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Brain and Cognition 58 (2005) 75–83
Brain and Cognition
www.elsevier.com/locate/b&c

Multidimensional sequence learning in patients with focal basal ganglia lesions

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Accepted 16 September 2004
Available online 2 December 2004

Abstract

Parkinson's patients have been found to be impaired in learning movement sequences. In the current study, patients with unilateral basal ganglia lesions due to stroke were tested on a serial reaction time task in which responses were based on the spatial location of each stimulus. The spatial locations either followed a fixed sequence or were selected at random, with learning operationalized as the difference in reaction time between these two conditions. In addition, three response-to-stimulus intervals were used, and these either followed a fixed sequence or were randomized. Compared to control participants, the patients showed normal learning of the spatial and temporal sequences, as well as normal cross-dimensional learning. This was true for performance with either the contralesional or ipsilesional hand. Sequence learning was not correlated with maximum tapping rate, a simple measure of motor impairment. These results raise questions concerning the use of Parkinson's disease as a model for studying basal ganglia dysfunction.

1. Introduction

Many of our every day activities consist of a sequence of actions, such as speech, playing a tune on a musical instrument, or driving down a familiar route. Previous research has revealed that the production of sequential actions is associated with various cortical and subcortical areas. Lesions in frontal and parietal cortex, especially in the left hemisphere, have been linked to apraxia, a disorder that involves an impairment in the production of coherent action sequences (Heilman, Rothi, & Valenstein, 1982). In addition, dysfunction in subcortical areas, such as the basal ganglia and the cerebellum, have been associated with sequence decomposition (Benecke, Rothwell, Dick, & Marsden, 1986; Holmes, 1939).

Research investigating learning of action sequences has utilized the serial reaction time task, first used by Nissen and Bullemer (1987). In this task, a speeded choice response is given to a visual stimulus based on some property such as its location, shape, or color. The stimuli are selected to either follow a fixed sequence or at random, and learning is operationalized as the difference in response latency between sequence and random blocks. The serial reaction time task is considered a test of implicit skill learning because participants show significant reductions in latency on sequence blocks yet are often unaware of the stimulus sequence.

Neuroimaging studies using this serial reaction time task point to the involvement of a distributed network of cortical and subcortical areas. Learning associated changes in activation have been discovered in cortical areas, such as the primary motor cortex, supplementary

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doi:10.1016/j.bandc.2004.09.015

motor area, premotor cortex, prefrontal cortex, and inferior parietal cortex (Grafton, Hazeltine, & Ivry, 1995; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Karni et al., 1995). Subcortical activation has been consistently observed in the striatum with the serial reaction time task (Grafton et al., 1995; Seitz, Roland, & Bohm, 1990) and in the cerebellum with other sequencing tasks (Seitz et al., 1990).

Neuropsychological studies have also been conducted with the serial reaction time task. While a number of studies have consistently reported a complete absence of learning in patients with cerebellar lesions (Doyon et al., 1997, 1998; Gomez-Belderrain, Garcia-Monco, Rubio, & Pascual-Leone, 1998; Molinari et al., 1997; Pascual-Leone et al., 1993), the results are mixed with respect to the role of the basal ganglia in sequence learning. Patients with Huntington's disease (Willingham & Koroshetz, 1993) or Parkinson's disease (Knowlton, Mangels, & Squire, 1996) have been found to show learning impairments. However, the magnitude of the deficit found in Parkinson patients varies considerably across studies, ranging from severe (Jackson, Jackson, Harrison, Henderson, & Kennard, 1993) to moderate (Ferraro, Balota, & Connor, 1993; Pascual-Leone et al., 1993) to none (Girotti et al., 1986), and an understanding of the discrepancies across these studies remains elusive (see Helmuth, Mayr, & Daum, 2000).

In most serial reaction time studies, the stimuli vary along a single dimension. However, most skills require the integration of information across multiple dimensions. For example, the pianist must not only play the keys in the right order, but must also impose an appropriate rhythm. Schmidtke and Heuer (1997) modified the standard serial reaction time task to examine multidimensional sequence learning, as well as cross-dimensional sequence integration. Healthy subjects were presented with two interleaved sequences. One sequence was defined by the spatial position of visual signals, and responses to these events were manual. The second sequence was formed by auditory events, where participants made a foot response to tones of a target pitch. In one condition, the two sequences were of unequal length and thus uncorrelated (e.g., one was of length 6 and the other of length 5). In a second condition, the two sequences were of equal length (e.g., both length 6), and the phase relationship was maintained across blocks. In this condition, the visual and auditory events formed a 12-element inter-dimensional meta-sequence.

Three types of learning probes were used. Two probes assessed intra-dimensional learning: for one, the visual events were randomized, and for the other, the auditory events were randomized. To assess inter-dimensional sequence integration, the phase relationship between the visual and auditory events was altered, a manipulation that was only applicable to the condition in which the two sequences were correlated (i.e., of equal length). Visual and auditory sequence learning were observed in both the uncorrelated and correlated conditions. The degree of learning was greater for the correlated condition compared to the uncorrelated condition. Moreover, inter-dimensional integration was observed in the correlated condition as indicated by an increase in mean reaction time following the phase-shift manipulation. This study demonstrates that people are capable of learning and integrating two simultaneous sequences. Furthermore, sequence integration appears to benefit sequence learning of the individual sequences.

Sequence integration also benefits performance when the secondary sequence is temporal and does not require an overt response. Shin and Ivry (2002) tested participants on a spatial serial reaction time task. In addition, the interval between the response and subsequent stimulus (the response-to-stimulus interval, or RSI) was varied from trial to trial. In one condition, the RSIs were presented in a sequence the same length as the sequence of spatial locations, and the phase-relationship between the two sequences was maintained across training blocks. In another condition, the two sequences were of differing lengths and were uncorrelated. Since the responses were solely dictated by the spatial location of each stimulus, the temporal manipulation was incidental. Similar to the results of Schmidtke and Heuer (1997), a phase-shift cost was observed in the correlated condition, indicating subjects integrated the two sequences into a common spatial-temporal representation. Importantly, spatial learning appeared to be greater when sequence integration occurred than when sequence integration did not occur. Together, these studies suggest that cross-dimensional integration can improve sequence learning when the secondary sequence requires a response, as in Schmidtke and Heuer, or is incidental, as in Shin and Ivry.

To explore the role of subcortical areas in sequence integration, patients with cerebellar lesions, Parkinson's disease, and matched control participants were tested on the version of the spatial-temporal serial reaction time task in which the two sequences were correlated (Shin & Ivry, 2003). An interesting dissociation was found between the two patient groups. The patients with cerebellar lesions failed to exhibit any evidence of learning when probed on either sequence alone or in the phase-shift probe, which was used to assess sequence integration. In contrast, the Parkinson patients showed unidimensional learning for both the spatial and temporal sequences. However, compared to controls, they were impaired in their ability to integrate the two sequences. This dissociation points to a general role for the cerebellum in sequence learning and a more limited role for the basal ganglia specific to sequence integration. The massive degree of convergence within the striatum (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000) has been hypothesized to provide an important

anatomic substrate for multidimensional integration (Graybiel & Kimura, 1995; Matell & Meck, 2000).

To date, all of the neuropsychological studies examining the role of the basal ganglia in sequence learning have involved patients with degenerative disorders, either Huntington's disease or Parkinson's disease. While these disorders have proven to be useful models for studying basal ganglia dysfunction, it is important to keep in mind that these diseases produce both direct and indirect changes in cortical function. In Parkinson's disease, cortical function is not only altered by increased inhibition from pallido-thalamic inputs, but also by alterations in other dopaminergic pathways such as the nucleus accumbens (Javoy-Agid & Agid, 1980). Given this, the current study was initiated to extend the work of Shin and Ivry (2003) by testing patients with focal basal ganglia lesions. We hypothesized that these patients should show similar deficits as those found in Parkinson patients, assuming that the lesions encompassed critical regions within the basal ganglia for sequence learning and integration. In addition, by testing patients with unilateral lesions, a within-subject comparison can be made between performance with the impaired, contralesional hand and the unimpaired, ipsilesional hand. Molinari et al. (1997) conducted a similar study with patients with unilateral cerebellar lesions. Surprisingly, the cerebellar patients failed to learn when tested with either hand. In the current study, we can evaluate whether patients with focal basal ganglia lesions also present similar bilateral deficits in sequence learning and integration.

2. Methods

2.1. Participants

Four unilateral basal ganglia patients and seven age-matched control participants were included in this study. Table 1 summarizes demographic, anatomical, and neuropsychological data regarding the patients. All patients had lesions resulting from stroke restricted to the striatal and pallidal areas, two in the left hemisphere and two in the right hemisphere. The patients were 64.8 years of age on average (ranging between 53.5 and 77.9 years, $SD = 10.1$ years), and had 16.8 years of education on average (ranging between 14 and 19 years, $SD = 2.2$ years). Three were male and 1 was female. All but one patient (with a score of 20) had a score of 29 or 30 on the Mini-Mental State Exam (maximum score 30).

The control participants were 67.7 years of age on average (ranging between 60 and 73 years, $SD = 4.1$ years), and had 16.9 years of education on average (ranging between 16 and 18 years, $SD = 1.2$ years). Five were male, and two were female. All the control participants had a score of 29 or 30 on the Mini-Mental State Exam.

2.2. Stimuli and procedure

All participants were tested on two tasks, a serial reaction time task and a fast-tapping task. The fast-tapping task was used as a simple measure of motor impairment, with the expectation that the patients would be slower when tapping with their contralesional hand. For the control participants, both tasks were performed during the same experimental session using their dominant right hand. The patients were tested on the serial reaction time task twice, once with each hand, in separate experimental sessions separated by between nine days to five months. Each patient performed the serial reaction time task with the contralesional hand during the first session and the ipsilesional hand during the second session. Each patient performed the fast-tapping task in each session with the hand used for the reaction time task.

2.2.1. The serial reaction time task

A variant of the serial reaction time task was used in which the stimuli defined both a spatial and temporal sequence. On each trial, a visual stimulus (an "*X*") was presented at one of four horizontal locations on a computer monitor. The participants' task was to press the corresponding response key as quickly as possible. The mapping between the stimulus locations and the response keys was consistent (e.g., left-most key corresponded to left-most position). The *X* was displayed for 300 ms or until the participant responded on trials in which the reaction time was faster than 300 ms. The next stimulus was presented after one of three response-to-stimulus (RSI) intervals, 200, 500 or 800 ms.

The experiment consisted of 21 blocks of 56 trials each. In *sequenced-location* blocks, the location of the *X* followed an eight-element sequence of the syntax

Table 1
Demographic, anatomical, and neuropsychological information regarding focal basal ganglia patients

Patient	Sex	Age	Years of education	Lesion	Mini-Mental State Exam
BF	M	77.9	14	(Left) caudate	29
RP	M	65.3	18	(Left) putamen, caudate and internal capsule	20
DI	F	62.6	19	(Right) basal ganglia	30
EC	M	53.5	16	(Right) putamen and internal capsule	30

14213243, which repeated seven times. The mapping of the numbers 1–4 to response locations was varied across participants and between testing sessions for the patients with the constraint that mappings were avoided that produced four-element runs from left to right or right to left. On *random-location* blocks, the location of the *X* for each trial was selected at random with the constraint that first-order and second-order probabilities on the random blocks were matched to the sequenced blocks. Thus, each position was selected on approximately 25% of the trials and only transitions used in the sequence were presented. For example, the sequence element 1 was only followed by 3 or 4 and not by 1 or 2.

The RSIs were also sequenced or random. In *sequenced-RSI* blocks, the RSIs followed a repeating eight-element sequence of the syntax ACBCABCB. As with the location sequences, the mapping between the letters A–C and RSIs was varied across participants and between testing sessions for the patients. On *random-RSI* blocks, the RSIs varied randomly from trial to trial under similar constraints as in the random-location blocks. Thus, four types of blocks were included in the experimental design formed by the factorial combination of whether the spatial locations were sequenced or random and whether the RSIs were sequenced or random (Table 2). Except for the phase-shift block (see below), the phase-relationship on blocks in which both dimensions were sequenced was fixed and maintained, creating a constant inter-dimensional sequence from block to block. For these blocks, the starting point was chosen at random on each block to reduce the likelihood that the participants would develop awareness of the sequences.

As shown in Table 2, the experiment started out with two blocks in which both the spatial and timing dimensions were random. This was followed by five blocks of sequence learning. For these blocks, both dimensions were sequenced, and the phase relationship was held constant. To measure sequence learning, three types of probes were used, each composed of four blocks. In each probe, the first and fourth blocks used the training condition (i.e., both dimensions sequenced with original phase relationship). The stimuli were altered in the middle two blocks, either by randomizing the spatial or temporal sequence, or by introducing an inter-dimensional phase shift. In the latter condition, the phase relationship was altered by shifting the RSI sequence forward by one position. Thus, whereas the training sequence had been 1A–4C–2B–1C–3A–2B–4C–3B (where numbers denote stimulus locations, and letters denote RSIs), during the phase-shift blocks the pairs were 1C–4B–2C–1A–3B–2C–4B–3A. Learning scores were obtained by comparing the difference in reaction time between the middle two and outer two blocks for each four-block probe. The basic training condition (both sequenced) was used between each probe. Note that in this manner, each alteration of the sequence, either by randomizing one of the dimensions or through the phase shift, was preceded by at least three blocks of the training sequence. The order of the phase-shift, spatial, and timing probes was counterbalanced across participants and between experimental sessions for the patients.

Table 2
Arrangement of blocks in the serial reaction time task

Block number	Location	RSI	Learning probe
1–2	Random	Random	
3–7	Sequenced	Sequenced	
8	Sequenced	Sequenced	Phase-shift
9–10	Phase-shifted	Phase-shifted	Phase-shift
11	Sequenced	Sequenced	Phase-shift
12	Sequenced	Sequenced	
13	Sequenced	Sequenced	Spatial
14–15	Random	Sequenced	Spatial
16	Sequenced	Sequenced	Spatial
17	Sequenced	Sequenced	
18	Sequenced	Sequenced	Timing
19–20	Sequenced	Random	Timing
21	Sequenced	Sequenced	Timing

Note. The order of the probes was counterbalanced among participants.

2.2.2. Fast-tapping task

As a measure of motor impairment, a speeded tapping task was administered to the participants. In this task, a tone sounded signaling the participant to begin tapping as fast as possible with the index finger. After 32 taps, a tone sounded to end the trial. Each patient performed three trials. This fast-tapping task was performed once by the control participants using the dominant hand. Each of the patients performed this task twice, once during each experimental session with the hand used during that session for the serial reaction time task.

2.2.3. Post-experiment interview

After the serial reaction time task was completed in the final experimental session, each participant was asked whether they noticed any patterns in the stimulus display. None of the control participants or patients could correctly report parts of either sequence longer than two successive sequence elements. This aspect of the study will not be mentioned further.

2.2.4. Stimuli and equipment

For the serial reaction time task, stimuli were presented on a computer monitor stationed approximately 60 cm from the participant. On each trial, an *X*, subtending a visual angle of about 0.5°, was presented at one of four locations along the horizontal meridian. The four locations were continuously marked by four

horizontal lines approximately 0.5° in length with a 1.5° gap between adjacent lines.

Responses were given by pressing one of four keys aligned horizontally on a response board. Each key was 10.2×2.0 cm with an inter-key spacing of .6 cm, and a minimal level of force was required to activate an underlying microswitch. The participant rested the palm of his or her hand on the response board, positioning the four fingers above the keys. This response board was also used for the fast-tapping task, where the left-most key of the four keys was used for tapping with the left index finger, and the right-most key was used for tapping with the right index finger.

2.3. Data analysis

2.3.1. Serial reaction time task

For each participant, the median reaction time was computed for each block excluding incorrectly responded trials and the first trial in each block. For each participant, a learning score was computed for both response latency and accuracy. The latency learning score for each probe was computed by subtracting the mean of the median reaction time for the two outer blocks (training sequence blocks) from the mean of the median reaction time for the two inner blocks (altered blocks), and then dividing this by the mean of the median reaction time for the two outer blocks. The accuracy learning score was calculated in a similar manner, although here, the mean accuracy for the two inner blocks of each probe was subtracted from the mean accuracy for the two outer blocks, and then divided by the mean accuracy for the two outer blocks. In this manner, a positive learning score indicated learning for both the latency and accuracy measures. In essence, the learning scores represent the cost in performance during the altered blocks proportional to performance in the sequence maintained blocks. Each of the learning scores was evaluated as to whether it was greater than zero using a one-tailed t test. Learning scores were also compared between the patient and control groups. Two-tailed t tests were used when the variance in each of the compared groups was statistically comparable to each other. In other cases, a Mann–Whitney test was conducted.

2.3.2. Fast-tapping task

For each trial, the mean and standard deviation of the last 30 tapping intervals were calculated. The average of the mean inter-tap intervals and the average of the standard deviations of the inter-tap intervals were then computed over the three trials. The relationship between sequence learning performance and motor impairment in the patients was examined by computing a Pearson correlation between each of the learning scores and the measures on the fast-tapping task.

3. Results

The participant with the abnormal Mini-Mental State Exam score (patient RP) performed similarly to the other patients on the serial reaction time task and the fast-tapping task[1]. We therefore report the results including his data.

Reaction times below 50 ms indicated that a key was depressed at the time of the appearance of the visual stimulus X. For the control participants, this occurred on 3.6% of all trials. For the patients, this occurred on 20.4 and 13.5% of all trials during the first and second experimental sessions, respectively. 94.3% of these occurred when the stimulus followed the shortest RSI of 200 ms, consistent with the interpretation that the preceding response had not been completed prior to the onset of the subsequent stimulus. The high proportion of the extended key presses for the patients is likely a manifestation of their motor impairment. These trials with reaction time below 50 ms were excluded from further analysis.

3.1. Learning scores in the serial reaction time task

3.1.1. Response latency

Over all blocks, the average median reaction time was 588 ms ($SE = 25$) for the control participants. For the patients, the average median reaction time was similar to the control participants when tested with either hand, $M = 603$, $SE = 38$ with the contralesional hand and $M = 549$, $SE = 55$ with the ipsilesional hand. Note that while the patients were 54 ms slower when using their contralesional hand, the one we would expect to be affected by the stroke, this hand was always tested first.

[1] Patient RP's average median reaction times (695 ms with the contralesional hand and 689 ms with the ipislesional hand) were high relative to the other patients (contralesional: $M = 572$, $SE = 28$; ipsilesional: $M = 503$, $SE = 36$). However, this patient's learning scores were well within the range of scores for the other patients. His learning scores with the contralesional hand for the spatial, timing, and phase-shift probes were .07, .09, and .11, respectively. His learning scores with the ipsilesional hand were .05, .03, and .13. With respect to accuracy, patient RP's accuracy with the contralesional hand ($M = .83$) was lower than the average of the other patients ($M = .93$, $SE = .04$), but his accuracy with the ipsilesional hand ($M = .93$) was similar to the other patients ($M = .91$, $SE = .06$). Again, the learning scores were within the range of scores for the other patients. His learning scores with the contralesional hand for the spatial, timing, and phase-shift probes were .037, −.034, and .031, respectively. His learning scores with the ipsilesional hand were .007, .022, and .002. Finally, patient RP's performance on the fast-tapping task was similar to the other participants. Patient RP's mean inter-tap intervals were similar to the other patients (183 ms with the contralesional hand and 206 ms with the ipsilesional hand). The standard deviations of the inter-tap intervals for this patient were also similar to the other patients (41 ms with the contralesional hand and 42 ms with the ipsilesional hand).

Thus, it is not possible to conclude if the difference is due to the stroke or is an order effect.

The learning scores are plotted in Fig. 1 for individual participants in the control (H) and patient groups. For the patients, learning scores are plotted separately for the contralesional (C) and ipsilesional (I) hands.

The control participants exhibited learning as assayed by the intra-dimensional spatial and temporal probes as well as in the inter-dimensional phase-shift probe. The learning scores for the spatial ($M = .074$, $SE = .023$), timing ($M = .061$, $SE = .020$), and phase-shift probes ($M = .071$, $SE = .021$) were all significantly greater than zero, all t's > 2, p's $< .01$ for the spatial and phase-shift probes and $p < .05$ for the timing probe. The patients also showed clear evidence of sequence learning when tested with their contralesional hand. All four patients showed positive learning scores for each of the sequence learning probes when the serial reaction time task was performed with the contralesional hand, $M = .087$, $SE = .028$ for the spatial probe, $M = .145$, $SE = .033$ for the timing probe, and $M = .171$, $SE = .054$ for the phase-shift probe, ts > 3, ps $< .05$.

Surprisingly, learning appeared to be greater in the patients than in the control participants for the timing probe, $t(9) = 2.34$, $p < .05$, and marginally so for the phase-shift probe, $t(9) = 2.08$, $p = .07$. However, sequence learning as measured by the spatial probe did not differ significantly for the two groups, $t(9) = .34$, $p > .7$.

Patients' performance with the ipsilesional hand showed trends that were similar to the control group for the timing ($M = .063$, $SE = .032$) and phase-shift probes ($M = .057$, $SE = .041$), although these did not reach significance, $t(3) = 1.96$, $p < .08$ for the timing probe and $t(3) = 1.39$, $p > .1$ for the phase-shift probe. An unexpected result was the lack of learning with the ipsilesional hand when measured by the spatial probe ($M = .003$, $SE = .022$), $t(3) = .15$, $p > .4$.

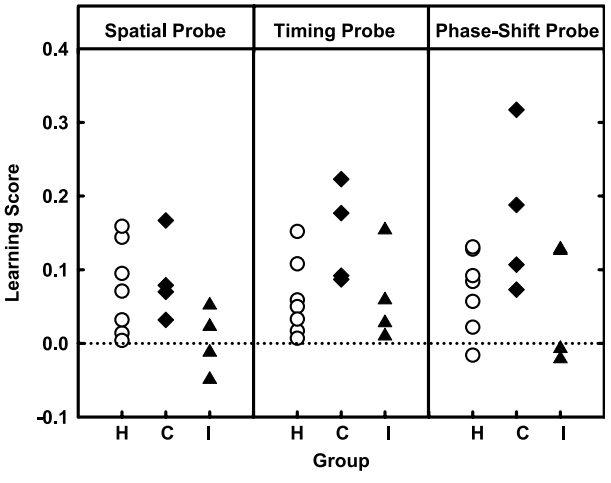

Fig. 1. Latency learning scores for the spatial, timing, and phase-shift probes plotted for individual participants. Learning scores are plotted separately for the control ($n = 7$) (H) and patient ($n = 4$) groups. Learning scores for the patients are further divided into those produced with the contralesional hand (C) and those produced with the ipsilesional hand (I).

The influence of probe order on overall mean reaction time and the learning scores was assessed.[2] While significant effects of probe order were found, they did not affect the pattern of data reported above.

3.1.2. Response accuracy

Overall, the proportion of correct trials was .95 ($SE = .011$) for the control participants, .90 ($SE = .035$) for the patients when using the contralesional hand, and .92 ($SE = .046$) for the patients when using the ipsilesional hand. The difference in proportion correct between the control participants and the performance of patients using the contralesional hand was not significant, $t(9) = 1.73$, $p > .1$. In terms of sequence learning, only one accuracy measure was significant: for the control participants, accuracy was higher on sequence blocks compared to random blocks for the spatial probe ($M = .023$, $SE = .009$), $t(3) = 2.62$, $p < .05$. All other accuracy scores were not significantly different than zero.

3.2. The relationship between basic motor ability and sequence learning

In general, the patients exhibited little evidence of persistent motor problems during clinical examination, similar to previous reports of the effects of focal basal ganglia lesions in the chronic state (Caplan et al., 1990; Giround, Lemesle, Madinier, Billiar, & Dumas, 1997). However, the fast-tapping task provides a simple measure of motor competence, and the results indicated that the patients continued to exhibit subtle motor impairments. When comparing performance with the contralesional hand, the mean inter-tap interval (MI)

[2] Given the small number of participants, we conducted a single-factor ANOVA focusing on the effect of probe order condition for each group separately. Overall mean reaction time was similar regardless of probe order condition in the control group and in the patient group. However, probe order did influence the learning probes. For the control group, the learning score for the spatial probe was largest when this probe was administered last ($M = .133$, $SE = .024$) compared to when it was administered first ($M = .042$, $SE = .028$) or second ($M = .018$, $SE = .014$). Note that the amount of practice with the training sequence increases over the course of the experiment. However, the magnitude of learning as measured by the temporal or phase-shift probe did not vary with order. There were a couple of order effects for the patients. As with the controls, greater learning was found for late probes compared to early probes, although the significant effects were not consistent. The timing probe was largest when this probe was tested second compared to when it was tested first. The phase-shift probe was largest when it was tested third compared to when it was tested second. All other order effects were not significant.

for the patient group ($M = 240$, $SE = 49$) was greater than for the control group ($M = 171$, $SE = 6$), Mann–Whitney $U = 3.0$, $p < .05$. Also, the mean standard deviation of the inter-tap intervals (SDIs) was greater on average for the patients ($M = 50$, $SE = 7$) than for the controls ($M = 27$, $SE = 6$), $t(9) = 1.89$, $p < .05$. Similar results were found for the ipsilesional hand; MIs were greater for the patient group ($M = 203$, $SE = 15$) than for the control group, $t(9) = 2.36$, $p < .05$, although the SDIs ($M = 24$, $SE = 8$ for the patients) were similar for the two groups, $t(9) = .31$, $p > .7$. These results indicate key-pressing movements were more difficult to produce for the patient group than for the control group. Further evidence of a motor impairment is given by the higher proportion of prolonged responses for the patients (see above).

To evaluate the relationship between the degree of motor impairment and sequence learning, we computed the correlation between performance with the contralesional hand on the fast-tapping task and performance on the serial reaction time task. This correlation should be negative if learning is related to the degree of motor impairment. Contrary to this prediction, the correlations were positive: learning was greatest in the patients who tapped the slowest. A similar pattern of results was found with respect to the ipsilesional hand.

4. Discussion

Skilled coordination of complex actions relies on the ability to integrate sequenced action components with information about the temporal relationships among these components. Although healthy individuals are capable of such integrative learning, Parkinson's patients have been found to be impaired in integrating a response sequence and a sequence of time intervals (Shin & Ivry, 2003), suggesting a role for the basal ganglia in sequence integration. The central question underlying the current research is whether a similar deficit is observed in patients with focal basal ganglia lesions. In addition to comparing the patients with matched control participants, we also made a within-subject analysis, comparing learning when the sequencing task was performed with the contralesional, affected hand to that observed when the task was performed with the ipsilesional, unaffected hand.

Sequence learning was measured using a serial reaction time task in which a spatial and a temporal sequence were presented simultaneously and in which the two sequences were correlated. The main results were that both the control participants and the patients produced similar patterns of learning. Both groups learned the spatial and temporal sequences as well as the invariant cross-dimensional relationship between the sequences. This was true regardless of whether the patients used their contralesional or ipsilesional hand. Importantly, the facility with which finger movements could be produced, indexed by performance in the fast-tapping task, did not appear to influence sequence learning performance.

The absence of a learning deficit in our group of patients with focal basal ganglia lesions is surprising given previous empirical and theoretical work concerning the role of this structure in skill acquisition (see Willingham, 1998). Much of that work has involved patients with degenerative basal ganglia disorders, namely Parkinson's disease and Huntington's disease. These patients tend to show reduced learning on the serial reaction time task, although the nature and extent of the deficit has varied across studies (Ferraro et al., 1993; Girotti et al., 1986; Jackson et al., 1993; Knopman & Nissen, 1991; Pascual-Leone et al., 1993; Willingham & Koroshetz, 1993; Willingham, Koroshetz, Treadwell, & Bennett, 1995). Using the multidimensional variant of the task reported here, we (Shin & Ivry, 2003) have also found that Parkinson patients show reduced spatial and integrative sequence learning compared to control participants. Procedural learning deficits are not restricted to the serial reaction time task. Learning impairments during visuomotor tracking tasks have also been reported in Parkinson and Huntington patients (Gabrieli, 1995; Harrington, Haaland, Yeo, & Marder, 1991; Heindel, Butters, & Salmon, 1988, Heindel, Salmon, Shults, Walicke, & Butters, 1989).

There are a number of reasons why we observe normal learning in our group of patients with focal lesions given the prevalence of procedural learning problems associated with degenerative basal ganglia lesions. The extent of basal ganglia damage may be much more limited in our focal patient population. Not only are the focal lesions restricted to one side of the basal ganglia, they encompass only part of the striatum and/or globus pallidus. Degenerative disorders, when symptomatic, are likely to involve pathology across the striatum. At present, our group of patients is not of sufficient size to allow an analysis of subgroups of patients with focal basal ganglia lesions, for example a comparison of lesions of the caudate or putamen.

Related to this issue is the fact that the damage in degenerative disorders is bilateral. It may be that normal procedural learning can be sustained as long as one side of the basal ganglia is intact. Drawing on the literature of cortical strokes, there are many examples in which deficits associated with unilateral lesions are minimal compared to the profound problems associated with bilateral lesions. The contrast between the devastating memory impairments following bilateral medial temporal lobe lesions in patients like HM with the subtle memory impairments seen in patients with unilateral temporal lobectomy is instructive. Similarly, the attentional deficits observed in Balint's patients is much

greater than the "sum" of what is observed in patients with unilateral left or right parietal damage. Cortical inputs to the striatum project bilaterally (Selemon & Goldman-Rakic, 1985) and a significant percentage of the ascending output fibers from the globus pallidus cross over to the other hemisphere (Hazrati & Parent, 1991). These pathways may allow the intact half of the basal ganglia to be recruited by both hemispheres.

A third potential source of the discrepancy may lie in the extent of cortical damage—particularly the frontal areas. These areas are likely to have been compromised significantly in patients with degenerative disorders, but only minimally, if at all, in the focal patients. The involvement of the frontostriatal circuit in working memory (Brown & Marsden, 1991; Gabrieli, 1995; Goldman-Rakic, 1995; Lustig, Matell, & Meck, 2004; Menon, Anagnoson, Glover, & Pfefferbaum, 2000) and set-switching functions (Hayes, Davidson, Keele, & Rafal, 1998; Meck & Benson, 2002; Owen et al., 1993) may be crucial for forming associations among elements in a complex sequence (Cohen, Ivry, & Keele, 1990) as well as between multiple sequences. Alternatively, sequence integration processes themselves might take place in both cortical and subcortical areas, in that sequence integration may rely on frontostriatal functioning that specifies movement context related to action outcomes (Matell & Meck, 2004; Schultz, Tremblay, & Hollerman, 2000).

While such functional hypotheses will require further investigation, the current results do suggest that we be cautious in inferring basal ganglia function solely on the basis of deficits observed in patients suffering from degenerative disorders such as Parkinson's disease. Studies involving patient with focal lesions offer a relatively untapped resource for the analysis of basal ganglia function.

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