Spatial and Temporal Sequence Learning in Patients with Parkinson's Disease or Cerebellar Lesions

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Abstract

■ The functional role of different subcortical areas in sequence learning is not clear. In the current study, Parkinson's patients, patients with cerebellar damage, and age-matched control participants performed a serial reaction time task in which a spatial sequence and a temporal sequence were presented simultaneously. The responses were based on the spatial sequence, and the temporal sequence was incidental to the task. The two sequences were of the same length, and the phase relationship between them was held constant throughout training. Sequence learning was assessed comparing performance when both sequences were present versus when the dimension of interest was randomized. In addition, sequence integration was assessed by introducing phase-shift blocks. A functional dissociation was found between the two patient groups. Whereas the Parkinson's patients learned the spatial and temporal sequences individually, they did not learn the relationship between the two sequences, suggesting the basal ganglia play a functional role in sequence integration. In contrast, the cerebellar patients did not show any evidence of sequence learning at all, suggesting the cerebellum might play a general role in forming sequential associations. ■

INTRODUCTION

Fluent performance of many sequential activities requires carrying out component actions in the appropriate order and in the appropriate temporal relation to one another. To throw a baseball, the gestures about the shoulder, elbow, wrist, and fingers must follow a specific sequence. For the ball to reach a target with pinpoint accuracy, the timing of the ball's release must be precisely coordinated with the position and orientation of the arm (Hore, Watts, & Tweed, 1994). In this article, we examine the performance of patients with either Parkinson's disease or cerebellar lesions on a sequence learning task that involves the coordination of spatial and temporal information.

Previous research has revealed that the production of sequential actions is associated with many cortical and subcortical areas. Lesions in the frontal and the parietal cortices, 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, has been associated with sequence decomposition (Benecke, Rothwell, Dick, & Marsden, 1986; Holmes, 1939).

One method that has been used to study the role of various brain areas in sequence learning is the serial reaction time (SRT) task (Nissen & Bullemer, 1987). In this task, a series of stimuli, usually visual, are presented one at a time, and the task is to make a speeded choice response. The responses might be based on the location of the stimuli or some other property such as their color or shape. In separate blocks of trials, the stimuli are either presented randomly, or follow a fixed sequence. Reaction times decrease with practice. More important, sequence learning can be assessed by comparing reaction times on sequence blocks relative to random blocks; sequence learning is reflected in the shorter reaction times on sequence blocks compared with random blocks.

The SRT task has been used in neurophysiological and neuropsychological studies to investigate the neurobiology of sequence learning. PET studies suggest a distributed network of areas associated with sequence learning. As learning progresses, increases in activation have been observed in numerous cortical areas such as the primary motor cortex, the supplementary motor area, the premotor cortex, the prefrontal cortex, and the inferior parietal cortex (Grafton, Hazeltine, & Ivry, 1995; Karni et al., 1995; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994). With respect to subcortical areas, increased activation has been consistently observed in the striatum (Grafton et al., 1995; Seitz, Roland, & Bohm, 1990). Learning-related changes in cerebellar activation have generally not been observed in the PET studies with the SRT task (see also Seidler et al., 2002), although

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imaging studies with other types of sequencing tasks have pointed to a role for the cerebellum in sequence learning (Seidler et al., 2002).

Patient studies using the SRT task have shown mixed results with respect to the role of the basal ganglia in sequence learning. Studies focusing on patients with Huntington's disease (Willingham & Koroshetz, 1993) and Parkinson's disease show reduced learning relative to controls. However, the magnitude of the deficit varies across studies (Ferraro, Balota, & Connor, 1993; Jackson, Jackson, Harrison, Henderson, & Kennard, 1993; Pascual-Leone et al., 1993). The Parkinson deficit is not restricted to spatial sequences; it has also been observed when the sequence is formed by a series of numeric characters (Helmuth, Mayr, & Daum, 2000). In contrast, the research on cerebellar lesions generally show severe learning deficits in the SRT task, in which very little if any learning is found (Gomez-Belderrain, Garcia-Monco, Rubio, & Pascual-Leone, 1998; Molinari et al., 1997; Pascual-Leone et al., 1993; Doyon et al., 1997, 1998).

The SRT task has frequently been combined with a secondary task such as monitoring the pitch of tones that are presented between the visual events (Cohen, Ivry, & Keele, 1990; Nissen & Bullemer, 1987). This secondary task is included to increase the attentional load and as such, prevent participants from developing awareness of the sequence. However, the effects of the secondary task may not be best considered in terms of attentional distraction; rather the stimuli for this task may directly influence associative mechanisms. This point was made clear in an elegant study (Schmidtke & Heuer, 1997) in which the subjects responded to two interleaved sequences. One sequence was formed by visual events, with manual responses based on the spatial position of the visual signals. The second sequence was formed by the tones. For these stimuli, participants made a foot response to tones in a target pitch. Critically, Schmidtke and Heuer manipulated the relationship between the visual and auditory sequences. 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 another condition, the two sequences were of equal length (e.g., both length 6). Thus, in combination they formed a meta-sequence that was 12-elements long in which visual events predicted auditory events and vice-versa.

Learning was assessed by randomizing the events on one dimension or the other. In addition, the integration of the two sequences was assessed through a phase-shift manipulation: The stimulus order within each dimension was maintained, but the interdimensional sequence was altered. While intradimensional learning of the visual and auditory sequences was observed in both the uncorrelated and correlated conditions, the degree of learning was greater in the correlated condition. Most importantly, interdimensional integration was observed in the correlated condition as indicated by an increase in mean reaction time following the phase shift. These results suggest that learning mechanisms can operate on both sources of information, forming integrated representations when such associations improve predictability.

Sequence integration can also benefit performance when the secondary sequence is temporal and does not require an overt response. Shin and Ivry (2002) used a standard SRT task in which responses were based on the position of visual stimuli. On sequence blocks, the locations formed an eight-element sequence. The interval between each response and the stimulus for the next trial (the response-to-stimulus interval, or RSI) was set to either 200, 500, or 800 msec. In one condition, the RSIs were presented in a sequence of the same length as the spatial sequence (eight elements), and the phase relationship was maintained across training blocks. In a second condition, the RSI sequence was seven elements long; thus, the two sequences were not correlated. Similar to the results of Schmidtke and Heuer (1997), a phase-shift cost was observed in the correlated condition, indicating that the participants had formed an integrated representation of the spatial and temporal information. Further support for this interpretation comes from the finding that the cost observed with randomizing the spatial events was greater for participants in the correlated condition. Finally, temporal sequence learning (measured as a cost in responding to the visual events when the temporal sequence was randomized) was limited to the correlated condition.

The benefit of sequence integration could be attributed to two possible sources. First, the consistent timing between the responses and subsequent stimuli could allow anticipatory scheduling for orienting and response planning processes. The fact that an uncorrelated temporal sequence did not facilitate learning suggests that such anticipatory processes would be linked to specific events rather than associated with generic expectations (e.g., expect a particular stimulus rather than any stimulus). Second, redundant information from a secondary source, temporal or auditory, might prime information about the response-relevant sequence, and thus facilitate sequence learning. This hypothesis is not tied to temporal processing per se, but rather emphasizes that sequence learning can involve the integration of information from multiple sources.

Regardless of whether sequence integration allows anticipatory scheduling or facilitates the formation of associations in a sequence, sequence integration appears to benefit sequence learning performance. The goal of the current experiment was to explore the role of the basal ganglia and the cerebellum in sequence integration. Parkinson's patients, cerebellar patients, and age-matched control participants performed a variant of the SRT task identical to the task used by Shin and Ivry (2002), in which a spatial sequence and a temporal sequence were presented simultaneously. Specifically,

the spatial location of a visual stimulus *X* varied from trial to trial among four locations and formed a repeating eight-element sequence. The key-pressing response was based on this spatial dimension. The RSI also varied from trial to trial (200, 500, or 800 msec) and formed an eight-element sequence. The two sequences were correlated; they were of the same length and presented in a consistent phase relationship across repetitions throughout the experiment. Learning of the individual sequences was measured by observing the cost incurred when we randomized the sequence dimension of interest. We also measured how well participants learned the relationship between the two sequences by including phase-shifted blocks. It is worth noting that learning of spatial versus temporal sequences could not be directly compared given the two dimensions differed in many ways, including the fact that they involved different numbers of alternatives. The main questions were whether Parkinson's patients and cerebellar patients would learn the spatial and temporal sequences and whether they would integrate the two sequences.

In addition, we evaluated whether sequence learning for the patient groups was related to the ability to produce fast key-pressing responses using the *fast-tapping* task, described in the Methods section.

RESULTS

Data Analysis

A key was depressed at the time of the appearance of the visual stimulus *X* on 7.2% of the trials. Almost all of these (87%) were for stimuli following a short RSI (19 % of trials in this condition), indicating that the preceding response had not been completed prior to the onset of the subsequent stimulus. These trials were excluded from the analysis of both the latency and accuracy data. The proportion of these trials did not differ significantly between groups, $F(2,25) = 2.06$, $MSE = .0085$, $p > .1$.

Performance in the SRT task was measured by calculating the median reaction time for each block using only the reaction times from correct trials over the last 55 trials per block. Sequence learning was measured by examining performance in *sequence learning probes*, each consisting of four blocks. In the middle two blocks, the sequenced presentation of at least one dimension was altered. In the surrounding two blocks, the sequenced presentation of both dimensions was maintained. Learning was evaluated by comparing performance for the middle two blocks of the probe with performance for the surrounding two blocks. Specifically, if learning occurred, performance would be worse in the altered blocks than in the blocks in which the sequenced presentation was maintained.

The *phase-shift* probe measured the extent to which the sequence of stimulus locations and the RSI sequence were integrated into a common sequence representation. In this probe, the spatial and timing sequences were maintained in all four blocks. However, a phase shift was introduced in the two middle blocks. To accomplish this, in these middle blocks, the RSI sequence was shifted forward by one position relative to the surrounding blocks. Thus, whereas the location/RSI pairs had been 1A–4C–2B–1C–3A–2B–4C–3B (where numbers denote stimulus locations, and letters denote RSIs) in the surrounding blocks, during the (middle) phase-shift blocks the pairs were 1C–4B–2C–1A–3B–2C–4B–3A. The difference in performance between the phase-shifted and surrounding blocks reflected learning of the relationship between the spatial and timing sequences.

The *spatial* probe measured learning of the spatial location sequence in the presence of the RSI sequence. In this probe, the spatial locations were randomized in the two middle blocks, whereas the spatial sequence was maintained in the surrounding two blocks. The RSIs in all four blocks in this probe were sequenced. Thus, the surrounding blocks preserved the spatial sequence, the timing sequence, and the relationship between the two sequences, whereas the middle blocks only preserved the timing sequence. Thus, the difference in performance between the middle and surrounding blocks of this probe could be affected by the extent to which the spatial sequence and the relationship between the spatial and temporal sequences were learned. In addition, these two types of implicit learning could interact with each other in the way they affected performance.

Similarly, the *timing* probe measured learning of the RSI sequence in the presence of the sequence of stimulus locations. The RSIs were randomized in the middle two blocks of this probe, and the RSIs remained sequenced in the surrounding two blocks. The spatial location of the stimulus remained sequenced in all four blocks of this learning probe. The surrounding blocks preserved the spatial, timing, and relational information, whereas the middle blocks only preserved the spatial sequence. Thus, the difference in performance between the middle and surrounding blocks could reflect temporal and relational learning as well as the interaction between the two.

We also examined learning of the spatial and timing sequences when the other dimension was random. The *spatial-RSI random* probe was identical to the spatial probe, except that the RSIs were randomized throughout all four probe blocks. This probe could only reflect learning of the spatial sequence. Similarly, the *timing–location random* probe was identical to the timing probe, except that the stimulus locations were random in all blocks of the timing–location random probe. The timing–location random probe could only reflect learning of the timing sequence. Table 1 summarizes the potential effects of different sequence learning components on performance.

Table 1. Potential Effects of Sequence Learning on Sequence Learning Probes

Probe	*Potential Learning Effects*
Phase-shift	Relational
Spatial	Spatial Relational Spatial–relational interaction
Timing	Temporal Relational Temporal–relational interaction
Spatial-RSI random	Spatial
Timing–location random	Temporal

We used two methods to estimate spatial, temporal, and integrative learning. First, following previous studies of dual-sequence learning (Shin & Ivry, 2002; Schmidtke & Heuer, 1997), we focused on the spatial, timing, and phase-shift probes as basic indicators of learning. For each, a learning score was computed by subtracting the mean of the median reaction times of the outer sequenced blocks from the mean of the median reaction times of the altered blocks in the middle of the probe. A learning score was also calculated based on response accuracy, defined as the mean proportion correct in the outer sequence blocks minus the mean proportion correct of the (middle) altered blocks. For both latency and accuracy, a positive learning score indicated learning had occurred. To assess learning, we conducted one-tailed t tests on the learning scores for these probes, testing whether the observed learning scores were significantly greater than zero.

Second, we carried out a componential analysis of sequence learning using a model-based analysis to determine the contribution of different forms of learning on performance utilizing all five probes. The details of this analysis are described below.

Learning Probes

Reaction Time

The block medians of the reaction times were averaged over participants in each group. These means are plotted for each block in Figure 1. Excluding the first two blocks where both spatial locations and timing were randomized, the mean of the median block reaction times over all 25 blocks was 464 msec (SE = 24) for the control subjects, 541 msec (SE = 53) for the Parkinson's patients, and 665 msec (SE = 45) for the cerebellar patients. An ANOVA testing the effect of participant group on reaction time revealed that the main effect of group was significant, $F(2,25) = 5.45$, $MSE = 17668$, $p < .05$. This effect of group reflected the fact that the cerebellar patients were slower than the control participants, $t(16) = 4.19$, $p < .001$. The mean reaction time for the Parkinson's patients did not differ significantly from either of the other groups, ps $> .1$.

The mean learning scores for the spatial, timing, and phase-shift probes are plotted separately for each of the three groups in Figure 2. Individual scores are shown in Figure 3. For the control group, spatial learning was significant as measured by the spatial probe, $M = 44$, $SE = 9$, $t(9) = 4.92$, $p < .001$. Temporal learning was also significant, as indicated by the timing probe, $M = 26$, $SE = 7$, $t(9) = 3.50$, $p < .01$. As found in previous research with young participants (Shin & Ivry, 2002), the control participants successfully integrated the spatial and temporal sequences, as indicated by a statistically reliable learning score for the phase-shift probe, $M = 17$, $SE = 5$, $t(9) = 3.26$, $p < .01$.

Next, we examined the learning probes for the Parkinson's patients and compared them with learning in the control group. The spatial probe was significant, $M = 15$, $SE = 7$, $t(9) = 2.30$, $p < .05$. Consistent with previous research, learning was smaller in this group relative to the control participants, $t(18) = 2.54$, $p < .05$.

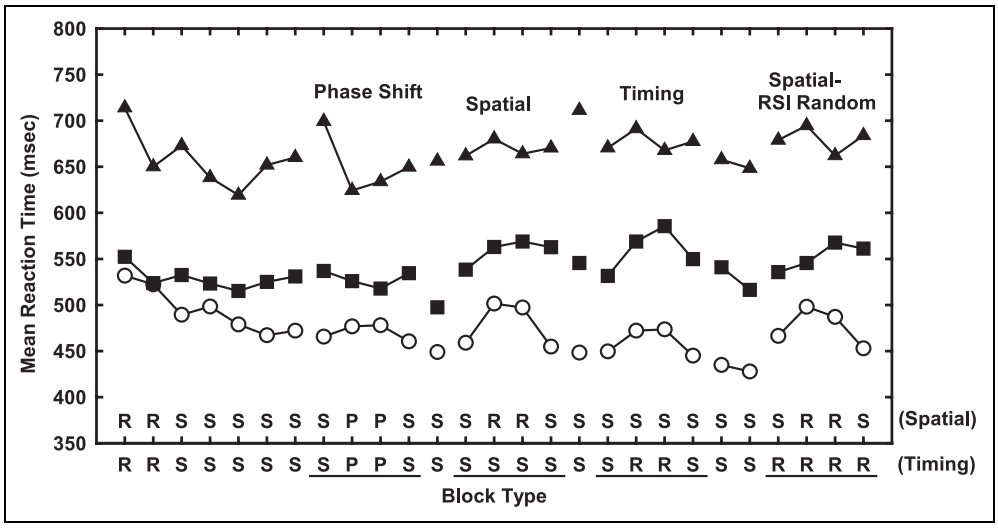

Figure 1. Mean of median reaction times in each block for each participant group. The circles represent the healthy control group; the squares represent the Parkinson's group; and the triangles represent the cerebellar group. The data are presented by probe type, although the actual order of blocks in the experiment was counterbalanced for the spatial and the spatial-RSI random probes. There are three types of blocks for both the spatial and temporal dimensions: S = sequenced; R = random; P = phase shift; RSI = response-to-stimulus interval.

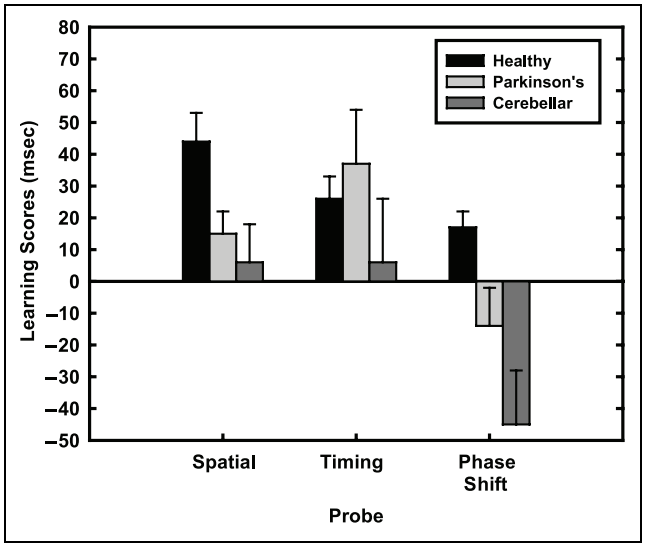

Figure 2. The learning scores for each probe for the healthy control, Parkinson's, and cerebellar groups.

Despite these divergences from the control group, the Parkinson's patients exhibited significant temporal sequence learning, $M = 37$, $SE = 17$, $t(9) = 2.14$, $p < .05$, and the magnitude of this form of learning was no different than that observed with the controls, $t(18) = .58$, $p > .2$. Importantly, the Parkinson's disease patients did not appear to have integrated the spatial and temporal sequences; the learning score computed from the phase-shift probe was a nonsignificant negative value, $M = -14$, $SE = 12$, $t(9) = -1.17$, $p > .2$.

In contrast to the results for the control and Parkinson's groups, the cerebellar patients did not show any evidence of reliable sequence learning. Spatial learning was not significant as measured by the spatial probe, $M = 6$, $SE = 12$, $t(7) = .29$, $p > .3$. Temporal learning was also unreliable, as indicated by the timing probe, $M = 6$, $SE = 20$, $t(7) = .47$, $p > .3$. As would be expected given the lack of learning on the single dimension probes, the cerebellar group also failed to exhibit any evidence of sequence integration. The learning probe for the phase-shift probe was negative, $M = -45$, $SE = 17$, $t(7) = -2.05$, $p < .05$, indicating faster reaction times on the phase-shifted blocks compared to the blocks in which the consistent relationship between the spatial and temporal sequences was maintained. Inspection of Figure 3 suggests this can be attributed largely to an outlier (−163 msec), which was approximately 3 standard deviations away from the other participants' phase-shift scores. Excluding this outlier, the magnitude of the negative phase-shift score was reduced to −29 msec ($SE = 16$), and this value was not significantly different from zero, $t(6) = -1.71$, $p > .1$. Exclusion of this patient's data did not change the other results significantly; all of the learning scores remained insignificant, $M = 21$, $SE = 15$, $t(6) = 1.28$, $p > .1$ for the spatial probe and $M = 14$ msec, $SE = 10$, $t(6) = 1.33$, $p > .1$ for the timing probe.

We also examined the effect of RSI on learning. Was the improvement in reaction time on sequenced blocks consistent across the three RSIs or did it increase with RSI? To answer this question, we compared the learning scores for each RSI condition. We excluded data from one Parkinson's patient in this analysis because this subject lacked trials with a 200-msec RSI in Blocks 11 and 17—blocks that were used for calculation of the phase-shift probe and the timing probe, respectively. Figure 4 shows the learning score of the spatial probe separately for each of the RSIs for each participant group. We compared the learning score for each RSI with a one-way ANOVA. The control group showed a significant effect, $F(2,18) = 4.16$, $p < .05$, reflecting the fact that spatial sequence learning was unreliable in the middle RSI condition (500 msec RSI), $t(9) = -.32$,

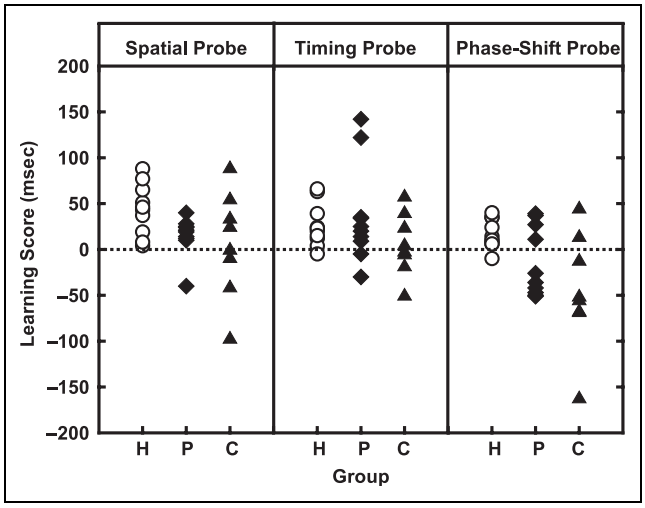

Figure 3. The learning scores for each probe for each participant in the healthy control (H), Parkinson's (P), and cerebellar (C) groups.

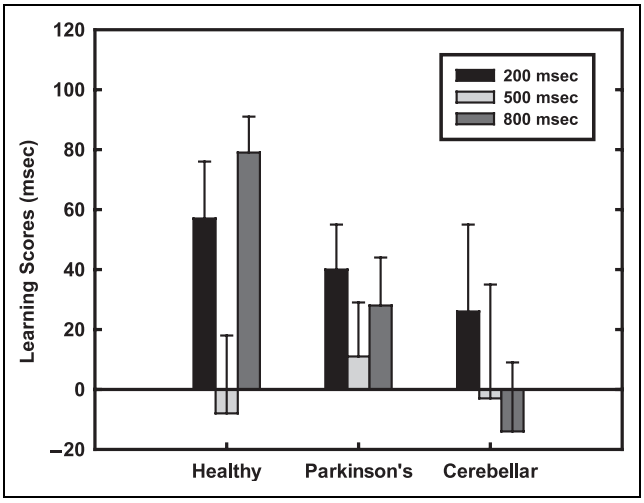

Figure 4. The learning scores for the spatial probe as a function of the RSI for the healthy control, Parkinson's, and cerebellar groups.

$p > .7$, whereas spatial learning was significant in the other RSI conditions, ts > 3, ps $< .05$. However, no reliable effects of RSI were found for either of the patient groups, Fs < 1, ps $> .5$. The same type of analysis was conducted for the timing and phase-shift probes. No effect of RSI was found in these analyses. In sum, there does not appear to be a systematic relationship between learning and RSI.

The order of the spatial and spatial-RSI random probes was counterbalanced across participants. As revealed by two-tailed t tests, none of the probes were affected by probe order for the control (ps $> .2$), Parkinson's (ps $> .1$ for the spatial and phase-shift probes and $p > .09$ for the timing probe), or cerebellar groups (ps $> .2$).

Proportion Correct

For each participant, we computed the proportion correct for Blocks 3–27. The mean proportion correct was 0.95 ($SE = 0.016$) for the control group, 0.89 ($SE = 0.022$) for the Parkinson's group, and 0.90 ($SE = .027$) for the cerebellar group. ANOVAs testing the effect of group did not reveal any significant effects on mean proportion correct, $F(2,25) = 2.56$, $p > .09$, nor on the learning score for the spatial, timing, and phase-shift probes, Fs < 1.3, ps $> .2$, which were not reliably greater than zero, ts < 2, ps $> .1$. One exception was that for the cerebellar group, the phase-shift probe yielded a negative learning score, $M = -0.023$, $SE = .007$, $t(7) = -3.17$, $p < .05$. This negative trend remained when we excluded the outlier identified in the analysis of reaction time, $M = -0.02$, $t(6) = -2.71$, $p < .08$. In the absence of a priori hypotheses about this result, we suspect that this effect was due to chance variation in performance.

Model-Based Regression Analysis

The spatial and timing probes reflect a mixture of learning influences on performance (see Table 1). In previous research (Shin & Ivry, 2002), a model-based regression analysis showed that for healthy college-aged participants, learning of the spatial sequence, temporal sequence, and the relationship between the two sequences had independent effects on the learning probes, allowing for an additive logic for interpreting the probe scores. Here, similar computations were carried out to determine whether the same type of additive logic could be applied to the data from the current study. Specifically, we estimated the learning components from all five sequence learning probes using a series of linear equations:

$$
\begin{aligned}
Y_{1j} &= \beta_3 + e_{1j},\\
Y_{2j} &= \beta_1 + \beta_3 + \beta_{13} + e_{2j},\\
Y_{3j} &= \beta_2 + \beta_3 + \beta_{23} + e_{3j},\\
Y_{4j} &= \beta_1 + e_{4j}, \text{and}\\
Y_{5j} &= \beta_2 + e_{5j}.
\end{aligned}
$$

Here, Y_{ij} ($i = 1, 2, \ldots, 5$) represents the learning probes for the jth participant, where Y_{1j} represents the learning score from the phase-shift probe, Y_{2j} represents the learning score from the spatial probe, Y_{3j} represents the learning score from the timing probe, Y_{4j} represents the learning score from the spatial-RSI random probe, and Y_{5j} represents the learning score from the timing–location random probe. β values represent the effects of the hypothesized effects of sequence learning components on the learning scores. β_1 is the effect of spatial sequence learning, β_2 is the effect of temporal sequence learning, β_3 is the effect of the relational learning, β_{13} is the interactive effect between the spatial and relational information, and β_{23} is the interactive effect between the temporal and relational information. Finally, the ε values represent random error.

We computed the least-squares estimators of the β values using formulas based on the general linear model, detailed in Shin and Ivry (2002). The results of this analysis are shown in Table 2. For the control participants, the estimators of the interaction between relational learning and spatial and temporal learning, b_{13} and b_{23}, were not reliably greater than zero, $p > .3$ for

Table 2. Mean and Standard Error (in msec) of Effect Sizes for Different Sources of Sequential Representation for each Participant Group

	b_1(S)		b_2(T)		b_3(R)		b_{13}(S–R)		b_{23}(T–R)	
Group	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Control	30	8	−4	6	17	5	−3	8	13	12
Parkinson	8	7	−9	15	−14	12	21	9	60	23
Cerebellar	−3	18	6	24	−46	22	55	18	45	31

S = spatial; T = temporal; R = relational.

b_{13} and $p > .1$ for b_{23}. Thus, the influence of the spatial, temporal, and relational components on the learning scores was independent allowing us to use additive logic in decomposing the learning probes. b_1, the estimator of the spatial component, and b_3, the estimator of the relational component, were significantly greater than zero, ts > 3, ps $< .01$, suggesting the learning score for the spatial probe reflected additive effects of spatial and relational learning. However, b_2, the estimator of the temporal component, was not significant, $t(9) = -.64, p > .2$, suggesting the learning score for the timing probe only reflected relational learning. The pattern of results for the control group mirrors those for the young participants in Shin and Ivry.

In contrast, for the Parkinson's patients, the estimators of the interactive effects, b_{13} and b_{23}, were greater than zero, ts > 2, ps $< .05$. Similar results were found for the cerebellar patients, $t(9) = 2.98, p < .05$ for b_{13} and $t(9) = 1.45, p < .09$ for b_{23}. For the latter group, these results did not substantially change by excluding the outlier mentioned in the analysis of learning probes in reaction time, $M = 62$, $SE = 19$, $t(6) = 3.20$, $p < .01$ for b_{13} and $M = 38$, $SE = 35$, $t(6) = 1.11$, $p > .1$ for b_{23}. For both Parkinson's and cerebellar patients, the presence of interactive effects among learning components precludes a simple decomposition of the learning probes into spatial, temporal, and relational learning components.

None of the estimators varied as a function of probe order for the control (ps $> .2$), Parkinson's ($p > .08$ for b_{13} and ps $> .1$ for the other estimators), or cerebellar groups (ps $> .2$).

Individual Differences

The above results showed slower reaction times for the cerebellar patient group compared with the control group, presumably reflecting their difficulties in producing movements with the ipsilesional, impaired hand. Although the difference was not statistically significant, the Parkinson's group was also slower on average by 77 msec than the control participants. In this section, we evaluate the relationship between response speed and the amount of sequence learning in the patient groups. We focus on two measures of response speed, mean reaction time on random blocks and performance on the fast-tapping task.

Mean Reaction Time on Random Blocks

We conducted a correlational analysis between each probe and the mean reaction time of Blocks 1 and 2, in which both stimulus locations and RSIs were random.[1] Negative correlations would indicate that learning was greater for participants who responded the fastest. We restricted this analysis to the patients because our interest was in determining whether learning impairments could be related to a measure of movement competence. Sequence learning was significantly correlated with mean reaction time for the spatial ($r = -.49$) and phase-shift probes ($r = -.58$), ps $< .05$. However, the learning scores were not significantly correlated with mean reaction time for the timing probe ($r = -.10$), $p > .6$. In all cases, we observed a consistent trend for negative correlations. Although the number of data points in this correlational analysis is relatively small, the negative trends suggest that higher learning scores were related to faster responses, consistent with the idea that differences in motor abilities led to reduced learning scores in the patient groups. Alternatively, the reaction times in the random blocks could have reflected the ability to learn general aspects of the SRT task, which could have correlated with sequence-specific learning.

Performance on the Fast-Tapping Task

If sequence learning was affected by the general ability of patients to produce fast key-pressing responses, the learning scores for each probe and the mean intertap interval in the fast-tapping task should be negatively correlated. Contrary to this prediction, the correlations were not significant in all three cases and were nearly zero or positive regardless of whether tested before or after the SRT task (spatial probe, rs $= -.08$ both *before* and *after,* ps $> .7$; timing probe, $r = .31$ *before* and $r = .40$ *after,* ps $> .1$; and phase-shift probe, $r = -.08$ *before* and $r = -.10$ *after,* ps $> .6$). These results argue against the interpretation that slow finger movements led to difficulties in sequence learning. Perhaps, the results concerning mean reaction time on random blocks above reflected a correlation between general learning and sequence-specific learning abilities in the patients.

We also explored the possibility that difficulty in temporal control affected sequence learning. If so, the standard deviation of the intertap intervals should be negatively correlated with sequence learning. Contrary to this expectation, the correlation between the standard deviation of the intertap intervals and the learning score was not reliable for the spatial probe, $r = .20$ *before* and $r = .15$ *after*, ps $> .4$; and the phase-shift probe, $r = -.18$ *before* and $r = -.05$ *after*, ps $> .4$. For the timing probe, the correlation was significant and in the opposite of the predicted direction, $r = .78$ *before* and $r = .72$ *after*, ps $< .001$. That is, learning was greatest for those participants showing higher variability on the tapping task.

DISCUSSION

The goal of our study was to investigate the functional role of the basal ganglia and the cerebellum in sequence learning. We tested Parkinson's patients, cerebellar

patients, and healthy age-matched control participants in a version of the SRT task in which a spatial and a temporal sequence were presented in a correlated manner. Similar to results obtained with college-age participants (Shin & Ivry, 2002), healthy elderly participants in the current study showed learning of both the response-relevant spatial dimension and the incidental temporal dimension. Moreover, they integrated these dimensions into a common sequence representation, as shown by the learning scores in the phase-shift probe. Our main finding was that the two groups of patients evidenced different types of sequence learning deficits. The Parkinson's patients showed both learning of the response-relevant spatial sequence and the incidental temporal sequence although the magnitude of spatial learning was smaller than that found for the controls. However, the Parkinson's patients did not show any evidence of sequence integration. The cerebellar patients, on the other hand, failed to show evidence of learning either sequence.

Previous research on sequence learning in Parkinson's patients has yielded mixed results. Some studies have reported severe sequence learning problems with the SRT task (Jackson et al., 1993), whereas others only reported minor deficits (Pascual-Leone et al., 1993). Our results add to this literature, again indicating that sequence learning is attenuated in Parkinson's patients. Our results are at odds with the claims of Helmuth et al. (2000). This study also involved two sequences, one that was response relevant (i.e., responses based on the identity of numerals) and one that was incidental (i.e., the spatial position of the numerals). Helmuth et al. reported that the Parkinson's patients failed to learn the response-relevant sequence. Our results show that the patients could learn both the response-relevant and incidental sequences, but that learning was weaker than for the controls on the response-relevant dimension. One explanation for the discrepancy between the two studies is that responding to numerals presented in the Helmuth et al. study required learning the arbitrary mapping between numerals and response keys. Such arbitrary mappings may be especially difficult for people with Parkinson's disease.

Importantly, the current study allowed us to evaluate whether sequence learning deficits on the SRT task are due to slow access of learned representations or should be attributed to problems in learning per se. Studies revealing severe sequence learning deficits in Parkinson's patients employed shorter RSIs (200 msec in Jackson et al., 1993) than those revealing minor sequence learning deficits (500 msec in Pascual-Leone et al., 1993). Similarly, given that the cerebellar patients were considerably slower than the controls overall, it is possible that the lack of learning in this group was due to the high motor demands associated with making rapid successive responses (see Ravizza & Ivry, 2001). If either patient group could learn the spatial sequence normally but were slow to prime the sequence representations, one would expect learning scores to increase with RSI for that group. However, our data do not show that pattern for any of the groups in this study; sequence learning did not vary consistently with RSI. We also ruled out the hypothesis that the sequence learning deficits in the patient groups were a function of slow motor responding. Sequence learning scores were not correlated with measures of response speed and timing taken from the fast-tapping task.

The results concerning the Parkinson's patients reveal an interesting dissociation. Although the degree of learning was reduced compared to the controls, the patients were able to learn both the spatial and temporal sequences. However, the patients' performance did not reveal any evidence of sequence integration. This pattern is consistent with the hypothesis that intradimensional associations can be supported by dimension-specific mechanisms, but that interdimensional associations engage additional mechanisms that have access to multiple sources of information. The idea that the basal ganglia might perform an integrative function is congruent with anatomical observations. The basal ganglia receive input from various sensory, motor, and association cortical areas as well as output information to prefrontal motor areas (reviewed in Middleton & Strick, 2000).

Because our study only focused on integration of spatial and temporal information, it does not allow us to generalize to processing of nontemporal information. Indeed, Parkinson's patients appear to have deficits in time perception and production (Harrington, Haaland, & Hermanowicz, 1998; O'Boyle, Freeman, & Cody, 1996). However, our results showing a normal learning score for the timing probe suggests such deficits did not prevent Parkinson's patients from acquiring time intervals of the range used here. One possibility is that temporal integration is a prerequisite for anticipatory scheduling of actions, and that the basal ganglia are important for such co-ordinative functions (Brotchie, Iansek, & Horne, 1991). The role of the basal ganglia in dynamic action control is an important topic for future research.

Turning to the results concerning the cerebellar patients, our results are consistent with those of previous studies showing a striking lack of sequence learning in these patients. The severe learning deficits associated with cerebellar lesions are puzzling given the fact that many imaging studies have reported a lack of learning-related changes within the cerebellum (see Seidler et al., 2002). It is possible that intact learning is obscured by the patients' performance problems. However, two aspects of the current study argue against a performance problem. First, the learning impairment was statistically equivalent across the range of RSIs used in the current study. Performance problems would be expected to be most pronounced when the interval between successive events is shortest. Second, the cerebellar patients not only failed to learn the response-relevant spatial sequence, but

also showed no evidence of having learned the incidental temporal sequence, even though these associations did not directly relate to performance.

It is possible that cerebellar damage can induce a general deficit in sensorimotor learning, perhaps reflecting a role for this structure in learning and optimizing complex movements (Thach, 1997). While this hypothesis can account for the patients' failure to learn on the response-relevant sequence, it does not account for their impairment on the incidental temporal sequence learning task. However, incidental temporal sequence learning appears to only occur when this sequence is correlated with the response-relevant sequence in healthy participants (Shin & Ivry, 2002). Thus, learning of the spatial sequence may be a prerequisite for learning the temporal sequence.

An alternative explanation is that cerebellar patients have a problem in allocating attentional resources (Akshoomoff, Courchesne, & Townsend, 1997) rather than a problem in sequence learning per se. In our task, cerebellar patients might have allocated attention to making and terminating individual finger movements resulting in fewer resources allocated to forming associations between sequence elements. Assuming attentional resources are required for forming associations between sequence elements with ambiguous transitions (i.e., if a given element x is followed by two different elements, y and z, in different parts of the sequence, Cohen et al., 1990), an attention deficit in cerebellar patients would be expected to lead to a sequence learning deficit. Congruent with this resource allocation hypothesis, cerebellar patients can learn short sequences with no ambiguous transitions (Marks, Wild, Grafman, Higgins, & Massaquoi, 2000). Similarly, Pascual-Leone et al. (1993) reported that, while cerebellar patients could explicitly learn a sequence verbally, they were not able to express this knowledge in the context of an SRT task. Apparently, motor coordination can exacerbate problems related to attentional allocation in these patients (Ravizza & Ivry, 2001).

A third possibility is that timing is critical for forming associations between successive stimuli and that the deficits on the SRT task are related to an impairment in temporal processing in the cerebellar group (see Ivry, 1997). In the SRT task, timing may be crucial for at least two reasons. First, to the extent that sequence learning enables anticipatory responses, anticipation of stimulus onset would facilitate faster responding to sequenced than to random stimuli. Second, timing may be an integral part of forming associations between stimulus events. Various parameters specifying the temporal relationship among stimulus events are an essential part of forming associations in eye-blink conditioning (Weidemann, Georgilas, & Kehoe, 1999; Kehoe & Napier, 1991; Millenson, Kehoe, & Gormezano, 1977). Assuming that the importance of temporal information in forming associations can be extended from the conditioning paradigm to the SRT paradigm, the severe impairment in sequence learning for the cerebellar group should be observed regardless of whether or not patterns were presented in the temporal dimension. That is, their inability to form associations regarding a series of spatial locations or responses might result from noise associated with the representation of the temporal relationships between these successive events.

In sum, our results suggest dissociable contributions of two major subcortical structures to sequence learning. The role of the basal ganglia appears to be especially pronounced when integrating patterned information from multiple sources. In contrast, the cerebellum appears to play a more central role in sequence learning in general, although its functional contribution remains to be determined.

METHODS

Participants

Ten Parkinson's patients, 8 cerebellar patients, and 10 healthy elderly controls participated in the experiment. The average age of the normal control participants was 71 years, ranging between 60 and 89 years. Six were women, and 4 were men. These participants had an average of 16 years of education (SD = 2 years, range 14–19 years).[2]

The Parkinson's patients had bilateral symptoms and were tested under their normal medication regimen. These patients had been diagnosed with Parkinson's disease for an average of 14 years (SD = 6.6 years, range 3–23 years).[3] The average age of the Parkinson's patients was 64 years, ranging between 51 and 73 years. Three were women and 7 were men. These patients had an average of 15 years of education (SD = 2.1 years, range 12–18 years).

Six of the eight patients in the cerebellar group had unilateral lesions due to either stroke (n = 4) or tumor (n = 2). Of these, three had lesions that extended into the right cerebellar hemisphere and three had lesions that extended into the left cerebellar hemisphere. Two of these patients had lesions resulting from a tumor—one patient had a tumor in the left hemisphere, and one patient had a tumor in the right hemisphere. The others had lesions attributed to stroke. The remaining two patients had bilateral cerebellar degeneration likely related to chronic alcohol use with the pathology most prominent in the vermal region. The cerebellar patients had been diagnosed for an average of 10 years (SD = 11.5 years, range 2–38 years). The average age of these patients was 64 years, ranging between 49 and 76 years. All the cerebellar patients were male. These patients had an average of 13 years of education (SD = 3.0 years, range 8–16 years).[4] All Parkinson's and cerebellar patients scored normally on the Mini-Mental State Examination (range 28–30) except for one cerebellar patient who scored 25.

The SRT Task

Stimuli and Equipment

Participants performed an SRT task in which manual responses were required to indicate the location of visual stimuli. 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. The *X* was displayed for a duration of 300 msec or until the participant responded if the reaction time was smaller than 300 msec. The *X* appeared at a new location after an RSI of 200, 500, or 800 msec.

The participant responded by pressing one of four keys aligned horizontally on a response board. Each key was 10.2 by 2.0 cm with an interkey spacing of 0.6 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. The mapping between the stimulus locations and keys was compatible (e.g., leftmost key corresponded to leftmost position). For the Parkinson's patients and the healthy participants, four fingers of the dominant hand (excluding the thumb) were used to press the keys. The symptoms of the Parkinson's patients were apparent bilaterally. For the cerebellar patients, the hand ipsilateral to the lesion was used. For the atrophy patients, the dominant hand was used.

Procedure and Design

In each block of 56 trials, the position of the *X* either followed a repeating sequence (''sequenced-location'' blocks) or was determined randomly (''random-location'' blocks), subject to the constraints outlined below. The RSIs were also set to either follow a repeating sequence (''sequenced-RSI'' blocks) or were determined randomly (''random-RSI'' blocks). In sequenced-location blocks, the stimulus locations followed a repeating sequence of eight elements. The same syntax, of the form 14213243, was used for all participants. The mapping of numerals to locations was counterbalanced across participants with the constraint that the sequence did not entail a run in which the stimuli appeared in the four horizontal positions in succession (left to right or right to left). For each sequenced-location block, the eight-element sequence repeated seven times, starting at a randomly selected position in the sequence. In random-location blocks, the stimulus location was selected randomly from trial to trial. 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

Table 3. Arrangement of Blocks and Sequence Learning Probes

Block Number	*Locations*	*RSIs*	*Sequence Learning Probe*
1–2	random	random	
3–7	sequenced	sequenced	
8	sequenced	sequenced	
9–10	phase shift	phase shift	phase shift
11	sequenced	sequenced	
12	sequenced	sequenced	
13	sequenced	sequenced (random)	
14–15	random	sequenced (random)	spatial (or spatial-RSI random)
16	sequenced	sequenced (random)	
17	sequenced	sequenced	
18	sequenced	sequenced	
19–20	sequenced	random	timing
21	sequenced	sequenced	
22–23	sequenced	sequenced	
24	sequenced	random (sequenced)	
25–26	random	random (sequenced)	spatial-RSI random (or spatial)
27	sequenced	random (sequenced)	

The timing–location random probe was defined from the random-location blocks of the spatial probe and the spatial-RSI random probe (Blocks 14, 15, 25, and 26).

RSI = response-to-stimulus interval. Parentheses denote an alternative order of blocks or probes in the experiment. The order of the spatial and the spatial-RSI random probes was counterbalanced over participants.

example, Position 1 was only followed by Position 3 or 4, but not by 1 or 2.

For sequenced-RSI blocks, the RSI sequence was eight elements long, equaling the length of the location sequence. The syntax of RSIs was ACBCABCB with the letters referring to the three different RSIs of 200, 500, and 800 msec. As with the spatial sequence, the mapping of letters to RSIs was counterbalanced across participants. On random-RSI blocks, the RSIs were determined randomly with the constraints that the frequency of each RSI was similar to that used in the sequenced-RSI blocks and that the same RSI was not used for two successive trials. On the sequenced-location/sequenced-RSI training blocks, the same starting point was used for both sequences to ensure that the phase relationship between the two sequences was maintained across blocks.

The experiment consisted of 27 blocks (Table 3). The first two blocks were random-location/random-RSI blocks. Following this, five sequenced-location/sequenced-RSI blocks were administered. After these initial training blocks, sequence learning probes were presented, separated from one another by one or two sequenced-location/sequenced-RSI training blocks. Five learning probes were included—the spatial, timing, phase-shift, spatial-RSI random, and timing–location random probes, as detailed in the Data Analysis section of the Results.

For half the participants, the spatial probe was presented during Blocks 13–16 and the spatial-RSI random probe was presented during Blocks 24–27. For the other half of the participants, this order was reversed. The phase-shift probe (Blocks 8–11) and the timing probe (Blocks 18–21) occurred in the same blocks for all participants. We adopted this mixture of a fixed order for the phase-shift and timing probes and limited counterbalanced order for the two spatial probes because a full counterbalancing was not possible given the limited number of available patients.

Instructions and Feedback

The instructions stressed accuracy and speed equally. At the end of each block, feedback was visually presented on the computer screen. The feedback indicated the total number of errors and the mean reaction time of the correct responses for that block. The experimenter initiated each block when the participant was ready. The whole task took about 50–90 min to complete.

Participants were not informed about the sequential presentation of stimuli and time intervals. We assessed the degree of awareness participants possessed about the sequential information in the SRT task. After completion of the SRT task, we orally questioned each subject as to whether (s)he noticed any pattern in the locations of the *X*s or the RSIs. Two control participants correctly articulated up to four consecutive elements in the spatial sequence, whereas none of the Parkinson's or cerebellar patients met this criterion for explicit knowledge of the spatial sequence. No participant reported any specific knowledge of the temporal sequence.

Fast-Tapping Task

A simple measure of motor impairment was obtained twice from each patient—once before the SRT task and once after the SRT task. For this measure, the participants were tested on a speeded tapping task, using the index finger of the hand used during the SRT task. A tone sounded signaling the participant to begin tapping as fast as possible. After 21 taps, a tone sounded to end the trial. Each participant completed five trials. For each trial, the mean and standard deviation of the 20 tapping intervals were calculated. This was then averaged over trials for each participant for both administrations of the fast-tapping task.

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Notes

1. Data for one Parkinson's patient were missing for Blocks 1 and 2 and were excluded from this correlational analysis of mean reaction time.
2. We failed to obtain the number of years of education for two of the control participants; thus, the mean of 16 years is based on the other eight control participants.
3. We failed to obtain the time of onset for one of the Parkinson's patients; thus, the mean of 14 years is based on the other nine patients.
4. We failed to obtain the number of years of education for one cerebellar patient; thus, the mean of 13 years is based on the other seven patients.

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