</td>
<td>−16.8</td>
<td>468 ± 29</td>
<td>555 ± 85</td>
<td>28.5</td>
</tr>
<tr>
<td>15</td>
<td>99 ± 7</td>
<td>84 ± 15§</td>
<td>−14.6</td>
<td>449 + 68</td>
<td>572 ± 109</td>
<td>21.5</td>
</tr>
<tr>
<td>17</td>
<td>103 ± 3</td>
<td>95 ± 4*</td>
<td>−7.4</td>
<td>423 ± 18</td>
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<td>0</td>
</tr>
<tr>
<td>18</td>
<td>105 ± 3</td>
<td>97 ± 8</td>
<td>−7.3</td>
<td>409 ± 23</td>
<td>430 ± 28</td>
<td>5.0</td>
</tr>
<tr>
<td>Mean</td>
<td>100 ± 5</td>
<td>85 ± 9†</td>
<td>−14.5</td>
<td>440 ± 23</td>
<td>528 ± 91</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. GPi, globus pallidus pars interna.
* Differences are significant at P < 0.001. † Differences are significant at P < 0.01. ‡ Slow retrievals. § Differences are significant at P < 0.05.

some injections but not others could not be attributed to a more severe movement deficit during the reach to target. Peak velocity during the reach to target was not significantly different for the two groups (normal retrievals vs. slow retrievals).

To further explore the differential effect of GPi inactivation on elbow angular velocity in normal as opposed to slow retrievals, we examined the elbow flexion that occurred at the beginning of the reach (see Fig. 2) to see whether injections would also affect the angular velocity of that initial elbow flexion (Fig. 7). Injections in monkey T causing slow retrievals also caused slowing of elbow flexion angular velocity at the beginning of the reach from 120 ± 11 deg/s to 99 ± 13 deg/s (t = −5.70, P < 0.05). Injections that produced normal retrievals did not cause slowing of the initial elbow flexion during the reach, despite significant slowing of the elbow extension. In monkey T, angular velocity of the initial elbow flexion was 118 ± 19 deg/s in control measurements and 107 ± 33 deg/s after muscimol (NS). In monkey L, angular velocity of the initial elbow flexion was 113 ± 37 deg/s in control measurements and 119 ± 24 deg/s after muscimol (NS).

TABLE 2.  Kinematics of the elbow and shoulder before and after GPi inactivation with muscimol

<table>
<thead>
<tr>
<th>Injection</th>
<th>Peak Elbow Angular Velocity, deg/s</th>
<th>Peak Shoulder Angular Velocity, deg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Muscimol</td>
</tr>
<tr>
<td>Monkey T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>291 ± 26</td>
<td>218 ± 14*</td>
</tr>
<tr>
<td>5</td>
<td>283 ± 34</td>
<td>181 ± 34*</td>
</tr>
<tr>
<td>7</td>
<td>223 ± 5</td>
<td>128 ± 29*</td>
</tr>
<tr>
<td>9</td>
<td>263 ± 24</td>
<td>188 ± 25*</td>
</tr>
<tr>
<td>10</td>
<td>230 ± 16</td>
<td>147 ± 14*</td>
</tr>
<tr>
<td>12</td>
<td>244 ± 18</td>
<td>166 ± 26*</td>
</tr>
<tr>
<td>13</td>
<td>259 ± 25</td>
<td>209 ± 30*</td>
</tr>
<tr>
<td>14</td>
<td>253 ± 23</td>
<td>152 ± 18*</td>
</tr>
<tr>
<td>15</td>
<td>322 ± 17</td>
<td>250 ± 19*</td>
</tr>
<tr>
<td>Mean</td>
<td>263 ± 31</td>
<td>182 ± 39*</td>
</tr>
</tbody>
</table>

| Injection |            |         |          |         |         |          |
| Monkey L  |            |         |          |         |         |          |
| 2         | 296 ± 11  | 234 ± 24* | −20.9    | 282 ± 39 | 239 ± 24† | −15.4    |
| 9         | 249 ± 16  | 184 ± 31* | −26.1    | 290 ± 16 | 224 ± 39* | −22.8    |
| 12        | 272 ± 19  | 200 ± 24* | −26.6    | 286 ± 13 | 222 ± 20* | −22.3    |
| 15        | 293 ± 29  | 241 ± 33† | −17.8    | 304 ± 18 | 251 ± 41* | −17.2    |
| 17        | 336 ± 16  | 296 ± 21† | −11.9    | 330 ± 10 | 295 ± 12* | −10.6    |
| 18        | 328 ± 35  | 287 ± 17† | −12.7    | 319 ± 11 | 288 ± 15* | −9.9     |
| Mean      | 296 ± 33  | 240 ± 45* | −19.3    | 302 ± 20 | 253 ± 32* | −16.4    |

Values are means ± SD. GPi, globus pallidus pars interna.
* Differences are significant at P < 0.001. † Differences are significant at P < 0.01.
velocity of the initial elbow flexion was 86 ± 14 deg/s in control measurements and 75 ± 17 deg/s after muscimol (NS). Thus when retrieval was normal, elbow flexion angular velocity was normal in both the reach and retrieval, despite marked slowing of elbow extension angular velocity during the reach.

Timing of grasp components

Inactivation in GPi with muscimol caused an increased latency from the end of the reach to the start of retrieval for five injections in monkey T and for three injections in monkey L (Fig. 8). Averaged across these injections in monkey T, the latency from the end of the reach to the start of retrieval increased from 163 ± 32 ms to 488 ± 153 ms ($t = -4.77, P < 0.01$). In monkey L, the latency from the end of reach to the start of retrieval increased from 51 ± 48 ms to 167 ± 101 ms, but did not reach significance due to the small N ($P = 0.06$).

We divided the grasp period into two components for further analysis: the latency from the end of the reach to completion of the grasp, and the latency from the completion of grasp to the start of retrieval. GPi inactivation prolonged the latency from end of reach to grasp substantially more than the latency from grasp to start of retrieval in monkey T, but not in monkey L. In monkey T, the time from end of reach to grasp increased from 61 ± 26 ms (37% of total time) to 303 ± 103 ms (62% of total time) ($t = -4.64, P < 0.01$), whereas the time from grasp to the start of retrieval increased from 102 ± 27 ms (63% of total time) to 184 ± 60 ms (38% of total time) ($t = -3.42, P < 0.05$). In monkey L, time from the end of reach to grasp increased from 41 ± 8 ms (81% of total time) to 106 ± 75 ms (63% of total time), whereas the time from grasp to the start of return increased from 9 ± 40 ms (19% of total time) to 61 ± 30 ms (37% of total time).

GPi injections sites

All injections in both monkeys were in the posteroverentral portion of GPi (Fig. 9) and were placed at sites where previous
recording had demonstrated activity related to movements of the right upper extremity. In *monkey T*, injections that slowed both the reach and retrieval were located, on average, anterior to those that slowed the reach but not the retrieval. As described above, no injection in *monkey L* slowed the retrieval. There was no simple topographic difference between injections that impaired grasp and those that did not. Injections that did not cause slowing during the reach to target did not have consistent significant effects on retrieval. There was no impairment of the grasp in any injection that did not cause slowing of the reach.

**DISCUSSION**

Inactivation at GPI sites with muscimol produced movement deficits in a reach-grasp-retrieve task that can be summarized as follows: *1) decreased peak wrist velocity during the reach to target; 2) decreased elbow and shoulder angular velocities, with elbow angular velocity relatively more impaired than shoulder angular velocity; resulting in 3) higher maximum vertical wrist and index finger positions at the apex of the reach; 4) prolonged latency from the end of the reach to the completion of grasp, and 5) less impairment of retrieval than reach, with inactivation at the majority of sites causing no impairment despite slow reaching.*

Kinematics of reach and retrieval

Reaching was slowed after GPI inactivation, compared with preinjection control. Peak tangential wrist velocity, elbow angular velocity, and shoulder angular velocity were slowed, with elbow velocity relatively slower than shoulder angular velocity. This disproportionate slowing of elbow extension relative to shoulder flexion produced a more curved reach path. Further, the position of the index finger at the end of the reach was significantly higher in the vertical plane. Thus after muscimol injection into GPI, there was a flexor bias at the elbow that affected both movement velocity and endpoint position.

The muscimol injections that slowed reaching were subdivided into two groups based on peak velocity of retrieval: slow retrieval and normal retrieval. Inactivation at the majority of...
GPi sites had no effect on retrieval speed despite significant slowing of the reach. For those sites where muscimol did cause slowing of retrieval, the reach and retrieval were slowed to a similar degree. In our paradigm, there was a slight elbow flexion at the beginning of the reach as the monkey lifted its hand from the initial position. For those injections that did not impair the retrieval, the velocity of the initial elbow flexion were also unimpaired. Thus for most injections, extension was impaired, but not flexion.

**Slowing of movement after GPi inactivation**

Both slowing of movement and a flexor bias after GPi inactivation or ablation are consistent with previous work on movement deficits after pallidal lesions. Most prior studies described slowing of movement with a flexor positional bias (DeLong and Coyle 1979; Hore et al. 1977; Hore and Vilis 1980; Inase et al. 1996; Mink and Thach 1991) and little or no effect on reaction time after cooling, muscimol injection, or kainic acid lesions. Inactivation of GP with muscimol (Mink and Thach 1991) or cooling (Hore and Vilis 1980) impaired both visually guided and self-paced movements. In reaching tasks, kainic acid lesions, cooling, or muscimol inactivation of GP prolonged movement time but had no effect on reaction time (Horak and Anderson 1984a; Inase et al. 1996; Trouche et al. 1979). Thus similar deficits have been reported for single-joint and multijoint movements.

A criticism of previous studies has been that several of the lesions were large and involved GPe, and thus it could not be concluded whether damage to GPe or GPi, or both, caused the movement deficits. Based in part on the model of Alexander and Crutcher (1990) and DeLong (1990), in part on the apparent lack of deficits after GP lesions in older nonquantitative studies (reviewed in DeLong and Georgopoulos 1981), and in part on the observation that GPi lesions improve movements in Parkinson’s disease (Baron et al. 1996; Laitinen et al. 1992; Lang et al. 1997), it has been suggested that lesions restricted to GPi should not impair voluntary movement (Wichmann and DeLong 1997; Wichmann et al. 1995). However, lesions involving just GPi had effects similar to lesions involving both GPe and GPi (Mink and Thach 1991). In the present study, our goal was to selectively inactivate relatively small groups of
neurons restricted to GPi by 1) using a small injection volume of muscimol, 2) identifying the GPi borders physiologically before injection, and 3) injecting into areas of GPi where neurons were related to arm movements [in a separate task (Mink 1996b)].

The present results and those of another recent study of reaching after GPi inactivation (Inase et al. 1996) indicate that movement is indeed slow after focal inactivation of GPi with small injections of muscimol. Muscimol injections restricted to GPi in monkeys performing a two-dimensional arm movement in the horizontal plane caused slowing of movement with cocontraction and a flexor bias (Inase et al. 1996). The task used in those studies was a center-out planar reaching task to eight different targets requiring movements of up to \( \sim 7.5 \text{ cm} \) and holding of both initial and final positions. The authors proposed that the decrease in peak movement velocity was likely the result of an attempt to stabilize the limb against the flexor drift.

Although the results of the present study are consistent with those from other studies of reaching or single joint movements after GPi lesions, there are several distinguishing features of the present task. Our task required relatively large amplitude arm movements, comparable to those of Horak and Anderson (1984a), but much larger than those of Inase et al. (1996). Furthermore, there was no required hold period and no imposed limitation on movement time or accuracy to obtain the reward. The only limitation was that the monkey had to grasp and retrieve the apple bit without dropping it to eat it. Finally, our paradigm involved reaching without any instrumentation. Because of the few accuracy requirements in our task, we suggest that the slowing of movement and flexor bias are primary deficits and that the slowing does not represent a compensatory strategy. Despite the task differences between the present study and that of Inase et al. (1996), the findings are consistent. This strengthens the conclusion that the described deficits are directly due to GPi inactivation.

Is reaching impaired after GPi inactivation because of impaired inhibition of competing posture-holding mechanisms?

We have hypothesized that the basal ganglia act to facilitate desired motor patterns and inhibit potentially competing motor patterns (Mink 1996a; Mink and Thach 1993; Thach et al. 1993). Specifically, it was hypothesized that during a voluntary movement, a small subset of GPi neurons decrease discharge (under inhibitory influence from striatum) to remove tonic inhibition from thalamic and brain stem mechanisms and allow the desired movement to proceed. Simultaneously and in parallel, the majority of GPi neurons increase discharge (under excitatory influence from the subthalamic nucleus) to increase inhibition of mechanisms such as those involved in posture-holding and prevent them competing with the desired movement. Potentially competing posture-holding mechanisms were hypothesized to include tonic neck reflexes, contact righting and placing mechanisms, long-loop stretch reflexes, and vestibulospinal and reticulospinal mechanisms (Mink 1996a). For the primate sitting upright, the typical posture is one of flexed arms, legs, and neck. In that posture, tonic neck and vestibular mechanisms favor flexion (Magnus 1924), and movement of any one limb out of the initial position requires inhibition of those postural mechanisms in addition to activation of mech-
anisms involved in producing the desired movement. Inability to inhibit those posture-holding mechanisms for the moving limb would be expected to slow movement and to bias movement toward that initial position, i.e., flexion.

The data presented here support our hypothesis. Sitting in the initial posture before reaching, posture-holding mechanisms are active to maintain position of the body. These mechanisms would include tonic neck reflexes, labyrinthine reflexes, contact righting responses, optic righting responses, and possibly others. Movement away from the initial posture would be opposed by those posture-holding mechanisms, but movement back toward the initial posture would be assisted. That is what was seen after the majority of injections into GPi. However, not all potentially competing mechanisms favor flexion. For example, long-latency stretch reflexes are present in both flexors and extensors. Thus one might expect that both flexion and extension would be slowed by disinhibition of these reflexes. Indeed, after a few injections in GPi in one monkey, all components of the reach-grasp-retrieval task were slow.

Injection sites causing slow retrievals were topographically different from sites that did not affect retrieval. This is consistent with the idea that for a given movement, certain motor mechanisms must be expressed and others must be inhibited. By changing the location of injection, these mechanisms may be affected to different degrees, in some cases to favor flexion and in others not. Support for topographic representation of different mechanisms in GPi comes from three lines of evidence. First, there is anatomic evidence for parallel, functionally different circuits through the basal ganglia (see Alexander et al. 1986 for review) and for separation of GPi neurons that project via thalamus to different cortical areas (Hoover and Strick 1993; Middleton and Strick 1994). Second, microstimulation of some sites in GPi slows reaching, but microstimulation of others speeds reaching (Horak and Anderson 1984b). Third, neuronal discharge patterns indicate a somatotopic organization in GPi (DeLong et al. 1985). In light of these observations, different effects of inactivation at different sites in GPi is not surprising. It may seem more surprising that inactivation at most sites did not impair the retrieval movement in spite of significant slowing of the reach. However, this was predicted by the hypothesis (Mink 1996a).

Although we favor the hypothesis of selective facilitation and inhibition of competing motor patterns, other hypotheses of basal ganglia function have been proposed and are relevant to the present study. One such hypothesis is that the basal ganglia scale the magnitude of muscle activity to produce a movement of desired amplitude and velocity (Hallett and Khoshbin 1980). This hypothesis was supported by Horak and Anderson (1984a) and is inherent in the model of Alexander and Crutcher (1990). Although the present task did not look at scaling in a controlled manner, the slow reaching but normal retrieval after most injections suggests that the deficit is not one of scaling generally. The finding that elbow extension was relatively more impaired than was shoulder flexion during the reach could be interpreted as incorrect scaling of activity in one muscle to another, but this interpretation would not explain the similar impairment of elbow and shoulder during the retrievals. Likewise, it is difficult to interpret the deficits after GPi inactivation as impaired movement generation. Although reaction time was not measured in the present experiments, there is overwhelming evidence that GPi lesions do not impair movement initiation or generation (Mink 1996a). Furthermore, the component of the reach that was relatively most impaired was elbow extension. During reaching in the vertical plane, the forces that extend the elbow come primarily from gravity and interaction torques produced by shoulder movement (Bastian et al. 1996). Elbow extension is accompanied by gradual reduction of torque produced by the elbow flexor muscles and not by active force generation by elbow extensors. Thus the impairment of elbow extension is consistent with the findings of Mink and Thach (1991) that GPi lesions cause greater disability turning off previously active muscles than turning on muscles. An alternative hypothesis is that the basal ganglia are involved in movement sequencing. This hypothesis will be discussed below.

Comparison to pallidotomy in Parkinson’s disease (PD)

Our results confirm those of many previous studies showing that GPi lesions cause movement abnormalities in normal monkeys. However, GPi lesions (pallidotomy) improve many movement abnormalities in Parkinson’s disease (PD) (Baron et al. 1996; Laitinen et al. 1992; Lang et al. 1997). Because of the improved bradykinesia in PD and apparent lack of adverse effects, it has been argued that GPi lesions cause no long-term deficits and that deficits seen after GP lesions in monkeys are due to involvement of GPe or even of the internal capsule. (Wichmann and DeLong 1997). However, in the present study and in others where the lesion or inactivation site was restricted to GPi, the deficits are unmistakable. There may be a fundamental reorganization of basal ganglia circuits in PD that explains the opposite effects of GPi lesions in PD and in normal animals.

Prolonged grasp latency

In the present study, GPi inactivation at several sites prolonged the time required to grasp the apple bit as measured by the latency from the end of reach to the start of retrieval. When broken into components, the time from end of reach to completion of grasp was relatively more prolonged than the time from completion of grasp to start of retrieval in monkey T but not in monkey L. We attribute some of the discrepancy in these results between the two monkeys T and L to their individual reaching and grasping styles. Monkey T usually grasped the apple bit with the thumb and index finger, sometimes using the third finger also. In contrast, monkey L usually grasped the apple bit by contacting with the palm and curling all fingers around the bit. As a result, monkey T’s grasp required more precision of the fingers than did monkey L’s, and the greater effect of GPi inactivation in monkey T may have been due to that factor.

We observed, but were unable to quantify with the present methodology, a bias toward finger flexion after GPi inactivation. In the normal reach to grasp in human subjects, it has been shown that grip aperture is formed relatively early during the reach (Jeannerod 1984). In our monkeys, we also observed that formation of the grip aperture began early in the reach. However, after muscimol injection it appeared that the aperture was too small (i.e., the fingers were too flexed), so that when the target was reached the monkey had to extend the fingers to widen the
The prolonged latency from end of reach to grasp appeared to reflect the need to reextend the fingers from their overly flexed posture before grasping the apple bit. Thus the flexor bias slowed reaching and impaired the grasp, but had less or no effect on the retrieval that involved returning to a flexed posture.

**Present results do not support a primary role for the basal ganglia output in the generation of movement sequences**

A hypothesized role of the basal ganglia is that they contribute to the automatic execution of movement sequences (Bhatia and Marsden 1994; Brotchie et al. 1991; Houk et al. 1995; Marsden 1987). Specifically, it has been proposed that the basal ganglia contribute to the generation of the second and later components of a movement sequence, but not to the initial component (Brotchie et al. 1991; Marsden 1987). Supporting this hypothesis is the characteristic micrographia of PD where initial letters of a written sentence are substantially larger than subsequent letters. Some GP neurons change activity after the onset of the first movement in a sequence of two movements, but before the second (Brotchie et al. 1991) and some neurons in striatum and pallidum has been shown to correlate with movement sequence (Aldridge and Berridge 1998; Mushiake and Strick 1995). People with PD are more impaired when performing simultaneous or sequential movement than when performing each component separately (Benecke et al. 1986, 1987; Marsden and Obeso 1994). Furthermore, inactivation in putamen can disrupt the learning or execution of movement sequences (Miyachi et al. 1997). However, it should be noted that simple (nonsequential) movements are also impaired in PD (Evarts et al. 1981; Hallett and Khoshbin 1980) and after striatal or pallidal lesions (Kato and Kimura 1992; Mink and Thach 1991).

Several aspects of our results are not consistent with a specific basal ganglia role in the programming of movement sequence components subsequent to the initial one. First, the retrieval phase was never more impaired than the reach phase and in most cases was normal. If programming of latter sequence components was a primary function of the basal ganglia, one would expect the latter components of the sequence to be more impaired than the earlier ones. The greater prolongation of the latency from the end of reach to grasp compared with the latency from the grasp to start of retrieval in monkey T also argues against a specific deficit of sequence generation, per se. Studies of reach to grasp movements in normal human subjects suggest that the reach and grasp are programmed as one pattern rather than simultaneous execution of two separate patterns (Jeannerod 1984). Thus the movements involved in our task may be viewed as a sequence of two rather than three movements. Nonetheless, the latter component of the sequence was less affected than was the former. Although the present results do not support a primary role of the basal ganglia output in the programming of movement sequences, they do not exclude the basal ganglia as an important contributor to the control of movement sequences. The areas of GPi that were inactivated in the present study are in the “motor circuit” of the basal ganglia, and injections in more anterior portions may have disrupted sequencing. Furthermore, basal ganglia may play a role in some aspects of sequence control that were not required in our task. We favor the idea that dynamic inhibition of competing motor patterns is a critical feature in many movement sequences and suggest that the two hypotheses are compatible (Mink 1996a).

The results of this study show that reaching movements are impaired specifically after focal inactivation of GPi in previously normal monkeys. The nature of the impairment supports the hypothesis that GPi lesions disrupt the ability to inhibit competing motor mechanisms to prevent them from interfering with desired voluntary movement. Further study is required to specify exactly which motor mechanisms contribute to the described deficits and how they are represented topographically in GPi.

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Address for reprint requests: J. W. Mink, Dept. of Neurology, Washington University School of Medicine, Box 8111, 660 S. Euclid Ave., St. Louis, MO 63110.

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