Procedural Learning in Parkinson's Disease and Cerebellar Degeneration

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We compared procedural learning, translation of procedural knowledge into declarative knowledge, and use of declarative knowledge in age-matched normal volunteers (n = 30), patients with Parkinson's disease (n = 20), and patients with cerebellar degeneration (n = 15) by using a serial reaction time task. Patients with Parkinson's disease achieved procedural knowledge and used declarative knowledge of the task to improve performance, but they required a larger number of repetitions of the task to translate procedural knowledge into declarative knowledge. Patients with cerebellar degeneration did not show performance improvement due to procedural learning, failed to achieve declarative knowledge, and showed limited use of declarative knowledge of the task to improve their performance. Both basal ganglia and cerebellum are involved in procedural learning, but their roles are different. The normal influence of the basal ganglia on the prefrontal cortex may be required for timely access of information to and from the working memory buffer, while the cerebellum may index and order events in the time domain and be therefore essential for any cognitive functions involving sequences.

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Knowledge can be developed or expressed in two distinct ways. One way has been termed procedural knowledge and can be measured by tasks in which memory is expressed implicitly by changes in performance as a result of prior experience. The other way, declarative knowledge, can be measured by tests that require explicit recall or recognition of a prior episode. Procedural knowledge applies particularly to the acquisition of actions and skills. In contrast, declarative knowledge refers to the acquisition of facts and the deliberate recollection of information that is bound to a specific time and context. Acquisition of procedural knowledge through repeated practice may eventually result in the development of declarative knowledge of the task. Conversely, declarative knowledge of a task may hasten the acquisition of procedural knowledge.

Different central nervous system (CNS) structures may be responsible for the acquisition and storage of procedural and declarative knowledge. For example, in patients with temporal lobe lesions [1–3], dorsomedial thalamic lesions [2, 3], Korsakoff's syndrome [4, 5], Alzheimer's disease [6–8], as well as in young adults injected with scopolamine [9–11], procedural learning may be preserved in the presence of impaired declarative learning. On the other hand, selective impairment of procedural learning has been described in patients with cerebellar dysfunction [12], patients with Huntington's disease [13], patients with Parkinson's disease (PD) [14–17], and patients with progressive supranuclear palsy [7].

Given the numerous structures involved in the subcortical diseases mentioned above, it is likely that a network of neural structures subserve procedural knowledge. In these experiments, we decided to focus on the unique contributions of the cerebellum and neostriatum to procedural learning by studying patients with cerebellar degeneration and PD. Different experiments were conducted to address the rate of acquisition of procedural knowledge, the transfer of procedural to declarative knowledge, and the utilization of declarative knowledge for performance improvement.

Methods

Subjects

We studied 20 patients with PD (mean age, 56 yr; range, 39–72 yr), 15 patients with cerebellar degeneration (mean age, 57 yr; range, 30–74 yr), and 30 age-matched normal controls (mean age, 57 yr; range, 30–73 yr). Mini-Mental State Examination and Wechsler Memory Scale scores did not differ between the groups.

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Diagnosis of PD required the presence of an akinetic-rigid syndrome with a history of asymmetrical onset and responsiveness to levodopa. Our PD patients had a level of disability of II to III on the Hoehn and Yahr scale. Their clinical picture was dominated by moderate to severe akinesia/bradykinesia and a mild tremor. All patients were taking levodopa and eldepryl. In addition, 6 were taking bromocriptine, 3 anticholinergics, and 1 clonazepam. Medications had been stable for at least 4 months in all the patients. All of them were studied first on medications and 7 to 12 days later after holding medications for 12 to 36 hours.

The diagnosis of cerebellar degeneration was based on clinical, neurophysiological, and radiological evidence. Five of the patients were diagnosed as having olivopontocerebellar atrophy (OPCA) and 10 as having cerebellar–cortical atrophy (CCA). All had dysarthria, ataxia, and dysmetria; none of them had extrapyramidal signs, lower motor signs, clinical or electromyographic evidence of peripheral neuropathy. Patients with OPCA had upper motor neuron signs, and cerebellar and pontine atrophy on magnetic resonance imaging (MRI). Patients with CCA had no pyramidal tract dysfunction and isolated cerebellar atrophy on MRI.

Experiment 1: Acquisition of Procedural Knowledge

In all experiments, we used variations of the serial reaction time test (srtt) designed by Nissen and Bullemer [4]. In the first experiment, subjects were seated in front of a computer screen and a keyboard with four marked response keys on which subjects were asked to rest middle and index fingers of right or left hand. An asterisk appeared in one of four positions that were horizontally spaced on the screen and aligned above the response keys. The subjects had to press with one finger the key aligned with the asterisk that appeared as fast as possible. The asterisk did not disappear until the correct button was pushed, upon which the next stimulus appeared following a 500-msec delay.

Each test consisted of 7 blocks of 100 trials. The first block was considered practice and discarded from the analysis; the subsequent blocks were numbered 1 to 6. In blocks 1 and 6 the sequence of asterisk positions was random, in blocks 2 to 5 a 10-trial sequence of asterisk positions repeated itself 10 times. The subjects were not told that a repeating sequence was being presented. In this design, procedural knowledge is measured by the progressive shortening of response times and decrease in error rates during blocks 2 to 5, and a rebound lengthening of response time and increase in error rate in block 6. Procedural learning may occur without development of declarative knowledge of the sequence [4, 18].

Experiment 2: Effect of Sequence Length on the Acquisition of Procedural Knowledge

Each test consisted of 3 sets of 6 blocks. In each set, blocks 1 and 6 were random while blocks 2 to 5 showed a repeating sequence. The length of the repeating sequence varied in the different sets: it was 8 items long in set 1, 10 items long in set 2, and 12 items long in set 3. In all 3 sets the sequence was repeated 10 times in blocks 2 to 5. Therefore, the number of trials per block was different for the 3 sets (80 in set 1, 100 in set 2, 120 in set 3).

At the end of each set of blocks the subjects were asked whether the asterisks had been presented in a random or a repeating sequence. If they thought that there had been a repeating sequence they were asked to reproduce it or as much of it as they remembered. Following the criteria of Nissen and Bullemer [4], they were considered to have achieved declarative knowledge of the sequence if they were able to reproduce at least four components of the sequence in the correct order.

In a paired experiment, subjects and patients sat in front of the computer screen and were asked to concentrate on the series of asterisks but not to respond in any fashion. The asterisks automatically changed every 1 second. Subjects and patients were instructed about the possibility of a repeating sequence of asterisks and advised to concentrate on the screen and be prepared to reproduce the perceived sequence of asterisks at the end of the test. This allowed comparison of the development of declarative knowledge of the sequence through "visuomotor input," i.e., through motor performance of the response time task, and through "visual input," i.e., through mere observation of the asterisks appearing on the screen without any associated motor actions.

Experiment 3: Use of Declarative Knowledge in Performance Improvement

Each subject completed 9 blocks of 100 trials that for the purpose of analysis and display were divided in 90 sets of 10 trials. Before the test began, the subjects were taught what the sequence would be. For this purpose, each of the four response keys and possible asterisk positions were numbered (1–4) and the subjects were taught the numerical sequence of asterisk positions (4-2-3-1-3-2-4-3-2-1). The test did not begin until the subjects were able to verbally reproduce the sequence without errors (declarative knowledge). The subjects were not allowed to look at the response keys while learning the sequence and were told not to mentally practice by imagining the series of finger movements to do.

Before blocks 1 to 5 (sets 1–50) the subjects were told that the asterisks would be presented as a repeating sequence, but contrary to these instructions, the asterisks appeared in random order in block 5 (sets 41–50). Before blocks 6 to 8 (sets 51–80) the subjects were told that the asterisks would appear randomly, but contrary to these instructions, the asterisks appeared as a repeating sequence in block 8 (sets 71–80). Before block 9 the subjects were told correctly that the asterisks would appear in random order. Before and after each block the subjects were asked to verbally recall the sequence of asterisk positions that they had learned at the beginning of the test.

Data Analysis

In all three experiments, response time was defined as the interval between appearance of an asterisk and time of depression of the first response key, regardless of whether the response was correct or incorrect. We use the term response time instead of "reaction time," because it encompasses both the time between stimulus appearance and response initiation (reaction time) and the time for the execution of the response (movement time). Error rates express the percentage of incorrect keys pressed in the first place and requiring correc-

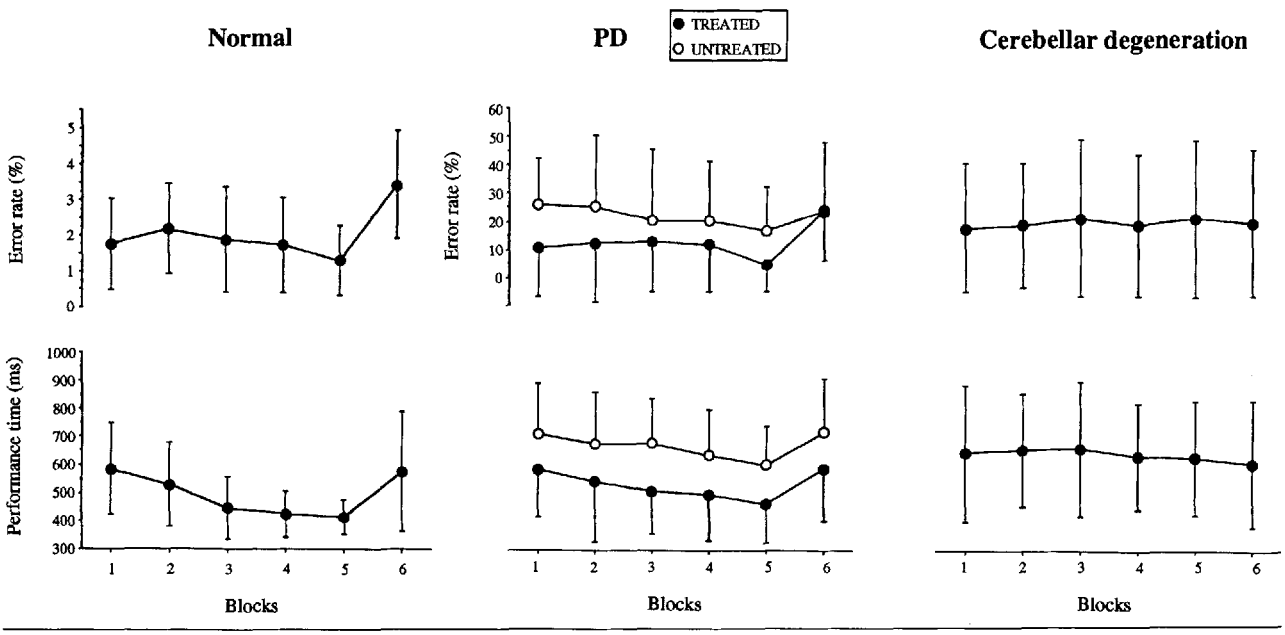

Fig 1. Response times (msec) and error rates (%) over the course of the 6 blocks of the serial reaction time test in 30 normal volunteer, 20 patients with PD in the treated and untreated conditions, and 15 patients with cerebellar degeneration. In the normal volunteers and in the patients with PD, note the progressive decrease in response time and error rate and the narrowing of the standard deviation over the course of the repeating blocks 2 to 5, and the rebound increases in both measurements in the random block 6. In contrast, in the patients with cerebellar degeneration there is no significant change in either parameter across the blocks. Note the error rates are much higher in the two patient groups than in the normal volunteers.

tion. The time until correction was not specifically studied. The results of the response times were unchanged if the trials with erroneous responses were discarded. For each group of subjects, mean and standard deviation response times were calculated of the individual median response times in each block of trials [4, 18]. Statistical analysis was performed with one-way analysis of variance (ANOVA) for subject/patient group and response time or error rate in a given block or with *t* tests comparing performance in a given block between normal subjects with patients with PD or cerebellar degeneration. In either case, significance level was set at $p < 0.05$.

Results

Experiment 1: Acquisition of Procedural Knowledge

Baseline response times in block 1 (random presentation of asterisks, choice response time paradigm) were slightly, though not significantly, higher in the untreated patients with PD than in the controls (Fig 1). Patients with cerebellar degeneration showed greater variability in their response times than the controls as indicated by the significantly larger standard deviation ($p < 0.01$ compared with normal subjects or patients with PD) (see Fig 1). Error rates were much higher in the two patient groups than in the controls ($p < 0.01$).

Normal volunteers and patients with PD acquired procedural knowledge of the sequence, as measured by a reduction in the response time and a decrease in error rates (Figs 1 and 2). In normal volunteers response times shortened, standard deviation decreased, and the error rate decreased progressively across blocks 2 to 5. In block 6, response time and error rate rebounded to the level of block 1. In patients with PD, response time shortened and error rate decreased across blocks 2 to 5 in a similar fashion as in the normal volunteers. Within group statistical analysis (ANOVA) the reduction in response time across the first five blocks of trials showed a greater level of significance for normals ($p < 0.001$) than for PD patients regardless of treatment ($p < 0.01$). Therefore, procedural learning did occur, although, its "degree" was less than in the normal volunteers ($p < 0.001$ for comparison of difference between blocks 5–1). Antiparkinsonian medication did not significantly affect these findings (see Fig 2). The decrease in error rate across the first five blocks of trials showed the greatest level of significance for the untreated PD patients ($p < 0.01$). However, this may in part be due to the overall greater number of errors made by the untreated PD patients due to their motor incapacity.

Patients with cerebellar degeneration did not show a significant reduction in response times or error rates across the first five blocks of trials although a trend toward decreasing response times was present (see Fig 2). Response time and error rates across blocks 2 to 5 were not significantly different from block 1. We found no differences between patients with OPCA and CCA. Therefore, no evidence of acquisition of procedural learning was detected in the cerebellar patients. This

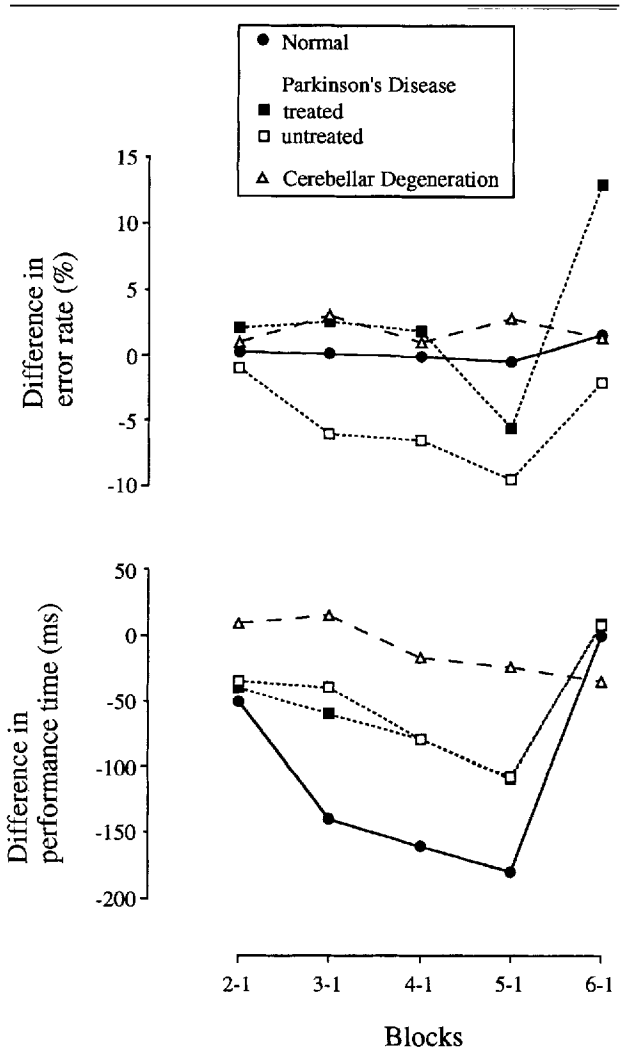

Fig 2. Mean differences in error rates (%) and response times (msec) between block 1 (random) and the subsequent blocks (2–5 repeating, 6 random) in 30 normal volunteers (filled circles), *20 patients with PD in the untreated* (open squares) *and the treated states* (filled squares), *and 15 patients with cerebellar degeneration* (open triangles).

could be due to an impairment in the acquisition of procedural knowledge of the sequence. However, the lack of significant change in response time may in part be due to the greater motor performance variability noted in the cerebellar patients and reflected in the greater standard deviation of their response times (see Fig 1, see above).

Experiment 2: Effect of Sequence Length on the Acquisition of Procedural Knowledge

Shortening of response times, and thus the "degree" of procedural learning, was inversely related to the length of the repeating sequence in normal subjects and patients with PD regardless of treatment condition (Fig 3). However, at longer sequence lengths, patients with PD showed significantly less performance improvement than normal volunteers, particularly in the untreated state (see Fig 3). Patients with cerebellar degeneration did not show any significant performance improvement at any of the sequence lengths tested.

At the end of each test, subjects and patients were asked whether the asterisks had been presented randomly or following a fixed sequence. In normal volunteers, within group statistics showed a highly significant dependency of the acquisition of declarative knowledge on sequence length ($p < 0.001$); 80% acquired declarative knowledge of the 8-item sequence but only 10% of the 12-item sequence (Fig 4). Patients with PD performed similarly to normal volunteers. Within group statistics also showed a significant influence of sequence length on the acquisition of declarative knowledge ($p < 0.01$). However, the percentage of PD patients that reached declarative knowledge of the sequence was significantly lower than among the normal volunteers ($p < 0.01$). In the untreated state, patients with PD tended to do worse than in the treated state, especially at longer sequence lengths (see Fig 4), but these differences were not significant. Finally, only a few patients with cerebellar degeneration achieved declarative knowledge of the sequence at any of the three sequence lengths. No significant effect of the sequence length on the acquisition of declarative knowledge could be demonstrated for the cerebellar patients. There were no differences in the clinical picture of the patients with cerebellar degeneration that achieved declarative knowledge and those that did not. Specifically, cerebellar patients who did achieve declarative knowledge did not show a better motor performance at baseline as indicated by the lack of significant differences in the standard deviation of the response time in the first block of trials.

In the paired experiment in which subjects and patients only observed the asterisks on the screen without having to respond in any fashion ("visual input"), the acquisition of declarative knowledge was significantly greater in normal volunteers ($p < 0.01$) and in patients with PD ($p < 0.001$) than in the original version of the experiment in which input of the information was through visuomotor performance ("motor input") (see Fig 4). These differences are likely to be due to the differences in instructions between the two tasks. In the visual input condition, subjects were instructed about the possibility of a repeating sequence of asterisks (see Methods section) and consequently they were concentrating on the nature of the sequence of the asterisks. The benefit from strictly visual rather than visuomotor input and the different instructions was most prominent in the patients with PD, who performed as well as normal volunteers. On the contrary, despite the differences in instructions and the lack of a motor output demand, only very few patients with

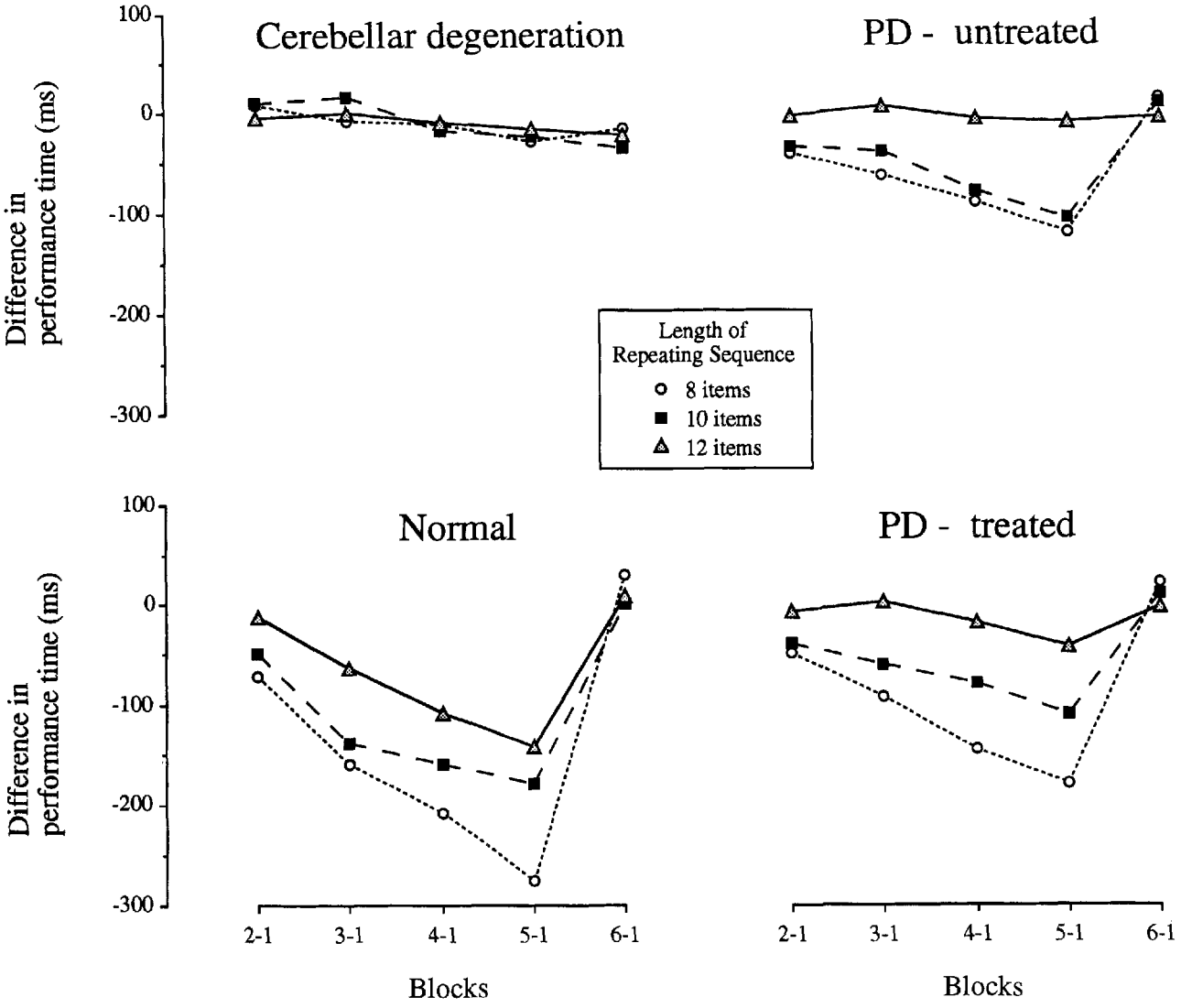

Fig 3. Mean differences in response time (msec) between block 1 (random) and the subsequent blocks (2–5 repeating, 6 random) in 30 normal volunteers, 20 patients with PD (untreated and treated), and 15 patients with cerebellar degeneration according to the length of the repeating sequence (open circles, *8 items;* filled squares, *10 items;* gray triangles, *12 items*).

cerebellar degeneration developed declarative knowledge of the sequence. Even in this visual input condition, cerebellar patients failed to show a significant dependency of the achievement of declarative knowledge from the sequence length. In fact, no significant differences in the likelihood of development of declarative knowledge regardless of sequence length was found for the cerebellar patients across the two test conditions.

Experiment 3: Use of Declarative Knowledge in Performance Improvement (Fig 5)

Normal volunteers were able to use the declarative knowledge of the sequence right away and their response time decreased dramatically. Response times of less than 30 msec were recorded indicating that the subjects were actually anticipating the asterisks rather than reacting to their appearance. None of them had any difficulty in promptly recognizing the misinformation in sets 41 to 50 (instruction repeating, presentation random) and the response times immediately lengthened to match their baseline performance. Finally, all promptly recognized the unannounced repeating sequence in sets 71 to 80 (instruction random, presentation repeating), response time shortened rapidly and the subjects once again anticipated the asterisks rather than reacted to their appearance. This dependency of response time on stimulus presentation despite instructions was statistically significant for all subjects. Response time in sets 71 to 80 was not significantly different from response time in sets 1 to 40. Similarly, response times in sets 41 to 50, 51 to 70, and 81 to 90 were not significantly different. However,

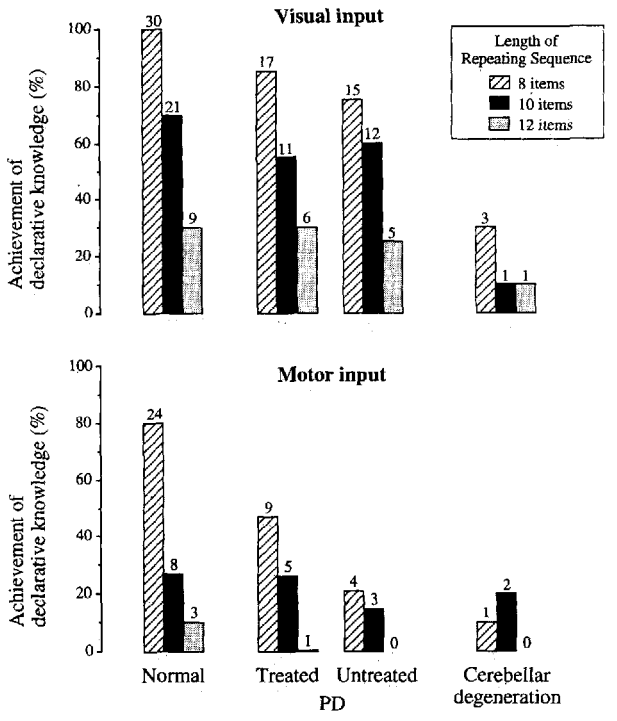

Fig 4. Number of subjects and patients (% of total number tested) that achieved declarative knowledge of the repeating sequence depending on mode of input and sequence length (hatched bar, *8 items;* filled bar, *10 items;* gray bar, *12 items). The number on the top of each bar indicates the actual number of subjects or patients.*

all these three blocks of sets had significantly longer response times than sets 1 to 40 ($p < 0.001$).

Patients with PD were eventually able to use declarative knowledge in a manner similar to normal volunteers as indicated by the lack of differences in response times in sets 30 to 40 between normal volunteers and PD patients. However, it took them more practice to do so ($p < 0.01$, for the difference in mean response times between normal controls and PD patients in sets 10 to 20). None of the PD patients had any difficulty in recognizing the misinformation in sets 41 to 50. In sets 71 to 80, all detected the unannounced sequence, but they showed significantly less shortening of response time than normal volunteers ($p < 0.001$). Within group statistical analysis revealed that response times in sets 41 to 50, 51 to 70, and 81 to 90 were not significantly different. However, similarly to the findings in normals, all these three blocks of sets had significantly longer response times than sets 1 to 40 ($p < 0.001$).

Patients with cerebellar degeneration were not able to use fully the declarative knowledge of the sequence and shorten their response time accordingly in sets 1 to 40. Nine of 10 did not recognize the misinformation in sets 41 to 50. None of them recognized the unannounced sequence in sets 71 to 80. Within group statistical analysis failed to demonstrate significant differences in response times across the different blocks of sets despite the fact that all patients remembered the sequence at the end of each block without difficulties. However, cerebellar patients showed a persistently

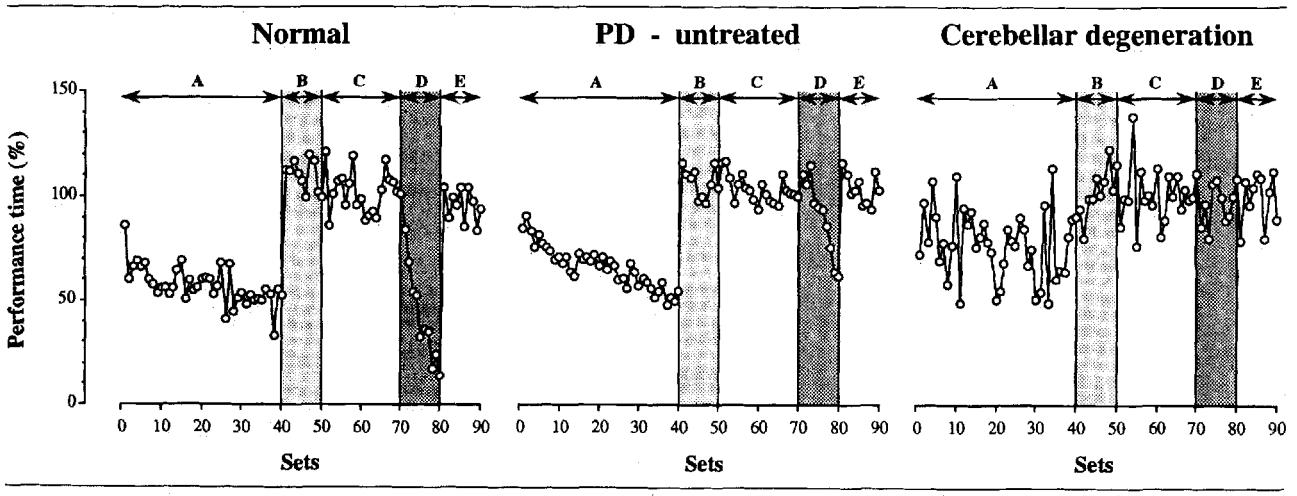

Fig 5. Mean response time in 30 normal volunteers, 20 untreated patients with PD, and 15 patients with cerebellar degeneration in experiment 3. Response time is normalized to the mean response time for 20 random practice sets (200 trials). In condition A (sets 1–40) a repeating sequence is presented and the subject is instructed appropriately. In condition B (sets 41–50, light gray), *presentation is random, but the subjects were told that the repeating sequence would be presented. In condition C (sets 51–70) presentation is random and the subjects were instructed appropriately. In condition D (sets 71–80,* dark gray), *the repeating sequence is presented although the subjects were told that the presentation would be random. In condition E (sets 81–90) presentation is random and instructions to the subjects were appropriate.*

high degree of variability in their response times. Their fastest response times (for example, set 30) were not different from those of normal volunteers, indicating that the findings cannot be solely explained as a floor effect due to motor impairment. Nevertheless, we cannot completely rule out that cerebellar patients were performing close to their maximum motor capacity during the early stages of the training of the task and that the lack of significant improvement is due to an impairment in performing rapid response times on a regular basis.

Discussion

In our experiments, normal volunteers showed an inverse relationship between length of the repeating sequence and performance improvement due to procedural learning and translation of procedural learning into declarative knowledge. These findings reproduce the results of previous studies [18]. In addition, translation of procedural knowledge into declarative knowledge was greater through visual input alone than through visuomotor performance. Using the same serial reaction time task, Howard and colleagues [19] found that when subjects were required to predict the position of the next asterisk in the final test block, their performance was superior following learning through observation than through responding. Our findings agree with theirs and suggest that when procedural (implicit) knowledge is acquired by focusing attention on the perceptual demands of the task, it is more easily translated into declarative (explicit) knowledge (and can therefore be remembered better) than knowledge acquired through visuomotor performance in which attention has to be divided between the perceptual input and the motor output.

A number of animal and human studies suggest that the cerebellum and the basal ganglia are critical for the acquisition of procedural knowledge [14, 20–23]. Seitz and colleagues [24] have described changes in regional cerebral blood flow (rCBF) in both of these structures during the course of learning a complicated finger sequence. Motor learning was accompanied by rCBF increases in the cerebellum and decreases in the striatum that changed to striatal increases as the motor skill was learned. Simultaneously, activation of initially contributing nonmotor parts of the cerebral cortex vanished. They concluded that both cerebellar circuits and striatal circuits are important for the acquisition and storage of motor skills in the brain. Using similar tasks, Saint-Cyr and co-workers [15] and Grafman and associates [25] have shown, respectively, a role of the neostriatum and of the cerebellum [25] in procedural learning involving cognitive planning. This could suggest that both structures are essential for procedural learning because of their link as elements of a neural network that involves the cerebellum, thalamus, basal ganglia, and frontal lobes [12, 26]. We found that patients with cerebellar degeneration failed to show the performance improvement associated with procedural learning in the serial reaction time task, while patients with PD acquired procedural knowledge but did so at a slower rate than normal volunteers. Therefore, our findings, while emphasizing that both the basal ganglia and cerebellum contribute to procedural learning, demonstrate that they make unique contributions.

In order to achieve procedural knowledge of the repeating sequence of asterisk positions, the serial reaction time task requires the "storage" of preceding asterisk positions in a "working memory buffer" [27] and the comparison of each new asterisk position with the previous ones. These functions are probably executed by the prefrontal cortex, which is highly connected with the basal ganglia and the cerebellum [28]. The demands on the memory buffer and on-line comparison grow with an increasing sequence length, thus increasing the difficulty of the task and decreasing the probability of procedural learning. In the case of the 8-item sequence, the subject has to retain in the memory buffer at least the previous 8 asterisk positions in order to identify the pattern. In the case of the 12-item sequence the minimal required storage is of 12 items, which in some individuals may exceed their declarative short-term memory. An essential demand on the memory buffer is the appropriate temporal indexing of the occurrence of asterisk positions so that the sequence can be stored and retrieved as a sequence.

Patients with PD may have difficulties in the use of advance information for motor preparation although the findings of different studies have been somewhat confusing (for review, see [29]). In a recent, careful study on simple and choice reaction times in PD, Jahanshani and associates [29] have convincingly shown that patients with PD can properly use advance information if given sufficient time and have suggested that their difficulties lie primarily in an abnormally slow response initiation. Response initiation in patients with PD appears to be mainly due to an abnormally slow buildup of the necessary premovement cortical excitation [30]. An abnormally low "energizing" influence of basal ganglia on cortical structures in PD is predicted by the functional and biochemical dysfunctions underlying PD [31, 32]. In a similar fashion, the necessary "energizing" influence of the basal ganglia on the prefrontal cortex may be deficient, thus accounting for an abnormally slow access of information to and from the working memory buffer. This would explain the greater difficulties of PD patients in procedural learning of longer asterisk sequences and the need for a greater number of repetitions than normal to achieve declarative knowledge through motor performance. On the other hand, patients with PD were able to achieve declarative knowledge of the sequence pre-

sented visually as well as normal volunteers, thus suggesting a limitation of their impairment to the motor domain.

Patients with cerebellar degeneration failed to show procedural learning of the asterisk sequence. The significance of this finding is somewhat obscured by the motor output demands of the task used in our experiments given the motor impairment of cerebellar patients. We cannot rule out that cerebellar patients were performing close to their maximum motor capacity during the early stages of training of the task and that therefore the apparent lack of procedural learning simply reflected the limitation of their motor system in generating an increase in the rate at which the motor sequence was performed. However, cerebellar patients also failed to acquire declarative knowledge of the repeating sequence presented through motor actions (visuomotor condition) or even visually (visual condition) despite specific instructions about the possibility of a repeating sequence of the asterisks in the latter condition. These results cannot be ascribed to motor impairment. The cerebellum plays a central role in the execution of serial movements [33] and the sequencing and timing of skilled perception and action [34–36]. The unique anatomical homogeneity of the cerebellum and its rich connections with cortical efferent and spinal afferent pathways provide an ideal substrate for a common operation across tasks [37, 38]. We propose that the cerebellum indexes and orders events in the time domain. In the serial reaction time task, the normal operation of the cerebellum is required to keep events in the memory buffer in their proper temporal sequence. In the absence of such information, normal access to the memory buffer and normal on-line comparison of previous asterisk position(s) with the present one are insufficient to detect the repeating sequence and thus procedural learning does not occur. Such a role would also explain the failure of patients with cerebellar degeneration to develop declarative learning regardless of whether information is provided by motor actions or by perceptual input. This inability to order events in the time domain is consistent with the deficit of these patients demonstrated previously for planning a series of actions to solve a problem [25].

These explanations for failures in procedural learning are inextricably linked to the nature of the task we used. As long as procedural or implicit learning tasks are composed of simple visual stimuli and motor demands, then our conclusions and implications about the contributions of specific neural structures should hold. However, when task variables vary from the ones we used here, it is possible that other neural structures and neural system configurations (and therefore additional cognitive processes) may contribute to learning and memory. In that case, a task analysis similar to the one we used in the present experiments should be sufficient to help explain results that are dependent upon variations in experimental design.

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