

# Effects of focal basal ganglia lesions on timing and force control

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## Abstract

Studies of basal ganglia dysfunction in humans have generally involved patients with degenerative disorders, notably Parkinson's disease. In many instances, the performance of these patients is compared to that of patients with focal lesions of other brain structures such as the cerebellum. In the present report, we studied the performance of patients with focal basal ganglia lesions on three fundamental motor tasks. The patients all had suffered unilateral damage in the striatum and were tested in the chronic state. The first task required the participants to tap with their index finger as fast as possible; this test provided a simple assessment of motor competence. Compared to controls, the maximum tapping rate was lower for the patients when tapping with their contralesional limb, although the deficit was not severe. The second and third tasks were designed to assess timing and force control, two functions that have been associated with basal ganglia function. The patients performed similar to controls on both tasks and showed no evidence of impairment when using their contralesional limb compared to their ipsilesional limb. The results indicate that unilateral basal ganglia lesions tend to produce minor motor problems in force control, and fail to support the hypothesized role of the basal ganglia in timing.

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## 1. Introduction

The functional contribution of the basal ganglia has been the subject of extensive research. Traditionally, the basal ganglia have been considered part of the motor pathways, although more recent theories have pointed to potential roles of this structure in learning and cognition (e.g., Doya, 2000; Krebs, Hogan, Hening, Adamovich, & Poizner, 2001; Sommer, Grafman, Clark, & Hallett, 1999). Other researchers have taken an information processing approach in exploring basal ganglia function, conceptualizing its role to be a type of gate that may inhibit unwanted motor plans (Marsden & Obeso, 1994; Mink, 1996) or correlate information from various cortical structures in an efficient manner (Borud, Bezdard, Bioulac, & Gross, 2002).

Much of this work has been motivated, at least in part, by consideration of the profound deficits observed in humans with Parkinson's disease. Given the prominent motor problems experienced by these patients, a considerable effort has been devoted to identify the functional contribution of the basal ganglia to various movement parameters. This line of research has catalogued many of the movement impairments associated with Parkinson's disease, including deficits in the temporal control of movements (Harrington, Haaland, & Hermanowicz, 1998; O'Boyle, Freeman, & Cody, 1996), and force control (Sheridan, Flowers, & Hurrell, 1987; Wing, 1988).

Parkinson's disease has been an essential model system for studying basal ganglia function. One concern with this approach, however, is that the effects of this degenerative disease are not limited to the basal ganglia. Alteration in brain function is observed outside of the basal ganglia, most notably in the frontal cortex. The cortical abnormalities may be a direct consequence of

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the disease process: the dopamine loss in the striatum is mirrored by a reduction in dopaminergic projections to the frontal cortex, although the extent of this reduction is markedly less than in the striatum (Piccini, Pavese, & Brooks, 2003; Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983). In addition, changes in cortical function may be an indirect consequence of alterations in basal ganglia function (Owen, Doyon, Dagher, Sadikot, & Evans, 1998). Given this, the motor deficits in Parkinson's patients may reflect abnormal function of not only the basal ganglia, but in other neural systems as well. This concern is, of course, inherent in all studies involving the use of brain lesions. It is difficult to localize function through the analysis of dysfunction, or to account for changes in neural structure that result in compensation of neurological injury. Nonetheless, degenerative diseases are especially problematic, given their systemic nature.

In the current paper, we employed a different patient population to assess the effects of basal ganglia damage, individuals who have suffered a stroke centered in the basal ganglia. In addition to determining how the performance of these patients compares to that of Parkinson patients, the focal lesion group allowed us to make a within-subject comparison between performance with the contra- and ipsilesional hand. This form of comparison has proven useful in the study of other motor disorders (e.g., Ivry, Keele, & Diener, 1988), but is not usually appropriate for Parkinson's patients given that their symptoms are generally bilateral. In this study we report the observation of patients with focal lesions of the basal ganglia on tests of movement speed, movement timing, and force control. Before turning to the Methods, we provide a brief review of lesion-based work in animals examining the role of the basal ganglia on these types of tasks, as well as previous studies involving human patients with focal basal ganglia lesions.

### 1.1. Basal ganglia modulation of force production

A variety of methods have been used to study the role of the basal ganglia in force control. The study of controlled lesions in animals has provided some insight into the movement parameters associated with basal ganglia function. Jeyasingham and colleagues reported hyperactive grip strength and impaired reaching in rats that had received nigrostriatal lesions unilaterally, and bilateral reaching deficits in rats receiving unilateral lesions to the striatum (Jeyasingham, Baird, Meldrum, & Dunnett, 2001). Similar deficits have also been observed in primates with experimental lesions of basal ganglia output pathways. Abolition of the globus pallidus nuclei produced slowed movement times in animals trained to reach to targets. However, reaction times appeared to be normal, suggesting deficits in the acceleration phase of reaching movements (Horak & Anderson, 1984).

Similarly, when monkeys were trained to reach and grasp an object, local lesions created by muscimol application to the globus pallidus produced slower movement times but only in extension of the elbow and not in flexion (see also Inase, Buford, & Anderson, 1996; Wenger, Musch, & Mink, 1999), suggesting deficits in the modulation of movement amplitude.

This work is complemented by studies of humans with Parkinson's disease (PD). A prominent feature of this disorder is bradykinesia, or movement slowness. Similar to experimental research conducted with animals, the study of movement times has implicated the basal ganglia system in the regulating the production of force. Analysis of the movement trajectories produced by PD patients, have revealed that slower movement times stem from abnormalities in the acceleration/deceleration phase of movement (Platz, Brown, & Marsden, 1998). The force control problem in PD patients, however, is not simply a matter of a reduction in the ability to produce maximum force. PD patients also are impaired on tasks requiring a decrease, or modulation in force (Wing, 1988).

EMG studies have also pointed to a problem in scaling muscular activity to match movement amplitude (Hallett & Khoshbin, 1980). When trying to achieve larger movements, PD patients tend to generate a series of agonist bursts of a stereotypic size, rather than increase the size of the burst. The end result may be accurate, but with abnormal kinematics. Similarly, on an isometric force control task, PD patients were as accurate as controls, yet they exhibited abnormal force–time profiles (Stelmach & Worringham, 1988). This result has led the researchers to conclude that a more accurate description of the deficit of the force regulation in PD patients may be in terms of regulating the force–time profile of an isometric contraction (Ivry & Corcos, 1993).

### 1.2. Temporal processing and the basal ganglia

The role of the basal ganglia in temporal processing has been the subject of considerable study. Much of this work has involved pharmacological and lesion methods with animals, focusing on the question of whether manipulations of dopamine levels alter the rate of an internal clock (see Gibbon, Malapani, Dale, & Gallistel, 1997; Malapani & Rakitin, 2003; Meck, 1983, 1996, 2003; Meck & Benson, 2002). These studies have tended to use a task that may best be characterized as one of time perception as the intervals studies are considerably longer than those required for motor coordination.

Of greater relevance for our present concerns are studies that have examined the performance of PD patients on repetitive movement tasks, focusing on the temporal consistency of such movements. Results from these studies are inconclusive and contradictory. In an experiment involving a group of PD patients performing

a temporal tapping task (Ivry & Keele, 1989; see also Duchek, Balota, & Ferraro, 1994; Spencer & Ivry, in press) reported that PD patients were as consistent as age-matched control participants. Moreover, the patients' performance was similar when tested on their normal levodopa medication cycle or after skipping their morning medication (OFF medication).

However, two studies have reported an increase in timing variability in PD patients on the same task. In one study, the patients showed a marked increase when tested in the OFF state (O'Boyle et al., 1996). Using a two-process model developed by Wing and Kristofferson (1973), the deficit was attributed to greater variability in an internal timing process rather than an increase in noise associated with response execution (see below). Similar results were obtained by Harrington et al. (1998), although in this study the deficits were apparent even when the patients were tested under their normal medication regimen. In addition to increased variability, PD patients have also been found to speed up their movements across successive cycles on repetitive movement tasks (Ivry & Keele, 1989; Pastor, Jahanshahi, Artieda, & Obeso, 1992).

An understanding for these discrepant findings remains elusive. It may be related to the fact that PD patients represent a very heterogeneous population given the variable response to L-dopa treatment. Keele and Ivry (1987) reported a case study in which a newly diagnosed patient was tested repeatedly over a two-week period following the onset of L-dopa treatment. Variability was elevated during the early sessions with the increase again attributed to the timing component; by the end of the observation period, the patients' performance was normal. It may be that PD timing impairments vary in a non-monotonic manner over the course of long-term levodopa treatment (e.g., become pronounced in some patients, either due to the development of hyperkinesias or reduced efficacy of the medication). The inconsistent findings with PD patients do emphasize the need for converging methods including neuropsychological studies with focal lesion patients.

### 1.3. Focal lesion studies in humans

Relatively few studies have been conducted with patients who have suffered focal lesions of the basal ganglia, at least in comparison to the extensive literature on Parkinson's disease. Bhatia and Marsden (1994) provide a meta-analysis of focal lesion patients, drawing on case reports from various studies. In patients with lesions restricted to the caudate nucleus, only 10 of the 43 cases presented any evidence of motor impairments, with the most frequent symptom being dystonia on the contralateral side. Caplan et al. reports a similar picture. Of 18 cases with focal caudate lesions, motor symptoms were modest and transient (Caplan et al., 1990). The most common problems were weakness in the face, arm, and

leg, clumsiness, and decreased spontaneous use of the contralesional limb. While some of these may have been due to the basal ganglia pathology, it is important to keep in mind that the internal capsule runs adjacent to the caudate. The weakness is likely due to cases, in which the damage extends into the capsule, directly disrupting descending corticospinal projections.

Clinical evidence of motor impairments is more common with putamen and globus pallidus lesions. In the Bhatia and Marsden review, 19 of 20 patients with putamen lesions exhibited some type of motor disorder, usually dystonia (15 cases). Interestingly, two patients with bilateral putamen lesions had Parkinson-like symptoms. A similar picture is found with globus pallidus lesions. Dystonia was present in 7 of 17 cases and Parkinson-like symptoms in four patients with evidence of bilateral lesions. The meta-analysis did not indicate whether the motor symptoms persisted past the acute stage. However, Giroud, Lemesle, Madinier, Billiar, and Dumas (1997) reported that motor deficits are absent in patients with chronic pallidal lesions. In contrast, patients with putamen lesions continue to present a contralesional dystonia and facial palsy.

Surprisingly, the overall picture indicates that unilateral lesions of the basal ganglia produce at most relatively minor motor impairments in the chronic condition. However, the tests used in these studies have generally been those used by clinicians in the course of general neurological exams of motor competence. Such tests may not be sufficiently sensitive to detect subtle motor impairments. In addition, the clinical tests do not allow for a fine-grained analysis of specific aspects of coordination such as force control or timing. In the present paper, we report the performance of patients with lesions restricted to the putamen and caudate nucleus on three motor tasks previously used in studies with PD patients. In one task, the patients were required to tap at their maximum rate. This procedure is similar to a task used in most clinical exams and is generally a sensitive test of motor dysfunction. The second and third tasks examined timing and force control, respectively. The patients performed each task with their contralesional and ipsilesional hands in separate blocks. In addition to this within-subject analysis, age- and education-matched control participants were tested to allow a between-group comparison.

## 2. Method

### 2.1. Participants

Six neurological patients were recruited for the experiment. Patients were identified through reviews of radiology records at the VA Medical Center in Martinez, CA and by referral from local outpatient clinics. Selected

patients were contacted and a medical history was obtained. They were also given a neurological exam that included a complete motor exam and limited neuropsychological testing. Inclusion criteria required that the patient have suffered a single neurological incident with pathology centered in the basal ganglia (Fig. 1). Patients were excluded if the damage extended into cortical structures; however, there was evidence of involvement of white matter structures either internal capsule or superior longitudinal fasciculus (SLF) in some of the patients.

The lesion was on the right side for all six of the patients, reflecting the fact that almost all of the referrals came from a speech rehabilitation clinic.<sup>1</sup> Aphasia is commonly seen shortly after focal basal ganglia lesions, especially in those with lesions extending into the SLF. In our group of chronic patients, only one (patient JG) had a persistent aphasia and this patient had the most dorsal lesion.

Ten participants were recruited from surrounding Berkeley community to serve as age-matched control participants. All of the participants were right-handed. Age and education information is presented in Table 1.

All participants provided informed consent according to the guidelines set forth by the Committee for the Protection of Human Subjects at the University of California, Berkeley.

## 2.2. Apparatus

Responses for the maximum speed and timed tapping tasks were collected on a custom-designed keyboard. The keys are large (10 × 3 cm) and are activated following a depression of about 1 cm. The keyboard was connected to a PC computer that measured response onsets with millisecond accuracy.

Isometric responses were obtained for the force control task by having the participants press on a button with their index finger. The button was mounted on a flat board and was situated over a strain gauge. The output of the strain gauge was sampled at a rate of 333 Hz.

## 3. Procedure

### 3.1. Maximum speed task

Participants were asked to tap as fast as possible with their index finger on the response key(s). Three condi-

tions were tested: right unimanual, left unimanual, and bimanual. The start of a trial was indicated by a tone. The participant then commenced tapping as fast as possible, and data were collected for 31 taps after the first response was recorded. At this point, a second tone was sounded to indicate the end of the trial. The instructions emphasized that the person should begin tapping when ready; they did not need to start as soon as they heard the imperative tone. At the end of each trial, feedback was provided indicating the mean intertap interval (ITI) and the standard deviation of the ITIs. The experimenter monitored performance closely to ensure that the participants depressed and released the response key over its full extension with every tap.

The primary dependent variable was the mean intertap interval. The mean interval was calculated for each trial and these values were averaged across trials for each condition. The relative phase between the hands was calculated by dividing the onset asynchrony between the taps of the left and right hand by the current interval duration for the left hand and converting to degrees.

### 3.2. Timed tapping task

A synchronization-continuation task (Wing & Kristofferson, 1973) was used to assess timing control. Movements were restricted to flexion–extension of the index finger. Each trial began with the presentation of an auditory metronome that presented 50 ms tones (500 Hz) every 400 ms. The participants were instructed to listen to the metronome for a few tones and then to begin tapping, attempting to synchronize their responses to the tones. After the first response was detected, an additional 14 tones were presented. Following this, the metronome was terminated and the participants were required to continue tapping until they had produced 31 unpaced intervals. The end of a trial was signaled by a single auditory tone. Feedback was provided at the end of each trial, indicating the mean intertap interval and standard deviation during the paced and unpaced portion of the trial.

Three conditions were tested: right hand only, left hand only, and bimanually. Fourteen trials were completed for each condition, divided into two blocks of seven trials each. The order of blocks was counterbalanced across participants.

Only the data from the unpaced phase of the trials in the unimanual conditions are reported here. For each trial, the mean unpaced intertap interval and standard deviation was calculated. The latter was calculated after variance due to any global linear drift in mean rate was removed by fitting a regression line through the time series and estimating the deviation of each interval from this line (Vorberg & Wing, 1996). Trials in which any intervals were shorter than 200 ms or greater than

<sup>1</sup> One patient with a right-sided basal ganglia lesion was also recruited from the radiology reviews. Given issues related to hand dominance and the fact that he was the only right hemisphere lesion, we chose to exclude this patient's performance from this report. However, his performance was similar to that observed in the group of patients with left-sided lesions.

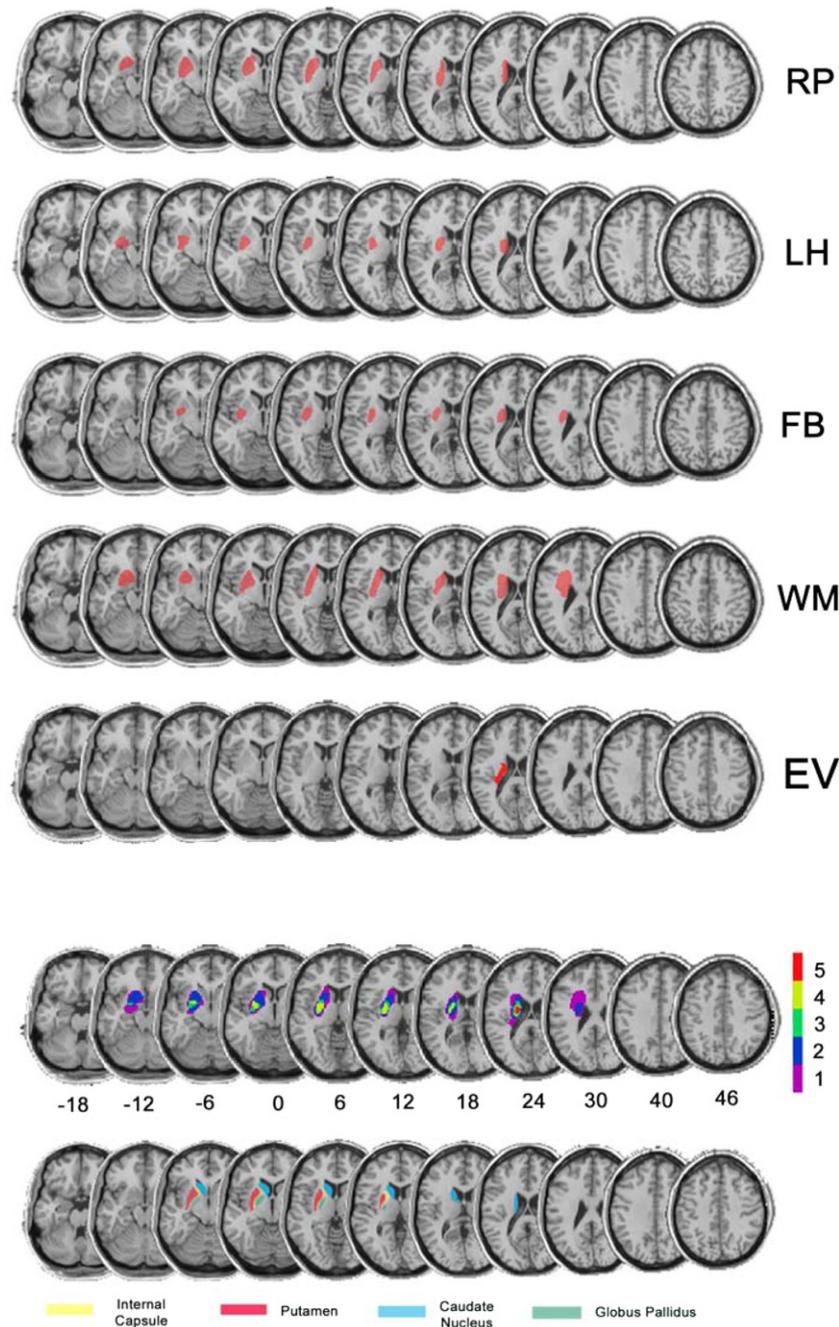


Fig. 1. Lesion reconstruction for five of the patients with focal lesions of the basal ganglia in the left hemisphere, presented on 11 horizontal sections. The striatum (putamen and caudate) is present in Sections 2–9; the globus pallidus in Sections 3–6. Bottom image is composite reconstruction, with color bar indicating the overlap area of the number of patient lesions, where clinical section number is marked below. Last figure displays location of basal ganglia nuclei. Figures were generated using the MRICro software package (Rorden & Brett, 2000).

600 ms were excluded from the analysis (6.7% for controls; 3.9% for patients when tapping with their contralesional hand; 7.7% for patients with tapping with ipsilesional hand).

The covariance function obtained from the detrended data were used to partition the total variability into estimates of clock (or more accurately, central, see Ivry & Hazeltine, 1995) and motor implementation variability (Wing & Kristofferson, 1973). In brief, this procedure

is based on two critical assumptions. First, total variability is the sum of these two component sources (i.e., the two sources are assumed to be independent). Second, successive responses are generated in an open loop, or feedback-free manner (for tests of these assumptions in healthy and neurologically impaired populations see Ivry et al., 1988; Ivry & Hazeltine, 1995; Wing, 1980). Given these assumptions, an estimate of motor implementation variability is given as:

Table 1  
Age, education, task participation, and lesion location for the patients

Group	N	Lesion location	Age	Education	Task		
					Maxtap	Wingtap	Force
Controls	11		62.5	15.5	6	7	3
RB			71	18		×	×
OC			61	14		×	
GJ			71	16		×	×
GP			60	16		×	
NS			57	17		×	
TF			66	16	×		×
RI			48	21	×	×	
RW			63	17	×		
SK			66	14	×	×	
LU			77	10	×		
PD			48	12	×		
Patients	6		66.2	14.3	6	6	3
FB		Putamen, Caudate	79	14	×	×	×
EV		Putamen, Caudate, SLF, and internal capsule	78	16	×	×	
JG		Not available	64	12	×	×	
LH		Putamen, possibly internal capsule, and globus pallidus	42	12	×	×	×
WM		Putamen, possibly SLF internal capsule, and globus pallidus	68	14	×	×	
RP		Putamen, Caudate	66	18	×	×	×

$$\sigma_{MD}^2 = -\text{autocovar.} \quad (1)$$

An estimate of clock variability can then be obtained by subtracting the motor variability from the total variability.

### 3.3. Force control task

The participants were instructed on the operation of the strain gauge device and given practice to familiarize themselves with it. During this phase, a vertical line appeared from the bottom of the computer screen after each response, with the height of the line corresponding to the produced force.

A horizontal line that spanned the monitor indicated the target force for each trial. The vertical position of the line indicated whether the target force was small (3.6 N), medium (4.8 N), or large (6.4 N). The trial was divided into two phases. In the first phase, a tone indicated when a response should be initiated and feedback was provided after every response in the form of a vertical line. If the line ended above the target line, the participant had used too much force; if the line ended below the target line, the participant had used too little force. This allowed the participant to use a trial-and-error method to adjust their force output to match the target force level. The interval between the end of the response and the next tone was randomly selected from 800 to 1200 ms so that participants could not adopt a rhythmic mode of responding. In the second phase, responses were again initiated after a tone. However, feedback for all six responses was only presented after six consecutive responses had been made. Our focus was

on how well the participants could match the target force without feedback and on their consistency in producing isometric force pulses without feedback.

Each participant completed two blocks of 30 trials each with each hand. Within each block, there were 10 trials for each target force, with each trial requiring six feedback and six no-feedback responses. Only results from the feedback-free phase are reported.

Trials in which the reaction time was less than 50 ms were considered anticipations and excluded from the analysis. The distribution of produced forces for each condition was also examined. Responses in which the maximum output of the strain gauge was reached (3.7% of trials) or in which the maximum force was clearly an outlier (1.7% of trials) were also excluded. Additionally, trials in which the participants failed to generate the maximum force with a single, rapid isometric response were excluded (7% for controls; 3% for patients). These trials were identified by visually examining each force–time response. For most of these trials, the participants generated a slow, gradual rise in force and the response had not returned to baseline by the end of the 1500 ms sampling period.

The dependent variables of primary interest include mean force, the standard deviation of the responses, the time to peak force, and response duration. The onset of each response was defined by manually marking the first visible increase in force above resting force level on a computer display of the force–time function for each trial. Similarly, the offset of each pulse was also defined by marking the point in time where the force produced had returned to resting level. The maximum force value for each response, and the time at which this force

level was achieved was also recorded for each trial. For each trial (six feedback-free responses), the mean force and standard deviation was calculated across the six pulses produced per trial. These values were then averaged for each condition. The mean time to peak force and mean response duration was calculated across all of the responses for a given condition (240 responses minus excluded responses per target level).

### 3.4. Test sessions

Each participant served in two sessions. The first session consisted of the maximal rate and paced tapping tasks. The second session consisted only of the force control task. The sessions lasted approximately 1 h each.

## 4. Results

### 4.1. Maximum rate tapping

Fig. 2 displays the mean intertap interval in maximal rate tapping. Two kinds of comparisons are possible with the current design: (1) a between subjects compar-

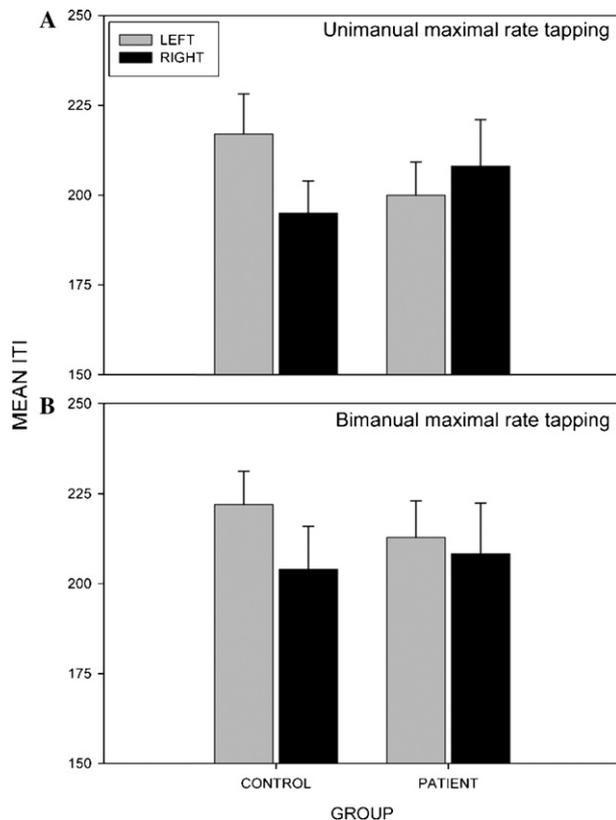


Fig. 2. Mean intertap interval on the maximum tapping speed task for (A) unimanual and (B) bimanual conditions. All of the participants were right-handed. The lesion was in the left hemisphere for all of the patients; thus, impairments, if present, were expected to be evident in the performance with the contralesional, right hand. Error bars indicate the standard error of the mean for each condition.

ison of patients vs. controls, and (2) a within subjects comparison between the ipsi- and contralateral hands of the patients. While a within-subject analysis is more powerful since each person serves as his or her own control, the effects of handedness might obscure possible deficits in the patients. Healthy individuals tend to have a faster maximum tapping rate with their dominant hand (Peters, 1980). Because all our participants were right-handed and all lesions were in the left hemisphere, deficits resulting from the lesions might be obscured by a handedness advantage. The comparison with age-matched controls allowed us to test this possibility.

In the unimanual condition, control subjects tapped faster on average with their dominant hand. The same pattern was observed in the bimanual condition. In contrast, patients tended to tap faster with their non-dominant hand in the unimanual condition and in the bimanual condition. To evaluate these effects statistically, a Group (Patients vs. Controls)  $\times$  Condition (Unimanual vs. Bimanual)  $\times$  Hand (Right vs. Left) repeated measures ANOVA was conducted. None of the main effects were significant. However, the Hand  $\times$  Group interaction approached significance, ( $F(1, 10) = 4.60$ ,  $p > .057$ ). On average, the patients actually tapped slightly faster than controls with their left (unaffected). More important, the patients tended to be slower when tapping with their dominant, contralesional hand, while the controls tended to be faster when tapping with this hand.

We also analyzed the phase relationship between the two hands in the bimanual condition. As can be seen in Fig. 3, the two hands were generally coupled for both the controls and patients: the relative phase distribution is not uniform, but is clustered around certain phases. The center of this distribution is not zero, indicating that one hand consistently led the other. For the controls, there was a consistent right-hand lead (mean relative phase of  $56^\circ$ , or 15 ms right-hand lead). Four of the patients showed a similar right-hand lead pattern, although the magnitude of the lead was reduced. For the other two patients, the left hand led the right.

In sum, the results on the maximum tapping rate task suggest a modest impairment for the patients when performing with their contralesional hand. The advantage usually observed for the dominant hand was absent and, at least for some patients, the dominant hand did not tend to lead the non-dominant hand during bimanual tapping. Nonetheless, the effect of the lesions on maximum tapping speed is subtle. Overall, the patients tapped as fast as controls with their contralesional hand, averaging around 5 Hz, a rate that is within the normal range for this age group.

### 4.2. Rhythmic tapping

The control participants and patients were successful in maintaining the target rhythm. The mean intertap

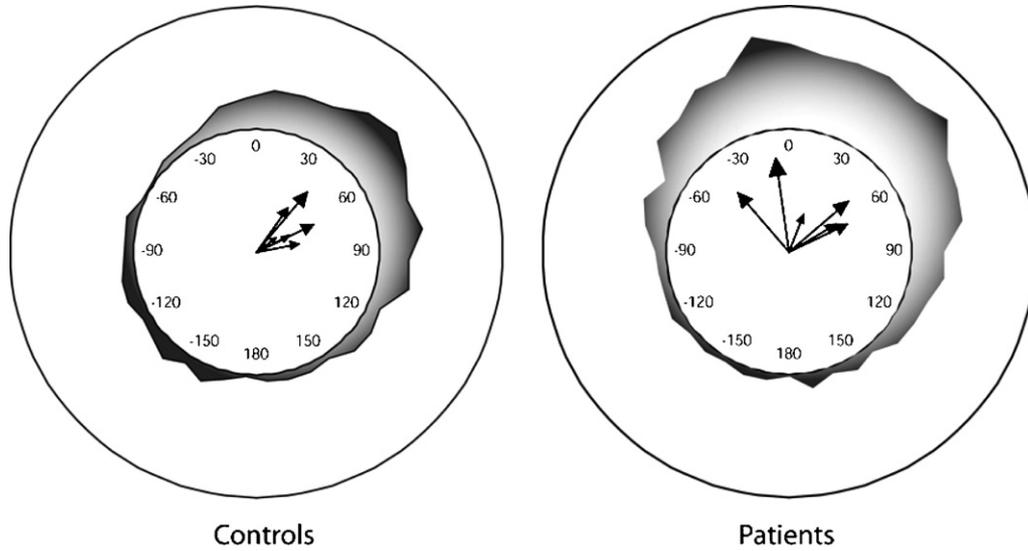


Fig. 3. Frequency distribution of relative phase in the bimanual condition of the maximum tapping rate task. Positive values indicate response pairs in which right hand led the left hand; negative values indicate when left hand led the right hand. The data were pooled for each group to create the frequency distributions. Individual values are indicated by the vectors with the mean relative phase indicated by the direction of each arrow and the variability for that individual indicated by the length of the arrow (longer arrow means less variability).

interval for the left and right hands for the controls was 391 and 387 ms, respectively. For the patients, the mean intertap intervals were 394 ms for the left hand and 391 ms for the right hand. These data were analyzed with in a Group (Controls vs. Patients)  $\times$  Hand (Left vs. Right) repeated measures ANOVA. Neither the main effect of group ( $F(1, 11) < 1$ ) or hand ( $F(1, 11) = 2.63$ ,  $p = .13$ ), nor the interaction ( $F(1, 11) < 1$ ) were significant. The ability of the focal basal ganglia lesions to maintain the target interval is different from previous reports with Parkinson patients. Ivry and Keele (1989) observed that Parkinson patients tended to speed up, although the target interval in their study was 550 ms (Pastor et al., 1992).

The average total variability estimates of the intertap intervals are presented for each condition in Fig. 4A.

Overall, the patients were more variable than the controls, and the increase was most pronounced for their performance when tapping with the contralesional hand. However, the increase in the group values was primarily due to high variability for Patient LH. In the statistical comparison, the main effect of Group was not significant ( $F(1, 11) = 1.03$ ,  $p = .33$ ) and the  $F$  values were less than 1 for the main effect of Hand and the interaction term.

The Wing and Kristofferson model (1973) was used to partition the total variability scores into two components, central, or clock variability and motor implementation variability. The application of the model to the current data sets was deemed appropriate given that the lag 1 autocovariance was negative for each participant when tapping with either the left or right hand,

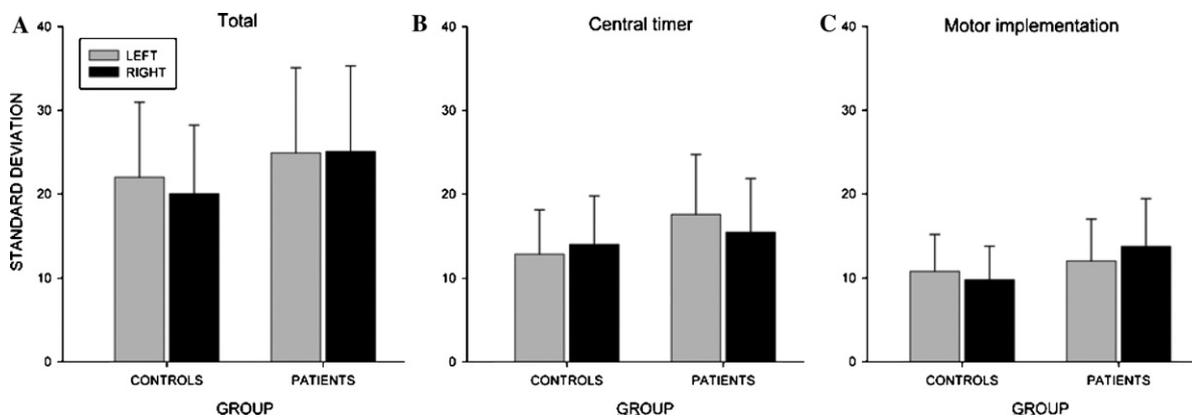


Fig. 4. Variability on the timed tapping task. (A) The standard deviation of the intertap intervals was measured for each trial and these values were averaged across trials. The Wing–Kristofferson model was used to decompose total variability into estimates of the central “clock” (B) and motor implementation (C) components.

with the exception of control subject GP when tapping with her left hand. The violation was treated by arbitrarily setting the motor implementation variability estimate to zero, and using the total variability score as the estimate of clock variability (see Ivry & Keele, 1989; for a discussion of such violations).

The estimates of clock variability are shown in Fig. 4B. As with the analysis of total variability, there was no effect of Group, ( $F(1,11) = 1.06$ ,  $p = .33$ ), Hand ( $F(1,11) < 1$ ), nor any indication of a Group by Hand interaction, ( $F(1,11) < 1$ ). The lack of a hand effect is similar to what has been observed with neurologically healthy college students (Helmuth & Ivry, 1996). Of greatest interest in the current study is the performance of the patients with focal basal ganglia lesions with their contralesional right hand. As can be seen in the figure, the patients actually showed a slightly lower estimate of clock variability when tapping with this hand compared to their left hand.

The estimates of motor implementation variability are shown in Fig. 4C. Helmuth and Ivry (1996) had found a hand effect on this measure, with lower motor implementation variability when tapping with the dominant hand. The means for the control participants are in this predicted direction. The motor implementation for the patients was slightly higher when tapping with their contralesional (dominant) hand. However, as with the other analyses, none of the effects were significant (main effect of Group ( $F(1,11) = 1.06$ ,  $p = .33$ ), while the  $F$  values  $< 1$  for the main effect of Hand and the Group  $\times$  Hand interaction).

In summary, the patients with focal basal ganglia lesions showed no evidence of impairment in their ability to produce rhythmic movements, even in the absence of an external metronome. The lack of a deficit on this task is especially surprising given that the task has proven to be extremely sensitive to motor impairments. For example, in our work with cerebellar patients, we typically observe increased variability on this task even when there is no evidence of any persistent deficit in a clinical exam. These results indicate that lesions to one side of the basal ganglia do not affect the ability to control the timing of rhythmic movements.

### 4.3. Isometric force production

We assessed force control with measures of accuracy, variability, and the time required to generate the force pulses. Fig. 5A depicts the mean force produced as a function of the target force. Both groups show a considerable compression of the range: pulses for the small force target were generally larger than required and pulses for the large force target were generally smaller than required. Note that this task does not measure maximum force; all of the target forces were selected to fall well below the maximum force level for elderly

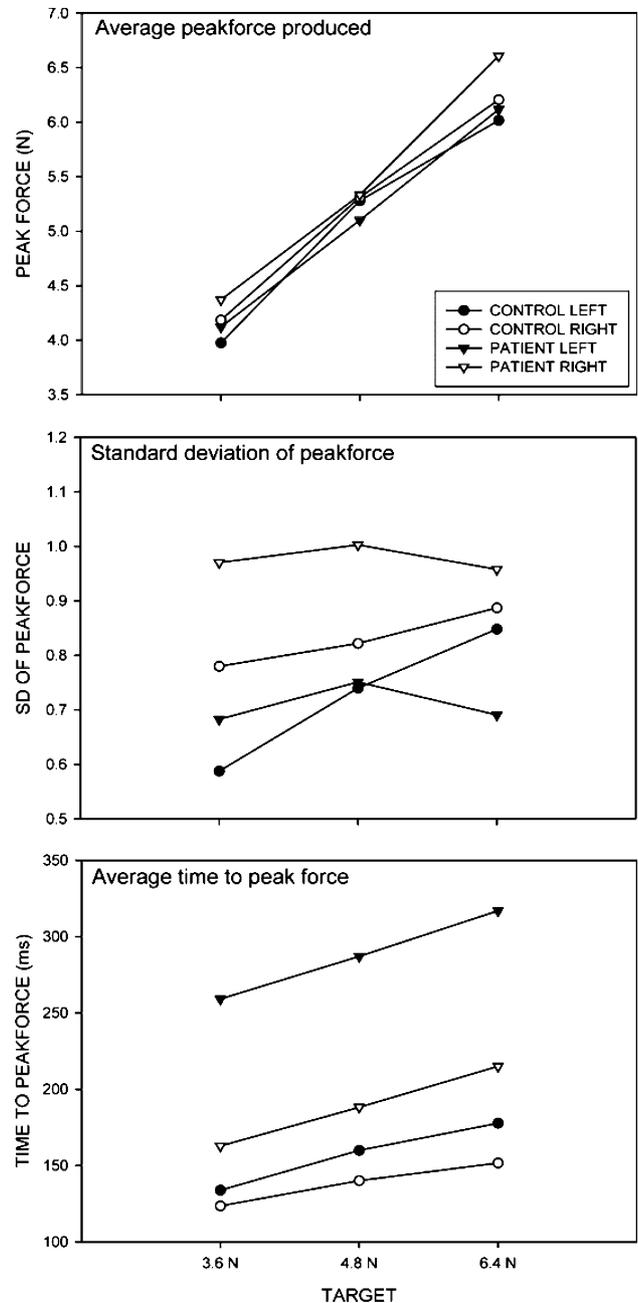


Fig. 5. Performance on the force control task, plotted as a function of the target force. Top: Mean produced force. Middle: Standard deviation of the force pulses. The  $SD$  was calculated for each trial and averaged across trials. Bottom: Time to peak force.

control participants and none of the patients reported difficulty in matching the largest target force.

This effect is similar to what has been reported in previous studies with elderly control and Parkinson patients (Stelmach & Worringham, 1988). Nonetheless, produced force was directly related to required force, indicating that the participants were able to perform the task.

A Group  $\times$  Hand  $\times$  Target Force (low, medium, high) ANOVA was used to analyze the data. As expected, the

main effect of target force was highly reliable, ( $F(2,8) = 778.4, p < .0001$ ). Neither of the other main effects were significant: Group ( $F(1,4) < 1$ ); Hand ( $F(1,1) = 1.73, p = .26$ ). However, the Group  $\times$  Target Force interaction was significant, ( $F(2,8) = 5.27, p < .05$ ). With either hand, the patients tended to produce slightly larger forces than the controls for the smallest and largest forces, but not for the middle force. The effect of Hand did not interact with either of the other two main effects nor was the three-way interaction significant (all  $F$  values  $< 1$ ). Thus, the patients were able to scale their force pulses in a similar manner for the ipsi- and contralesional hands.

Performance on the task was highly variable (Fig. 5B). To provide a measure of overall variability, we computed the coefficient of variation by dividing the standard deviation by the mean force produced. Averaging over the six conditions (two hands and three target levels), this value was 15.0% for the control participants and 15.9% for the patients with focal basal ganglia lesions. In previous studies with college-age students, values are typically on the order of 8.4%. This increases to about 9.4% for elderly controls and 9.5% for Parkinson patients (Stelmach & Worringham, 1988), at least when the target forces are submaximal. It is not clear why the values are higher with the current data set. Also indicative of the participants' difficulty with this task is the finding that there was little increase in variability from the low to high target force values. Most studies of force variability find that force variability increases with peak force (Carlton, Kim, Liu, & Newell, 1993; Newell & Carlton, 1988). This was not true in the current experiment, although there was a slight increase in the standard deviation over the three target forces, ( $F(2,8) = 4.7, p < .05$ ). The effect of Hand approached significance ( $F(2,8) = 6.97, p = .06$ ); as can be seen in the figure, variability was higher with the left hand in all conditions for both groups.

Turning to the statistics that assess the effects of the lesions, there was no effect of Group ( $F(1,4) = 1.37, p = .31$ ) and the two-way Group  $\times$  Hand interaction ( $F(1,4) = 1.35, p = .31$ ) and three-way Group  $\times$  Hand  $\times$  Target Level ( $F(2,8) < 1$ ) were also not significant. The only reliable interaction was for the Group  $\times$  Target Level comparison ( $F(2,8) = 4.71, p < .05$ ). This interaction reflects the fact that, in comparison to the controls, the patients had higher variability for the lowest target level and lower variability for the highest target level.

Force variability is not only a function of force; it also varies systematically with the dynamics of the force pulse. Specifically, force variability will be greater for faster responses: a form of a speed–accuracy trade-off (Carlton & Newell, 1988; Schmidt, Zelaznik, Hawkins, Frank, & Quinn, 1979). To evaluate the response dynamics, we examined the time to peak force (an anal-

ysis of response duration would yield similar results). These results are presented in Fig. 5C. The main effect of Target was significant, ( $F(2,2) = 26.0, p < .001$ ), indicated that the time to peak force increased as the target force increased. There was a main effect of Group ( $F(1,4) = 8.48, p < .05$ ), with the patients slower to reach peak force than the controls. There was also an effect of Hand ( $F(1,4) = 8.96, p < .05$ ). As can be seen in the figure, the patients were considerably slower to reach peak force when responding with their contralesional hand, a result that would be consistent with previous studies involving Parkinson's patients (Stelmach & Worringham, 1988). Surprisingly, the controls were also slower to reach peak force when using their right hand. This likely reflects the fact that patients produced slightly larger force pulses with their right hand. The time required to reach peak force increases with peak force. While the hand effect appears to be considerably larger for the patients, the Group  $\times$  Hand interaction was not significant ( $F(1,4) = 4.167, p = .11$ ), nor were any of the other interactions ( $F < 1$ ).

In summary, patients with focal lesions of the basal ganglia were able to match the target forces as well as the controls and there was no difference between the groups of measures of response variability. The only indication of a possible force control deficit was on the measure of response dynamics: the patients were slower to reach peak force than the controls and although not statistically reliable, this effect tended to be more pronounced for responses made with the contralesional hand.<sup>2</sup>

## 5. Discussion

The basal ganglia are considered one of the prominent subcortical pathways of the motor control system. The most compelling evidence has come from the study of people and experimental animals with lesions of the basal ganglia. Although the impairments may not be limited to the motor domain, the most prominent symptoms in both Parkinson's disease and Huntington's disease are of the motor system. Interestingly, the overt symptoms are not discernable in these degenerative disorders until the pathology is quite advanced (e.g., Grafton et al., 1990; Morrish, Sawle, & Brooks, 1996). However, acute disorders of movement can be induced in animals that receive focal basal ganglia lesions (Horak & Anderson, 1984; Inase et al., 1996; Wenger et al., 1999; see also DeLong & Georgeopoulos, 1981; for

<sup>2</sup> We also evaluated the data with a measure that assesses variability as a composite of the target force and response speed (Carlton et al., 1993). This analysis also failed to reveal any impairment in the patients.

review) or are administered MPTP (for review see Sedelis, Scwirting, & Huston, 2001), a synthetic drug that appears to selectively destroy the dopaminergic neurons of the substantia nigra.

In the current study, we tested a group of patients with focal basal ganglia lesions on a set of motor tasks that have been used in previous studies of patients with Parkinson's disease. We did not expect the patients' performance to be similar to that of Parkinson patients on these tasks given that their clinical picture, either during the acute or chronic state is quite different. Nonetheless, we were interested to see if the tasks presented problems for the patients. The guiding logic of the study was that, if the basal ganglia are involved in a particular motor function, then damage to the system should disrupt performance on tasks requiring that function. The exact manifestation of the deficit may differ for Parkinson and focal basal ganglia patients; but we would still expect the performance of both groups to be abnormal if the basal ganglia were essential.

The most interesting finding in this study is the relatively normal performance of the patients, even when performing with their contralesional hand. As part of our recruitment protocol, the patients were given a standard neurological exam that covered a range of motor functions. It was apparent at this stage that any deficits were likely to be rather subtle; none of the patients exhibited gross abnormalities and most showed no persisting motor signs. This was consistent with previous reports of patients with chronic basal ganglia lesions. However, our experimental tasks are considerably more sensitive than the types of tasks included in clinical batteries. Indeed, on the test of maximum tapping speed, we did find that the patients were slower in tapping with their contralesional hand. Even this deficit was minor. In fact, the patients were able to tap as fast with their contralesional hand as with their ipsilesional hand. We could only infer a deficit when we took into account the fact that normal participants tap faster with their dominant hand. This handedness effect was absent in our group of patients with left hemisphere lesions.

It is possible that the decrease in maximum tapping rate is not related to the basal ganglia damage, but rather due to involvement of the descending fibers of the internal capsule. Such damage is present in at least two of the patients. Alternatively, it may reflect a persistent effect of the basal ganglia damage. A decrease in maximum movement rate is a generic sign of motor dysfunction.

On the tests of timing, the results were clear. There was no indication of any impairment, either in a comparison of the patients to the control participants or in a within-subject comparison of the ipsi- and contralesional limbs. As reviewed in Section 1, previous studies involving patients with Parkinson's disease have yielded mixed results on the repetitive tapping task. Some re-

ports suggest increased variability in an internal timing process (Harrington et al., 1998; O'Boyle et al., 1996); other studies have reported normal performance in Parkinson patients (Duchek et al., 1994; Spencer & Ivry, *in press*). A more consistent picture has been found on tests of force control. Parkinson patients have difficulty generating force pulses, with the problems evident as increased variability (Stelmach & Worringham, 1988; Stelmach, Teasdale, Phillips, & Worringham, 1989; Vailancourt, Slifkin, & Newell, 2001; Wing, 1988) or more commonly, a slowness in the movement (Hallett & Khoshbin, 1980) or implementation of a change in isometric force (Wing, 1988). The current data suggest that a similar deficit may be present in patients with focal basal ganglia lesions. Compared to controls, the patients were slower to reach peak force and this effect was most pronounced for responses made with the contralesional hand. However, they were also slower to peak force when using the ipsilesional hand and interpretation of these effects is complicated by differences in the peak forces achieved. Further study of response dynamics is required.

What conclusions are to be drawn from this study? The strongest claim would be that the results question the involvement of the basal ganglia in the control of either the timing or intensity of a movement. A corollary of such a conclusion would be to question the utility of degenerative disorders such as Parkinson's disease for studying basal ganglia dysfunction. As noted previously, Parkinson's disease is only manifest when there has been a massive depletion of dopaminergic neurons. By this time, alterations in the function of other brain systems, both from the direct loss of dopamine in other brain systems or through indirect changes resulting from the basal ganglia dopamine loss are likely to be present. The movement problems associated with Parkinson's disease may not be directly related to basal ganglia dysfunction, but rather to changes in other systems or the interaction of these systems with the basal ganglia.

We believe the current results do provide a cautionary note against the over-reliance on the use of a degenerative disorder for studying the functions of a particular neural system. However, it is equally important to keep in mind some of the limitations associated with the current results and more generally, with the use of patients with focal lesions. First, most of the findings here constitute null results: the patients' performance was similar to that observed with the control participants. As with any set of null results, we must be wary of accepting the null hypothesis.

Second, there are various limitations with our current pool of focal basal ganglia patients. Not only is the sample size small, but also the lesions were in the left hemisphere for all of the patients and timing functions have often been attributed to the right hemisphere (e.g.,

Coull, Vidal, Nazarian, & Macar, 2004; Ferrandez et al., 2003). We hope to expand this group in future research to include patients with right hemisphere lesions as well as provide the opportunity to perform analyses in which we assess performance as a function of lesion location.<sup>1</sup> We would expect motor problems to be most pronounced in patients with either putamen or globus pallidus lesion, although there was little indication of this pattern in the current data set. Moreover, all of the current patients were tested in the chronic state, at least six months after their neurological insult. Not only does the clinical literature indicate that the prognosis for recovery from focal basal ganglia is good, but animals with unilateral basal ganglia lesions also show striking recovery when forced to use the contralesional limb (e.g., Tillerson et al., 2001). Patients tested shortly after a cerebral vascular incident may present a different picture. It should be noted, however, that in our studies involving patients with cerebellar lesions, we do observe qualitatively similar motor timing problems in acute and chronic patients, and that these patients with unilateral cerebellar lesions also show similar deficits as patients with degenerative cerebellar disorders.

Third, it is important to keep in mind that patients with focal lesions have an intact set of basal ganglia nuclei. Perhaps the non-lesioned side of the basal ganglia is sufficient to ensure normal performance with either hand, at least on these relatively simple motor tasks. There are many syndromes in the neurological literature in which the consequences of bilateral brain injury are severe and permanent, and seem extremely disproportionate when compared to the effects of unilateral damage. For example, the memory problems observed in patients with bilateral lesions of the medial temporal lobe region or the attention problems seen in patients with bilateral parietal lobe damage (i.e., Balint's syndrome) are much worse than would be expected based on the summed effects of unilateral damage to the associated brain regions. Animal studies suggest a similar pattern may hold for the basal ganglia. Recovery is excellent following unilateral striatal lesions, but not in animals given symmetric, bilateral lesions of the striatum (reviewed in DeLong & Georgeopoulos, 1981). The anatomical organization of the basal ganglia may make this subcortical structure especially immune to the effects of unilateral lesions. Cortical inputs to the basal ganglia are, at least from frontal cortices, bilateral (McGuire, Bates, & Goldman-Rakic, 1991). In addition, a significant percentage of the output fibers from the globus pallidus cross over to the other hemisphere (Hazrati & Parent, 1991). Such patterns of connectivity may, at a functional level, create a situation in which each half of the basal ganglia can provide the requisite computations for movements produced by either hand.

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