Differential Effect of Right and Left Basal Ganglionic Infarctions on Procedural Learning

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Objective: To assess the effect of ischemic infarctions affecting the basal ganglia (BG) region on a series of procedural learning tasks.

Background: The basal ganglia hypothesis of procedural learning is a matter of debate. As most of the relevant research so far is based on examination of patients suffering from Parkinson disease, this inconsistency might reflect either lesion heterogeneity existing in this pathologic group or the heterogeneity of the procedural learning tasks.

Method: Twelve patients with lesions confined to the right (BGr), 10 to the left (BGl) BG region, and 15 matched controls participated in the study. Three procedural learning tasks were used: Tower of Hanoi Puzzle, Mirror Reading, and Porteus Mazes. Declarative memory and general intelligence were also tested.

Results: Verbal declarative memory was impaired in the BGl group. For each procedural learning task, baseline performance and learning rate were analyzed. Tower of Hanoi Puzzle: Baseline performance of the BGl group was impaired compared with the other groups. The BGr group was the only group that did not improve over learning trials. MR: Baseline performance of the BGr group was impaired compared with the other groups. The groups' learning rate did not differ significantly. Porteus Mazes: Baseline performance of both patient groups was impaired compared with that of the control group. Learning rate over repetitive trials of the same maze was impaired in the BGr group. However, the transfer of procedural learning to a newly exposed maze was impaired in the BGl group.

Conclusions: First, right and left basal ganglia play different roles in different procedural learning tasks. Second, procedural learning is not a unitary capacity subserved by any single neural mechanism.

Key Words: basal ganglia, procedural learning, stroke

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Cohen and Squire[1] and Cohen and Eichenbaum[2] have distinguished between two forms of memory—declarative and procedural. Declarative memory is memory for facts and events, commonly evaluated through methods of recall and recognition. This form of memory is impaired in patients suffering from amnesia. Procedural learning is usually evaluated through repeated presentation of a given task, where decreased error rate or increased speed over practice reflects the extent of skill formation. Procedural learning was reported to be preserved in patients with amnesia when tested on a wide variety of tasks, (e.g., Tower of Hanoi Puzzle [TOHP],[3] Mirror Reading, [MR],[1] Serial Reaction Time,[4] and Porteus Mazes [PM]).[5]

Various studies have implicated a dominant role for the basal ganglia (BG) in the regulation of procedural learning. These claims are primarily based on animal studies[6] and studies of patients suffering from Parkinson disease and Huntington disease.[7,8] Patients with Parkinson disease were found to be impaired in a variety of skill-learning tasks, such as complex tracking,[9] Serial Reaction Time,[10,11] and the Tower of Toronto.[12] However, other studies do not support the BG hypothesis of procedural learning. Heindel et al[13] found that the impairment on learning the pursuit-rotor task in patients with Parkinson disease correlated with the severity of their accompanying dementia, but not with the severity of their extrapyramidal symptoms. Also, contrary to Saint-Cyr et al's[12] findings, other studies demonstrated that the performance of patients with Parkinson disease on a Tower puzzle did not differ from that of normal controls.[14,15]

The heterogeneity of patient groups suffering from Parkinson disease and Huntington disease, in terms of the severity of BG damage and the extent of damage to other brain structures, may be responsible for these conflicting findings. Indeed, several studies have demonstrated that the pathology in Parkinson disease[16] and Huntington disease[17] may extend far beyond the BG region. Furthermore, in the study mentioned above,[13] performance on procedural learning tasks was related to the severity of dementia in the group suffering from Parkinson disease. A recent study has shown that, whereas patients with Parkinson disease who manifested bradykinesia as their predominant symptom demonstrated procedural learning impairment, those who manifested tremor as their predominant symptom were not impaired.[18]

Other researchers have suggested that heterogeneity of procedural learning tasks, in terms of their underlying cognitive processes, has contributed to the conflicting findings in the literature. Harrington et al[19] found that, whereas patients with Parkinson disease were impaired in motor-skill acquisition tasks (i.e., rotary pursuit), they were not impaired in a visual-perceptual task (i.e., MR). However, a recent study has shown that when learning a specific sequence of locations in both motor and nonmotor versions of the Serial Reaction Time task, patients with BG lesions were impaired as compared with controls.[20]

In the present study, we attempted to shed light on this controversy by testing a different patient population, i.e., patients with first-event subcortical ischemic infarctions confined to either the right or left BG region. Participants were tested on three procedural learning tasks involving both verbal (MR) and nonverbal (TOHP and PM) materials, as well as on verbal and nonverbal intelligence and declarative memory tasks. We asked whether small infarctions affecting the BG region are likely to impair the procedural learning capabilities of the patients, and whether such BG lesions are likely to produce differential effects on the procedural learning tasks on the basis of material specificity and BG lesion side.

METHODS

Participants

Twenty-two patients admitted to the Loewenstein Hospital (Ra'anana, Israel) for rehabilitation after stroke were recruited on the basis of the following inclusion criteria: (1) first occurrence of a computed tomography (CT)–proven ischemic brain infarction confined either to the right or left BG region (BGr, BGl); (2) absence of significant mass effect, with possible unrecognizable distant structural damage, in the acute-stage CT scan; (3) absence of any neurologic or psychiatric past history; (4) absence of significant cortical atrophy or diffuse periventricular low density on CT; (5) a stable clinical and metabolic state at the time of testing; (6) right-handedness; (7) fair knowledge of oral and written (reading and writing) Hebrew. The patients gave informed consent to participate in the study.

In the BGr group, there were 12 patients (8 males and 4 females), with an age range of 47 to 74 years (mean = 59.4, SD = 8.5) and an educational level range of 7 to 17 years of formal schooling (mean = 10.5, SD = 2.8). Examination took place 8.2 ± 4.0 weeks after the onset of stroke. In the BGl group, there were 10 patients (8 males and 2 females), with an age range of 24 to 68 years (mean = 51.9, SD = 11.9) and an educational level range of 8 to 20 years of formal schooling (mean = 10.6, SD = 3.8). Examination took place 12.7 ± 6.8 weeks after the onset of stroke. Brain damage was caused by an ischemic infarction in all 22 patients. A follow-up CT scan performed 8 ± 2 weeks after onset served for lesion analysis. The follow-up CT examinations did not disclose cortical involvement in any of the patients. Individual lesion data of the 22 patients are presented in Table 1. None of the patients received major tranquilizers/psychotropic medications at the time of testing. Ongoing physiotherapy/occupational therapy/speech therapy was done in accordance with each patient's needs. The overall amount of therapy was quite similar in the two groups, with some patients in the BGl group receiving additional speech therapy that was not needed in the BGr group. Distribution of motor, sensory and visual field deficits was quite similar in both groups.

The control group consisted of 15 healthy individuals matched with the patient groups for age and educational level. This group comprised primarily university employees recruited through ads posted throughout the campus. Participants were paid for their participation in the study. The sample consisted of 8 males and 7 females, with an age range of 45 to 64 years (mean = 53.47, SD = 6.32) and an educational level range of 8 to 18 years of schooling (mean = 13, SD = 2.33). The three groups did not differ on age: $F(2, 34) = 2.45$, $P > 0.05$, or on education: $F(2, 34) = 2.98$, $P > 0.05$.

TASKS AND PROCEDURE

Participants were tested individually. Controls were tested in two sessions of approximately 5 to 6 hours each. Patients needed more sessions (range: 4–12, mean = 7) of shorter duration, in accordance with their concentration level, to complete all the experimental tasks. It is important to note that a single task was always performed within a single session.

Three procedural learning tasks were administered: TOHP,[3] PM,[21] and MR.[1] Performance on these tasks was analyzed using time and number of errors (or moves) as the dependent measures. The Wechsler Adult Intelligence Scale—Revised (WAIS-R)[22] was used as a measure of general intelligence. Declarative memory was measured by the Wechsler Memory Scale—Revised (WMS-R)[23] and by the Hebrew version of the Rey Auditory Verbal Learning Test (AVLT).[24]

Tower of Hanoi Puzzle

A computerized version of the task was used. Three pegs appeared on the screen, numbered 1 to 3. Four disks were arranged according to size with the largest disk at the bottom of the leftmost peg. Participants were told that the goal was to move the disks from the leftmost peg (# 1) to the rightmost peg (# 3) using a minimum number of moves. They had to adhere to the following rules: Only one disk could be moved at a time, a larger disk could not be placed on a smaller one, and the middle peg (# 2) had to be used. The optimal solution for 4 disks requires 15 moves. The computer program records both number of moves and time on task required for solving the puzzle. The task was administered four times consecutively.

TABLE 1. Demographic, Clinical, and Lesion Data of Individual Patients

Patient	Age/Sex	MI	SI	VFD	Neglect	Aphasia	Structural Damage
BG right							
DZ	48/M	±	−	−	−	−	PLIC
GS	55/F	++	±	−	−	−	LN, PLIC, PVWM
EE	53/M	+	−	+	−	−	LN, PLIC
LA	57/M	++	+	−	−	−	LN, PLIC
SD	54/M	±	−	−	−	−	ALIC, PVWM
PI	70/F	+	+	−	−	−	LN, ALIC, PVWM
CD	74/F	±	+	−	−	−	LN, ALIC, PVWM
YY	47/M	++	−	−	−	−	LN, ALIC, PVWM
DY	63/M	±	+	−	−	−	LN, ALIC, PVWM
MM	61/F	++	++	−/e	+	−	LN, PLIC, PVWM
KY	67/M	±	−	−	−	−	LN, PLIC, PVWM
PH	64/M	++	+	−	−	−	LN, PVWM
BG left							
KY	68/M	++	−	−	−	−	CN, ALIC, PVWM
TY	58/M	+	++	−	−	−	LN, PLIC, PVWM
BI	45/M	±	−	−	−	+ unclassified	LN, CN, ALIC, PVWM
VS	54/F	++	+	+	−	+ amnesic	LN, PLIC, PVWM
BM	24/M	++	−	−	−	+ amnesic	LN, PLIC, ALIC, PVWM
EA	55/M	++	+	−	−	−	LN, CN, ALIC, PVWM
KA	56/F	+	±	−	−	−	LN, PVWM
MJ	49/M	+	−	−	−	−	LN, PLIC, PVWM
BJ	48/M	++	+	−	−	+ conduction	LN, PLIC, PVWM
AS	62/M	++	±	−	−	−	LN, PLIC, PVWM

MI, motor impairment (− no impairment, ± mild impairment, + hemiparesis, ++ hemiplegia); SI, sensory impairment (− no, ± mild, + moderate, ++ severe sensory loss); VFD, visual field defect (− no, + hemianopsia, −/e, extinction upon bilateral simultaneous stimulation but no VFD); LN, lentiform nucleus; CN, caudate nucleus; PLIC, posterior limb of internal capsule; ALIC, anterior limb of internal capsule; PVWM, periventricular white matter.

Mirror Reading

Words appeared on the computer screen in mirror writing form. Participants were asked to read the words aloud as quickly as they could. Each presentation contained three words—a triad. As soon as the three words were read correctly, the experimenter pressed the spacebar, the computer recorded the reading time, and the next triad appeared. The experimenter also recorded the number of reading errors. There were five consecutive trials, each containing 10 triads. Five triads were repeated from trial to trial (old triads) and five new triads were added in each trial (25 new triads in total).

Porteus Mazes

Two "adult" level mazes, considered by Porteus[21] to be on the same level of difficulty, served as a "training maze" and a "testing maze." Half of the participants were trained on one maze and tested on the other. The other half underwent the reverse process. In the first session, participants were asked to solve the testing maze once. This was regarded as the participant's baseline performance. This was followed by 10 repetitive trials in which participants solved the training maze. Immediately afterward, participants were again asked to solve the testing maze to provide a measure of the transfer of procedural learning. Participants were instructed to mark the path from starting point to exit, without lifting the pencil. They were also told not to enter a dead-end alley and to avoid crossing over the maze's lines. In the event a participant actually entered a dead-end alley, the individual was told to stop and go back to the point prior to dead-end entry. The scores were determined according to the number of dead-end alley entrances and time on task.

RESULTS

In the next three sections the performance of the two patient groups and the control group on the three procedural tasks (i.e., TOHP, MR, and PM) will be analyzed. For each task baseline performance and learning rate will be analyzed and reported separately.

Tower of Hanoi Puzzle

Solution Time

Figure 1 presents the mean time (**A**) and mean number of moves (**B**) required by the three groups to solve the TOHP in the four learning trials. Solution time and number of moves were analyzed separately as dependent measures.

Baseline Performance

One-way ANOVA was used to analyze the difference in solution time among the groups (control, BGr, and BGl) on the first trial of the task. The groups' solution time on the first trial was found to be significantly different, $F(2, 32) = 4.22$, $P < 0.05$. Follow-up analysis using the least significant difference (LSD) procedure indicates that the BGl group required significantly more time to solve the TOHP than the BGr and control groups ($P < 0.05$). The BGr and control groups did not differ from each other.

Learning Rate

Mixed-design ANOVA for repeated measures was used to analyze group (control, BGr, and BGl) and learning trials (trials 1–4) effects: the former is a between-subjects factor, and the latter is a within-subjects factor. Group main effect did not reach significance, but the learning trials main effect and the group by learning trials interaction reached significance: $F(3, 96) = 12.99$, $P < 0.001$; $F(6, 96) = 2.46$, $P < 0.05$, respectively. As Figure 1A demonstrates, the groups differed in their learning rate over trials. To detect the source of the interaction, separate repeated measure analyses of the learning rate for each group were conducted. Results indicated that the control group: $F(3, 42) = 4.34$, $P < 0.01$, and the BGl group: $F(3, 24) = 9.56$, $P < 0.001$ showed significant learning. In contrast, the BGr group did not reveal significant learning over repeated trials: $F(3, 30) = 2.25$, $P > 0.05$.

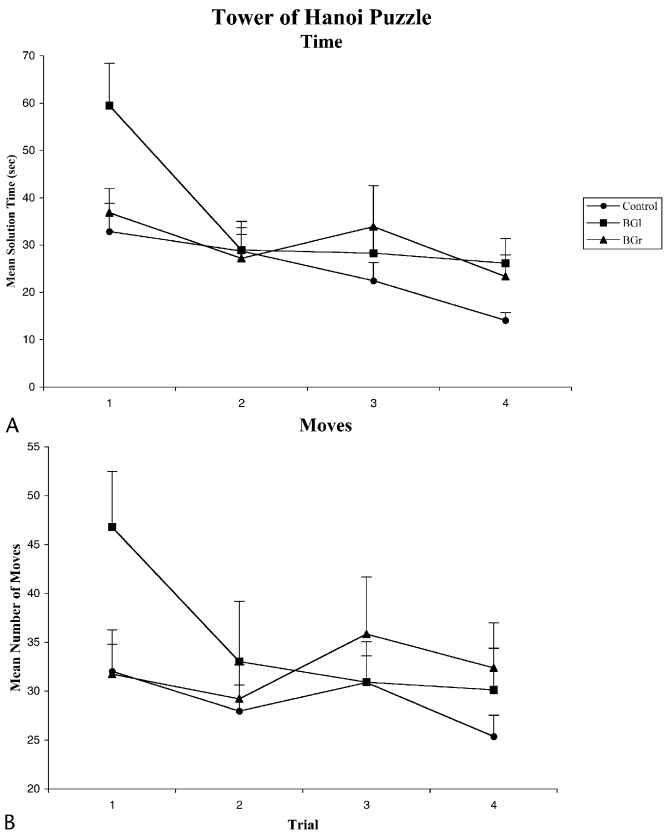

FIGURE 1. Mean solution time (A) (and SE) and mean number of moves (B) required to solve the Tower of Hanoi Puzzle in the four learning trials.

Number of Moves

Baseline Performance

One-way ANOVA was used to analyze the difference among the groups in the number of moves required to solve the task on the first trial of the task. The groups' number of moves on the first trial was found to be significantly different, $F(2, 32) = 3.31$, $P < 0.05$. Follow-up analysis using the LSD procedure indicates that the BGl group required more moves than did the BGr and control groups ($P < 0.05$), which did not differ from each other. A similar pattern was observed for solution time.

Learning Rate

Mixed-design ANOVA for repeated measures was used to analyze group (control, BGr, and BGl) and learning trials (trials 1–4) effects: the former is a between-subjects factor, and the latter is a within-subjects factor. The overall number of moves required to solve the TOHP did not differ significantly among the groups (Figure 1B). Fewer moves were required to solve the TOHP over consecutive learning trials: $F(3, 96) = 2.83$, $P < 0.05$. The group by learning trials interaction was not significant, indicating that the learning rate did not differ significantly among the groups.

Mirror Reading

Reading Time

The mean reading time for each group during the learning phase is presented in Figure 2, for nonrepeated (**A**) and repeated (**B**) words. Reading time and number of errors were analyzed separately as dependent measures.

Baseline Performance

One-way ANOVA was used to analyze the difference in reading time among the groups (control, BGr, and BGl) on the first trial of the task. It should be noted that since all words are new in the first trial, repeated and nonrepeated words were combined. The groups' reading time on the first trial was found to be significantly different, $F(2, 32) = 3.71$, $P < 0.05$. Follow-up analysis using the LSD procedure indicates that the BGr group's reading time was significantly higher than that of the

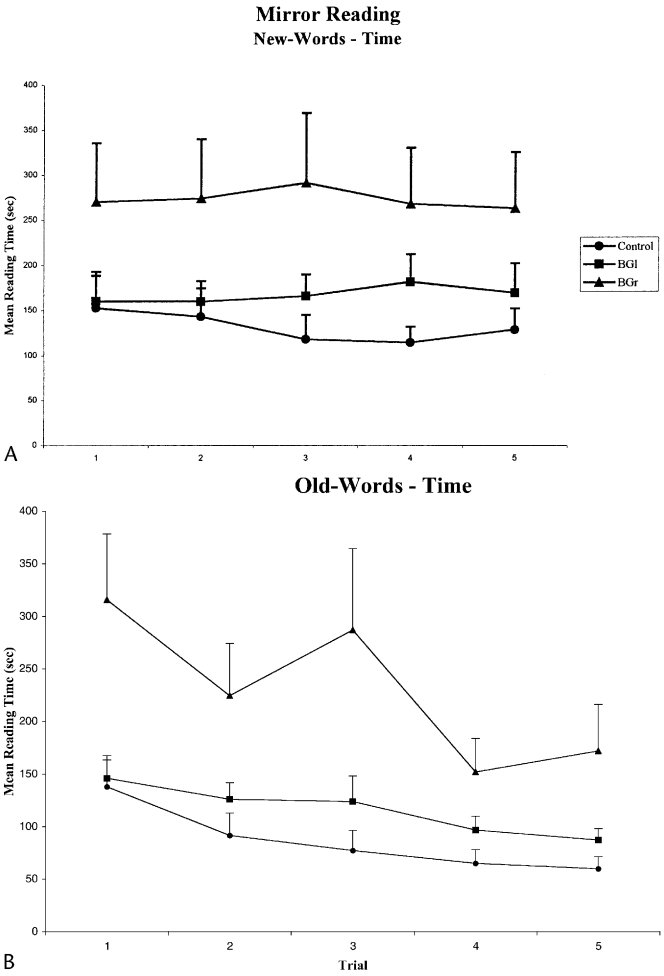

FIGURE 2. Mean reading time (and SE) during the learning trial for new (A) and old (B) words of the Mirror Reading task.

BGl and control groups ($P < 0.05$). The BGl and control groups did not differ significantly from each other.

Learning Rate

The effects of group (control, BGr, and BGl), repetition (old and new words), and learning trial (trials 1–5) were analyzed using a mixed-design ANOVA for repeated measures. The former is a between-subjects factor, and the latter two are within-subjects factors. The three main effects reached significance: group $F(2, 30) = 5.06$, $P < 0.05$, repeated words were read faster than nonrepeated words: $F(1, 30) = 9.02$, $P < 0.01$, and overall reading time improved over trials: $F(4, 120) = 5.38$, $P < 0.001$. The only interaction that reached significance was repetition by learning trials: $F(4, 120) = 5.15$, $P < 0.001$. To detect the source of the interaction, separate analyses were conducted for the repeated and nonrepeated words. In the analysis of the repeated words, both main effects group, $F(2, 30) = 7.74$, $P < 0.005$ and learning trials, $F(4, 120) = 7.30$, $P < 0.001$ reached significance, but not the interaction between them, indicating that the groups' learning rates did not differ significantly from each other. In the analysis of the nonrepeated words, none of the effects reached significance. As Figure 2 demonstrates, this result reflects the steeper learning rate (reduced reading time) of repeated, as compared with nonrepeated words.

Number of Errors

The mean number of errors made by each group during learning is presented in Figure 3, for nonrepeated (**A**) and repeated (**B**) words.

Baseline Performance

One-way ANOVA was used to analyze the difference in the number of errors among the groups (control, BGr, and BGl) on the first trial of the task. As with the reading time analysis, results of repeated and nonrepeated words were combined. The groups' number of errors on the first trial was found to be significantly different, $F(2, 32) = 4.86$, $P < 0.05$. Follow-up

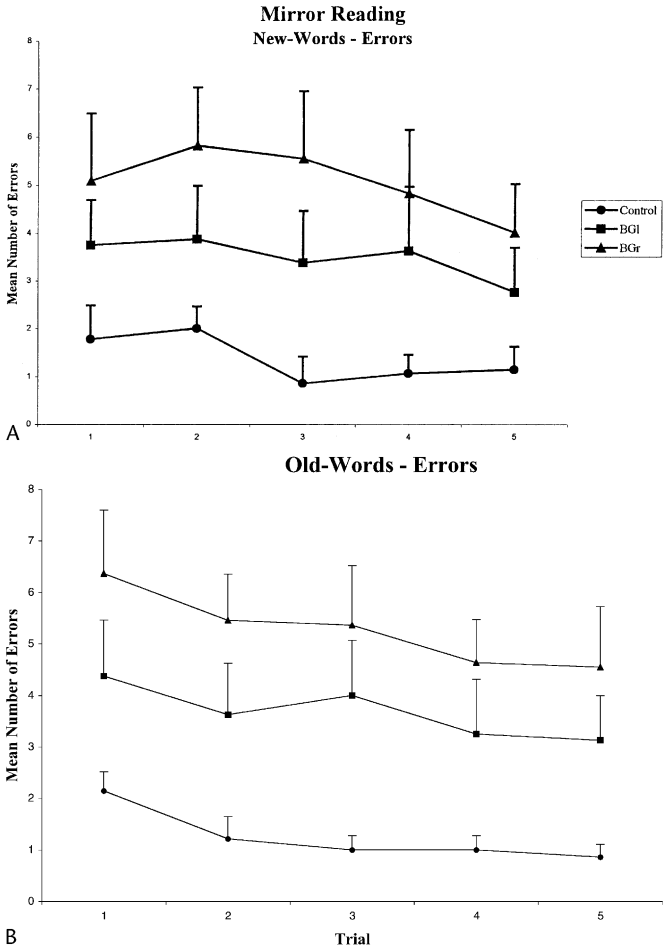

FIGURE 3. Mean number of errors (and SE) during the learning trial for new (A) and old (B) words of the Mirror Reading task.

analysis using the LSD procedure indicates that the BGr group's number of errors was significantly higher than that of the control group ($P < 0.005$) but did not differ from the BGl group. The BGl and control groups did not differ significantly from each other.

Learning Rate

The same effects as reading time were analyzed. The overall number of errors made by the three groups differed significantly: $F(2, 30) = 7.16$, $P < 0.01$. The main effect of learning trials indicates that over trials, fewer errors were made: $F(4, 120) = 7.41$, $P < 0.001$. None of the interactions reached significance.

Porteus Mazes

As described in the Methods section, two equivalent mazes were used: a training maze, repeated 10 times, and a testing maze, administered twice pre- and posttraining. This paradigm enabled us to assess two different aspects of learning. First, the capacity for procedural learning was evaluated by means of the specific maze used for training over the 10 repeated trials. Second, the testing maze was used to measure the extent of transfer of the learning effect from one specific maze to another. The dependent measures were solution time and number of errors (i.e., dead-end alley entrances).

Training Maze

Solution Time

Mean solution time and mean number of errors required by each group to solve the training maze in the learning trials are presented in Figures 4A and 4B, respectively.

Baseline Performance

One-way ANOVA was used to analyze the difference in solution time among the groups (control, BGr, and BGl) on the first trial of the task. The groups' solution time on the first trial was found to be significantly different, $F(2, 32) = 3.21$, $P < 0.05$. Follow-up analysis using the LSD procedure indicates that the patient groups did not differ from each other, but both groups' solution time was significantly slower than that of the control group ($P < 0.005$).

Learning Rate

A mixed-design ANOVA for repeated measures was used to analyze the effect of group (control, BGr, and BGl) and learning trials 1–10. The former is a between-subjects factor, and the latter is a within-subjects factor. Group and learning trials main effects reached significance, $F(2, 32) = 6.45$, $P < 0.01$, and $F(9, 288) = 12.20$, $P < 0.001$, respectively. The interaction between group and learning trials was also significant: $F(18, 288) = 2.41$, $P < 0.001$, indicating that the groups differ in learning rate. To detect the source of this interaction, follow-up analysis using repeated measure analyses for each group was conducted. Results indicated significant learning for each one of the groups over the ten learning trials: control group, $F(9, 126) = 6.85$, $P < 0.001$, BGl group, $F(9, 81) = 8.96$, $P < 0.001$, and the BGr group, $F(9, 81) = 2.88$, $P < 0.01$. In the first trial of the task, the two patient groups did not differ from each other and were significantly slower than the control group. By contrast, on the tenth trial the groups' solution time was found to be significantly different, $F(2, 32) = 6.25$, $P < 0.01$. Follow-up analysis using the LSD procedure indicates that the BGr group's solution time was significantly slower than that of the control and BGl groups ($P < 0.05$), and that the latter two did not differ from each other.

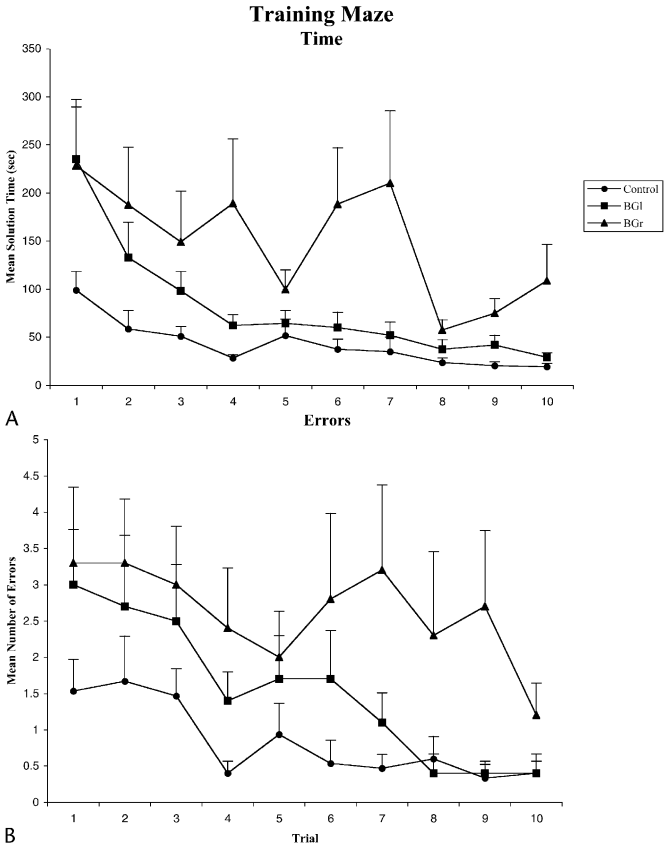

FIGURE 4. Mean solution time (A) (and SE) and mean number of errors (B) for the specific training maze in the learning trials.

Number of errors

Baseline Performance

One-way ANOVA was used to analyze the difference in the number of errors (dead-end alley entrances) among the groups (control, BGr, and BGl) on the first trial of the task. The groups did not differ significantly in the number of errors on the first trial, $F(2, 32) = 1.93$, $P > 0.05$.

Learning Rate

The same analysis as with solution time was conducted with errors as the dependent measure. Group and learning tri-

als main effects reached significance: $F(2, 32) = 3.38$, $P < 0.05$, and $F(9, 288) = 8.72$, $P < 0.001$, respectively. Unlike the analysis of learning on the basis of solution time, here the group by learning trials interaction did not reach significance, indicating a similar learning rate among the groups. Although the group by learning trials interaction in this case did not reach significance, the pattern of results is quite similar to that observed with solution time as a measure of learning: the BGl group is closer to the BGr group during the initial trials and closer to the control group during the final trials (Figure 4B).

Testing Maze

Solution Time

Mean solution time and mean number of errors performed by each group on the testing maze, pre- and posttraining, are presented in Figures 5A and 5B, respectively.

Baseline Performance: Pretraining

One-way ANOVA was used to analyze the difference in solution time among the groups (control, BGr, and BGl) on the pretraining trial. The groups' solution time did not differ significantly from each other, $F(2, 32) = 1.38$, $P > 0.05$.

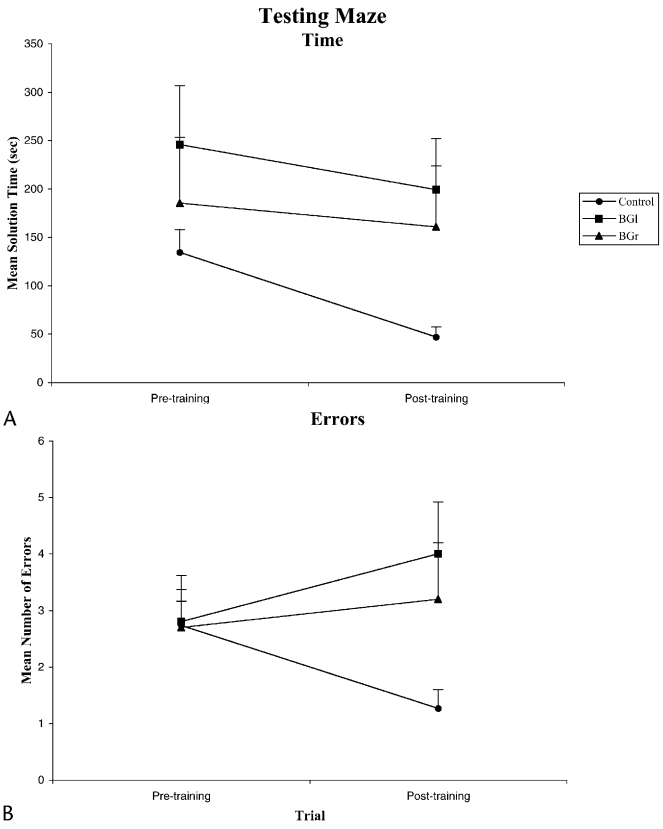

FIGURE 5. Mean solution time (A) (and SE) and mean number of errors (B) for the testing maze, pretraining, posttraining.

Learning Effect: Posttraining

One-way ANOVA was used to analyze the difference in solution time among the groups (control, BGr, and BGl) on the posttraining trial. The groups' solution time on the posttraining trial was found to be significantly different, $F(2, 32) = 4.03$, $P < 0.05$. Follow-up analysis using the LSD procedure indicates that the BGl group, but not the BGr group, was significantly slower than the control group ($P < 0.05$). The patient groups did not differ significantly from each other. The control group was the only group that showed improvement from pretraining to posttraining: $t(14)=3.21$, $P < 0.01$.

Number of errors

Baseline Performance: Pretraining

One-way ANOVA was used to analyze the difference in the number of errors (dead-end alley entrances) among the groups (control, BGr, and BGl) on the pretraining trial. The groups did not significantly differ in the number of errors on the first trial, $F(2, 32) = 0.01$, $P > 0.05$.

Learning Effect: Posttraining

One-way ANOVA was used to analyze the difference in the number of errors among the groups (control, BGr, and BGl) on the posttraining trial. The groups' number of errors on this trial was found to be significantly different, $F(2, 32) = 4.23$, $P < 0.05$. Follow-up analysis using the LSD procedure indicates that at posttraining the BGl group, but not the BGr group, made significantly more errors than the control group ($P < 0.05$). The patient groups did not differ significantly from each other. The control group was the only group that showed improvement, although marginally significant, from pretraining to posttraining (2.73 to 1.27 error): $t(14) = 1.98$, $P < 0.07$. The change in the patient groups did not reach significance. Furthermore, the BGl group demonstrates a negative effect, although not statistically significant (increment in error rate from 2.80 to 4.00), suggesting that the switch from one maze to the other probably interfered with the performance on the testing maze following the training phase. Although not as pronounced as in the BGl group, the BGr group showed some interference for pre- to posttraining trial (from 2.70 to 3.20).

Declarative Memory

The three groups (BGr, BGl, controls) were compared on the various scores generated from the WMS-R and the Rey-AVLT. Wherever a significant group effect was found, a follow-up analysis was conducted using the LSD procedure. As shown in Table 2, controls performed better than both patient groups on the different scales of the WMS-R, while the two patient groups did not differ significantly from each other. The verbal memory score was exceptional in showing a nonsignificant difference between controls and BGr patients, while these two groups performed better than the BGl group. On the Rey-AVLT, controls performed better than both patient

TABLE 2. WMS-R and Rey-AVLT Declarative Memory Scores (Mean ± SD) for the 3 Groups

					Follow-up Analysis	
Test	**BGl**	**BGr**	**Controls**	**F**	**Control vs. BG**	**BGl vs. BGr**
WMS-R						
Verbal memory	89.30 ± 17.38	105.17 ± 13.58	112.13 ± 14.23	7.10**	−	+
Visual memory	80.30 ± 17.93	90.17 ± 21.37	116.20 ± 14.04	14.07***	+	−
General MQ	83.80 ± 18.94	99.50 ± 16.42	115.73 ± 14.58	11.52***	+	−
Atten/Conc	71.60 ± 10.95	80.67 ± 11.23	105.53 ± 17.37	20.19***	+	−
Delayed MQ	79.33 ± 15.39	94.00 ± 17.87	116.87 ± 19.31	13.26***	+	−
Rey-AVLT						
Learning: t-1	4.10 ± 1.37	5.42 ± 1.62	7.20 ± 2.01	9.99***	+	−
Learning: t-5	9.20 ± 2.30	11.33 ± 1.61	11.87 ± 1.55	6.95**	−	BG1 < C & BGr
Learning: t 1+2+3+4+5	36.20 ± 7.99	44.66 ± 5.49	52.33 ± 8.23	14.4***	+	BG1 < BGr
Delay	5.80 ± 3.12	9.33 ± 2.31	10.20 ± 3.05	7.53**	−	BG1 < C & BGr
Recognition	10.7 ± 3.47	13.33 ± 2.02	13.20 ± 2.21	3.68*	−	−
Temporal order	0.42 ± 0.34	0.48 ± 0.28	0.65 ± 0.31	1.94	−	−

One-way ANOVA. *$P < .05$; **$P < .01$; ***$P < .001$.
BG, basal ganglia; Rey-AVLT, Rey Auditory Verbal Learning Test; WMS-R, Weschler Memory Scale—Revised.

groups, with the exception of delayed recall, recognition, and memory for temporal order. Post hoc comparisons between the two patient groups revealed a BGl disadvantage in part of the scores, while in other scores the difference in performance between the two patient groups was not significant.

General Intelligence

The WAIS-R full-scale IQ scores for each group (mean ± SD) were: 82.9 ± 9.21, 84.25 ± 8.2, and 106.14 ± 11.37, for the BGl, BGr and control groups, respectively. The verbal IQ mean scores were: 82.3 ± 9.21, 87.17 ± 8.22, and 112.07 ± 12.38, for the BGl, BGr and control groups, respectively. The performance IQ mean scores were: 82.1 ± 7.8, 81.67 ± 9.56, and 96.86 ± 11.59, for the BGl, BGr, and control groups, respectively. In each of the three composite measures, as well as in each of the WAIS-R subtests, the two patient groups did not differ significantly from each other, while both showed a disadvantage relative to controls. The BGl patients showed significant disadvantage relative to BGr patients on the Digit Symbol subtest (scale score: 4.7 and 7.0, respectively), probably due to BGl patients' motor impairment affecting the dominant right hand. Therefore, this score was not included in the overall analyses of the composite WAIS-R measures.

Patients With and Without Involvement of Anterior Basal Ganglia Regions

The primary aim of the present study was to assess the effect of right and left ischemic BG infarctions on procedural learning. We wanted to see whether such a population could serve as a complementary source of information—in addition to patients suffering from neurodegenerative diseases—with regard to the BG hypothesis of procedural learning. The available CT-based structural information and the number of patients in the present study preclude fine-grained assessments of the role of specific structures and physiological loops within the BG. However, we wished to obtain a preliminary measure of the possible role of frontal cortical deafferentiation that could result from damage to structures in the more anterior BG regions. Thus, patients with lesions affecting the anterior BG regions (head of the caudate nucleus and/or anterior limb of the internal capsule), across lesion side, and patients without such involvement were compared. Patients with anterior involvement comprised 5/12 (42%) of the BGr group, and 4/10 (40%) of the BGl group. All the above analyses were repeated using group (BG-anterior, BG-posterior, control) as a between-subjects factor in a mixed-design ANOVA. Analyses of the results revealed that the two patient groups did not differ significantly from each other. However, both groups showed a relative disadvantage compared with controls on general intelligence (full-scale, verbal, and performance IQ derived from the WAIS-R), as well as on the different measures of declarative memory (derived from the WMS-R and the Rey-AVLT). As for the procedural learning measures, the general pattern obtained for the procedural learning tasks was a slowness of response in the BG-anterior group relative both to normal controls and to the BG-posterior group. The learning rate itself was essentially similar.

In sum, for each procedural learning task, baseline performance and learning rate were analyzed. TOHP: Baseline performance of the BGl group was impaired compared with the other groups. The BGr group was the only group that did not improve over learning trials. MR: Baseline performance of the BGr group was impaired compared with the other groups. The groups' learning rate did not differ significantly. PM: Baseline performance of both patient groups was impaired compared with that of the control group. Learning rate over repetitive trials of the same maze (i.e., training maze) was impaired in the BGr group. However, the transfer of procedural learning to a newly exposed maze (i.e., testing maze) was impaired in the BGl group.

DISCUSSION

The neural organization of procedural learning is far from being clear. Destruction of medial temporal or diencephalic structures, causing severe deficits in declarative memory, may leave procedural learning relatively unimpaired.[1,3–5] Various studies over the past two decades point to a crucial role for the BG in the regulation of procedural learning. However, due to inconsistent findings in the literature, the BG hypothesis of procedural learning is a matter of debate. Since nearly all the relevant lesion studies at this time are based on examination of patients suffering from Parkinson or Huntington degenerative diseases,[7] this inconsistency might reflect either the functional or lesion heterogeneity existing in these pathologic groups, in addition to the possible heterogeneity of the procedural learning tasks used in different studies.

In the present study we attempted to shed light on this controversy by testing a different patient population, i.e., patients with ischemic BG infarctions of recent onset whose past medical history is negative for neurologic or psychiatric disturbances. We asked whether circumscribed vascular lesions affecting the BG region are likely to impair the procedural learning capabilities of the patients, and whether right and left BG lesions are likely to produce differential effects on three procedural learning tasks (TOHP, MR, and PM) on the basis of material specificity.

The selection of this patient population was found to be revealing. First, small BG infarctions were shown to affect procedural learning, thus encouraging further study of that patient population as a valid source of information regarding the BG hypothesis of procedural learning. The three procedural learning tasks showed a differential sensitivity to BG lesion side, although it did not reflect a straightforward material specificity (i.e., verbal vs. visuospatial). We propose here tentative explanations for the differential sensitivity of procedural learning tasks to BG lesion side.

In previous studies we have pointed out the dissociation between two components of procedural learning tasks—baseline performance and learning rate. It was found that aging[25] and mental retardation[26] affected baseline performance but not the learning rate of the TOHP task. Accordingly, when comparing groups of patients suffering brain damage with normal individuals, demonstration of impaired procedural learning is based on a differential learning rate following repeated trials (as revealed by an interaction between group and learning trials in the ANOVA), while a baseline disadvantage (resulting in a significant group effect on the first trial of a task) is interpreted as reflecting an impairment in the basic level of task processing. Consistent with this distinction, the findings of the present study revealed that small left or right BG infarctions could affect differentially either the baseline processing or the learning rate of different procedural tasks. Hence, participants' performance on the three tasks will be discussed with regard to these two components: baseline performance and learning rate.

Porteus Mazes

Probably the most revealing results came from the participants' performance on this task. Here, the training maze served to assess procedural learning as expressed in performance change over repeated trials using one and the same maze. The testing maze served to assess the generalization of procedural learning, as revealed by transfer of the training effect to a different maze. The baseline performance on the training maze of the patient groups did not differ from each other, but was impaired compared with that of the control group. The three groups showed significant learning over the training trials. However, while the patient groups did not differ from each other at baseline, the BGr group was significantly slower than the BGl and control groups by the end of training (i.e., trial 10). Pretraining performance of the three groups on the testing maze did not significantly differ. Posttraining, the BGl group's performance was significantly impaired compared with that of the control group. In terms of learning, only the control group showed gain when comparing the posttraining performance with the pretraining performance. None of the patient groups showed such generalization of the learning (actually, using number of errors as a measure, the patient groups demonstrated a negative effect, although not statistically significant, suggesting that repeated exposure to one specific maze interfered with performance on a different maze).

Thus, while the BGr group was more vulnerable than the BGl group on performance of the training maze, an opposite pattern of results was revealed on performance of the testing maze. These findings can be interpreted in terms of a dissociation suggested by Marsolek et al.[27] These researchers demonstrated right-hemisphere superiority in a lexical decision task following specific priming (repeated presentation of the target stimulus), as opposed to left-hemisphere superiority following abstract priming (when a different stimulus from the same category was used as a prime). Consistent with Marsolek et al's findings, the present study shows that right BG involvement is critical to the learning of the specific (training) maze, while left

BG involvement is critical to the transfer of learning from one maze to another, i.e., to a more abstract aspect of procedural learning, underlying generalization of the learning effect. The results of the present study expand upon Marsolek et al's findings in two ways. They demonstrate that the distinction between specific and abstract processing could apply not only to priming effects, but also to procedural learning tasks. In addition, we demonstrate here that the specific/abstract dichotomy applies not only to cortically mediated processes, but also to subcortical, BG mediated processes.

Tower of Hanoi Puzzle

Both measures of the TOHP (solution time and number of moves) indicate that the baseline performance of the BGl group is inferior to that of the BGr and control group. Analysis of the learning rate (measured by solution time) separately for each group indicated that the control group and the BGl group, but not the BGr group, showed significant learning over trials.

The findings that the BGl group has shown impaired baseline level while BGr group has shown impaired learning rate lend further support to our distinction between these two aspects of procedural task performance. These results can also be understood within the same theoretical framework[27] used above to explain the PM findings, i.e., the distinction between abstract and specific aspects of procedural learning, mediated dominantly by the left and right hemispheres, respectively. More specifically, the TOHP is an essentially problem-solving task that requires abstract thinking and planning, rather than memorization of a specific sequence of moves. Thus, the critical role of the left BG in the initial stage of task performance is consistent with Marsolek et al's findings. Similar to the training Porteus maze, BGr patients demonstrated impaired learning of the same task (i.e., specific) over repeated trials as would be expected by Marsolek et al.

The effect of damage to the left and right BG on baseline performance and learning rate, respectively, is consistent with findings from two case studies reported in the literature with damage either to the left or right BG. Robbins et al[28] reported a patient, FS, with an infarct damaging the left caudate-putamen who showed a selective deficit in a task, which requires self-ordered working memory and self-generated strategy. The initial phase (i.e., baseline) of attempting to solve the TOHP could also be viewed as requiring self-ordered working memory and self-generated strategy. Swainson and Robbins[29] reported a patient, PM, with infarct to the right BG and internal capsule who showed difficulties on a number of tasks in learning a rule that could have facilitated performance. This difficulty is similar to the impaired learning rate in patients with right BG damage observed in the present study.

It should be noted that much of the relative initial slowness displayed by the BGl patients on the TOHP may be related to involvement of the caudate nucleus, which was found in three of these patients but in none of the BGr patients. As described in the Results section, patients with lesions affecting the anterior BG regions (head of the caudate nucleus and/or anterior limb of the internal capsule), across lesion side, showed significant slowness in many of the procedural learning measures, relative to patients without such involvement. This effect was not related to a disadvantage of the "anterior" group in general intelligence or in declarative memory, nor was it related to the procedural learning rate itself (improvement over trials), which was essentially similar in the BG-anterior and BG-posterior groups. Elucidation of the specific role of distinct structures within the BG necessitates further research employing larger numbers of patients with exclusive, magnetic resonance imaging–proven, anterior or posterior BG infarctions.

Mirror Reading

The BGr groups' baseline performance, measured either by reading time or by number of errors, was impaired compared with that of the BGl or control group. None of the groups showed learning over trials of the nonrepeated words. It is possible that allowing more training trials would have resulted in improved performance (i.e., learning) even in the nonrepeated words. Significant learning, at the same rate, was observed in the three groups in the analysis of the repeated words. Thus, the BGr group, compared with the BGl and control groups, was impaired in processing (i.e., baseline performance) but not in the learning of the MR task.

As the task of MR deals essentially with verbal material, one could predict a greater impairment following BG damage on the left. However, baseline performance of the task, measured either by time or errors, was more impaired following lesions to the right BG. A recent fMRI study of the neural basis of MR found that learning of this task involves a progression from visuospatial transformation mediated by the right hemisphere to letter recognition, mediated by the left hemisphere.[30] In the present study, since training for MR was much shorter than in the study conducted by Poldrack et al, we have probably witnessed only the first learning phase, based on improved visuospatial transformation, which is mediated by the right hemisphere. Poldrack et al reported that the right dorsal visual stream is involved in this initial learning phase. The present findings suggest that the right BG are also important in the initial phase of MR learning. This interpretation should be taken cautiously since the BGr group was impaired, compared with the other groups, in baseline performance but showed the same learning rate as the other groups.

A study by Masson[31] suggested that learning in the MR task is very specific, i.e., the progress made through learning words that consisted of one set of letters was not transferred to words that consisted of letters not yet learned. Consistent with Masson's findings, in the present study, improvement over learning trials was observed with the repeated but not with the nonrepeated words. Thus, the MR task seems to tap predomi-

nantly specific procedural learning, which might explain its sensitivity to right BG damage, as explained in relation to TOHP and PM performance, based on the findings by Marsolek et al.[27]

The role of the BG in cognition extends far beyond the putative role of these structures in procedural learning, with converging evidence for BG involvement in decision-making, movement selection, behavioral shift, and working memory (see 32-34 for reviews). In the present study not only procedural learning, but also measures of general intelligence and of declarative memory were found to be sensitive to lesions in the BG region. The two patient groups showed a nonspecific decline in all the WAIS-R measures of general intelligence in comparison to age- and education-matched healthy controls. Although neither the acute-stage nor the follow-up CT scans revealed cortical involvement in any of the patients, the existence of regional cortical hypoperfusion, unaccompanied by visible density changes on CT, cannot be ruled out.[35,36] Cortical deafferentiation and diaschisis could also occur, and are actually of the essence of lesion effects when cortico-striatal regulatory loops are involved (see 37-40 for recent reviews of cortico-striatal interactions underlying various motor and cognitive functions). However, the two patient groups did not differ from each other in any of the composite measures of the WAIS-R (verbal, performance, and full-scale IQ) or in any of the WAIS-R subtests, except for digit-symbol. Therefore, the nonspecific decline in general intelligence cannot explain the differential sensitivity of different procedural learning measures to BG lesion side.

Some of the declarative memory measures (i.e., WMS-R and Rey AVLT) were sensitive to BG lesion side. More specifically, verbal memory was more impaired in the BGl group than in the BGr group. However, visual memory did not reveal the opposite pattern and did not differ significantly between the two patient groups. Several studies have previously demonstrated impaired declarative memory in addition to procedural learning impairment in patients with Parkinson disease.[41,42] However, other studies reported selective impairment of skill learning in patients with Parkinson disease and sparing declarative memory.[43,44] Given the functional and anatomic relations between the prefrontal cortex and the BG, numerous studies have pointed out the similarity of cognitive impairment in PD and frontal lobe patients. For example, PD patients were found to have deficient recall as a result of poor learning strategies.[42] Thus, a possible way to reconcile these conflicting findings in the literature is that only declarative memory tasks that require planning, organization, and strategic approach are vulnerable to BG damage because they are dependent on frontal BG structures.

In conclusion, the results of the present study reaffirm the importance of the distinction between baseline performance and learning rate, as performance on one aspect of the task did not necessarily predict performance on the other. Further research is required to have a better understanding of the underlying mechanism of each one of these components. The findings stress two additional issues: First, the right and left BG seem to play a different role in different procedural learning tasks and should not be treated as a single unit. Second, procedural learning is not a unitary capacity subserved by any single neural mechanism, as different procedural learning tasks seem to tap different cognitive processes with variant lateralization. The study of patients with vascular BG lesions can provide important insight with respect to the BG hypothesis of procedural learning, thus complementing the information derived from studies based on neurodegenerative populations.

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REFERENCES

1. Cohen NJ, Squire LR. Preserved learning and retention of pattern analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science*. 1980;210:207–210.
2. Cohen NJ, Eichenbaum H. *Amnesia and the Hippocampal System.* Cambridge, MA: MIT Press; 1993.
3. Cohen NJ, Eichenbaum H, Deacedo BS, et al. Different memory systems underlying acquisition of procedural and declarative knowledge. In: Olton DS, Gamzu E, Corkin S, eds. *Memory Dysfunctions: An Integration of Animal and Human Research From Preclinical and Clinical Perspectives.* New York, NY: New York Academy of Science; 1985;54–71.
4. Nissen MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. *Cognit Psychol*. 1987;19:1–32.
5. Brooks ND, Baddeley A. What can amnesic patients learn? *Neuropsychologia*. 1976;41:111–122.
6. Jog MS, Kubota Y, Connolly CI, et al. Building neural representations of habits. *Science*. 1999;286:1745–1749.
7. Saint-Cyr JA, Taylor AE. The mobilization of procedural learning: the "key signature" of the BG. In: Squire LR, Butters N, eds. *Neuropsychology of Memory.* New York, NY: Guilford; 1992;188–202.
8. Lawrence AD, Sahakian BJ, Robbins TW. Cognitive functions and corticostriatal circuits: insights from Huntington disease. *Trends Cognit Science*. 1998;2:379–383.
9. Frith CD, Bloxman CA, Carpenter KN. Impairment in the learning and performance of a new manual skill in patients with Parkinson disease. *J Neurol Neurosurg Psychiatry*. 1986;49:661–668.
10. Ferraro FR, Balota DA, Connor LT. Implicit memory and the formation of new associations in nondemented Parkinson disease individuals and individuals with senile dementia of the Alzheimer type: a serial reaction time (SRT) investigation. *Brain Cogn*. 1993;21:163–180.
11. Jackson GM, Jackson SR, Harrison J, et al. Serial reaction time learning and Parkinson disease: evidence for a procedural learning deficit. *Neuropsychologia*. 1995;33:577–593.
12. Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. *Brain*. 1988;111:941–959.
13. Heindel WC, Salomon DP, Shults CW, et al. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington, and Parkinson disease patients. *J Neurosci*. 1989;9:582–587.
14. Alberoni M, Della Sala S, Pasetti C, et al. Problem-solving ability of Parkinsonians. *Ital J Neurolog Science*. 1988;9:35–40.
15. Morris RG, Downes JJ, Sahakian BJ, et al. Planning and spatial working memory in Parkinson disease. *J Neurol Neurosurg Psychiatry*. 1988;51:757–766.

16. Taylor AE, Saint-Cyr JA, Lang AE. Memory and learning in early Parkinson disease: evidence for "frontal lobe syndrome." *Brain Cogn*. 1986; 13:211–232.
17. Stober T, Wussow W, Schimrigk K. Bicaudate diameter: the most specific and simple CT parameter in the diagnosis of Huntington disease. *Neuroradiol*. 1984;42:1169–1175.
18. Vakil E, Herishanu-Naaman S. Declarative and procedural learning in Parkinson disease patients having tremor or bradykinesia as the predominant symptom. *Cortex*. 1998;34:611–620.
19. Harrington DL, Haaland KY, Yeo RA, et al. Procedural memory in Parkinson disease: impaired motor but not visuoperceptual learning. *J Clin Exp Neuropsychol*. 1990;12:323–339.
20. Vakil E, Kahan S, Huberman M, et al. Motor and non-motor sequence learning in patients with basal ganglia lesions: the case of serial reaction time (SRT). *Neuropsychologia*. 2000;38:1–10.
21. Porteus SD. *The Porteus Maze Test and Intelligence.* Palo Alto, CA: Pacific Books; 1950.
22. Wechsler DA. *Wechsler Adult Intelligence Scale—Revised.* New York, NY: The Psychological Corporation; 1981.
23. Wechsler DA. *Wechsler Memory Scale—Revised.* New York, NY: The Psychological Corporation; 1987.
24. Vakil E, Blachstein H. Rey AVLT—developmental norms for adults and the sensitivity of different measures to age. *Clin Neuropsychol*. 1997;11: 356–369.
25. Vakil E, Agmon-Ashkenazi D. Baseline performance and learning rate of procedural and declarative memory tasks: younger versus older adults. *J Gerontol Psycholog Sciences*. 1997;52B:229–234.
26. Vakil E, Shelef-Reshef E, Levy-Shiff R. Procedural and declarative memory processes in children with mental retardation. *Am J Ment Retard*. 1997;102:147–160.
27. Marsolek CJ, Squire LR, Kosslyn SM, et al. Form specific explicit and implicit memory in the right cerebral hemisphere. *Neuropsychology*. 1994;8:588–597.
28. Robbins TW, Shallice T, Burgess PW, et al. Selective impairments in self-ordered working memory in patient with unilateral striatal lesion. *Neurocase*. 1995;1:217–230.
29. Swainson R, Robbins TW. Rule-abstraction deficit following a basal ganglia lesion. *Neurocase*. 2001;7:433–444.
30. Poldrack RA, Desmond JE, Glover GH, et al. The neural basis of visual skill learning: an fMRI study of mirror reading. *Cereb Cortex*. 1998;8: 1–10.
31. Masson ME. Identification of typographically transformed words: instance-based skill. *J Exp Psychol*. 1986;12:479–488.
32. Beiser DG, Hua SE, Houk JC. Network models of the basal ganglia. *Curr Opin Neurobiol*. 1997;7:185–190.
33. Brown LL, Schneider JS, Lidsky TI. Sensory and cognitive functions of the basal ganglia. *Curr Opin Neurobiol*. 1997;7:157–163.
34. White NM. Mnemonic functions of the basal ganglia. *Curr Opin Neurobiol*. 1997;7:164–169.
35. Metter EJ. Neuroanatomy and physiology of aphasia: evidence from positron emission tomography. *Aphasiol*. 1987;1:3–33.
36. Olsen TS. Regional cerebral blood flow after occlusion of the middle cerebral artery. *Acta Neurol Scand*. 1986;73:321–337.
37. Cotterill RMJ. Cooperation of the basal ganglia, cerebellum, sensory cerebrum and hippocampus: possible implications for cognition, consciousness, intelligence and creativity. *Progress Neurobiol*. 2001;64:1–34.
38. Doya K. Complementary roles of basal ganglia and cerebellum in learning and motor control. *Curr Opin Neurobiol*. 2000;10:732–739.
39. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Rev*. 2000;31:236–250.
40. Nakano K. Neural circuits and topographic organization of the basal ganglia and related regions. *Brain Dev*. 2000;22:5–16.
41. Daum I, Schugens MM, Spieker S, et al. Memory and skill acquisition in Parkinson disease and frontal lobe dysfunction. *Cortex*. 1995;31:413–432.
42. Taylor AE, Saint-Cyr JA, Lang AE. Memory and learning in early Parkinson disease: Evidence for "frontal lobe syndrome." *Brain Cogn*. 1990; 13:211–232.
43. Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. *Science*. 1996;273:1399–1402.
44. Ullman MT. The declarative/procedural model of lexicon and grammar. *J Psycholinguistic Res*. 2001;30:37–69.

