

# Habit Learning in Tourette Syndrome

## *A Translational Neuroscience Approach to a Developmental Psychopathology*

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**Background:** The etiology of Tourette syndrome (TS) involves disturbances in the structure and function of the basal ganglia. The basal ganglia mediate habit learning.

**Objective:** To study habit learning in persons with TS.

**Design:** Patients with TS were compared with normal controls in performance on a probabilistic classification, or habit-learning task (weather prediction).

**Setting:** University research institute.

**Participants:** One hundred twenty-three children and adults, 56 with a diagnosis of TS and 67 healthy control subjects.

**Main Outcome Measures:** Habit learning was assessed by the extent of improvement in accuracy of predictions and reaction times over trial blocks during performance of the weather prediction task. Declarative learning was assessed by performance on 3 tasks that required intact declarative memory functioning.

**Results:** Children with TS were impaired at habit learning relative to normal controls ( $P = .01$ ). This finding was

replicated in the independent sample of adults with TS ( $P = .01$ ). The rate of learning correlated inversely with the severity of tic symptoms across both samples ( $r = -0.34$ ;  $P = .01$ ). Thus, impaired learning accompanied more severe symptoms. Measures of declarative memory functioning, in contrast, were normal in the TS groups.

**Conclusions:** Striatal learning systems are uniquely dysfunctional in both children and adults with TS. The correlation of habit learning with symptom severity suggests that the number and severity of tics are a function of the degree to which the system for habit learning is dysfunctional. Thus, both the deficits in habit learning and the tic symptoms of TS are likely to be consequences of the previously reported anatomical and functional disturbances of the striatum in children and adults who have TS. The existence of a well-developed animal model for this learning system, which permits study of the neural and molecular bases of habit learning, has important implications for the neurobiological study of TS and for the development of new or improved therapeutics for this condition.

*Arch Gen Psychiatry.* 2004;61:1259-1268

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**N**EUROIMAGING STUDIES suggest that the pathophysiology of Tourette syndrome (TS) involves disturbances of the basal ganglia and related corticostriatal-thalamocortical circuitry.<sup>1</sup> Findings of smaller caudate volumes in children and adults with TS suggest that the motor and cognitive functions the striatum subserves may be dysfunctional in persons who have this condition.<sup>2-4</sup> One important function of the striatum, in particular the dorsal striatum, is the learning of skills, motor sequences, and habits, which is variously termed procedural, stimulus-response (S-R), or habit-based learning.<sup>5</sup> The neostriatal habit-learning system has been

shown, in lesion studies of both animals and humans, to be anatomically and functionally distinct from neural systems that subserved declarative learning.<sup>5-9</sup> Declarative learning, which includes the learning and memory of conscious facts, experiences, and semantics, is supported primarily by medial temporal lobe structures. Habit learning, in contrast, involves the gradual and incremental learning of S-R associations, a function that is based primarily within the basal ganglia.

Probabilistic classification learning is a form of habit learning in human subjects that circumvents the use of declarative memory by probabilistically associating cues with specific outcomes. One version of a probabilistic classification learning task is

a weather prediction game that requires the gradual learning of S-R associations. Declarative memory of the previous trial is not as useful in improving performance as is information gleaned across many trials. Subjects try to predict rain or sunshine based on the presentation of a varying combination of a set of cards on a computer screen.<sup>6,7</sup> Each card is independently and probabilistically related to the outcomes (rain or shine), each of which occurs equally often. For example, one card predicts sunshine 25% of the time and rain 75% of the time, whereas another card predicts sunshine 57% of the time and rain 43% of the time. A response is considered correct on a particular trial only if the selected outcome is more strongly associated with the cue combination that appears on that trial. Although subjects receive positive or negative feedback after each prediction, they can receive negative feedback even when they think that they have predicted the weather correctly. The cue-outcome associations are not absolute because cue combinations predict different outcomes in differing percentages. Thus, because of the probabilistic nature of the task, subjects usually believe that they are simply guessing at the outcome. Normal subjects do, however, exhibit learning on this task, in that they gradually improve in their ability to predict the correct weather outcome, although it is outside of their conscious awareness. Patients with diseases affecting the striatum, such as Huntington disease and Parkinson disease, exhibit impaired learning on this task, although they are able to answer explicit factual questions about the task.<sup>6,7</sup> This pattern of findings in humans is consistent with earlier studies in lower animals indicating that the dorsal striatum subserves habit learning.<sup>5,10-12</sup> Conversely, patients with temporal lobe lesions that affect declarative memory systems are impaired at answering explicit factual questions about the task,<sup>5-7,13</sup> whereas their learning on the probabilistic features of the task is intact.

The motor and vocal tics in persons who have TS are typically brief, nonpurposeful or semipurposeful fragments of motor behaviors that are often responses to stimuli or environmental cues either from within their bodies or from the outside world.<sup>14</sup> Sensitivity to these cues is usually experienced as a compulsive urge that is only relieved by performing the tic.<sup>1,14,15</sup> These urges and the patient's preoccupation with them bear a phenomenological resemblance to the obsessional urges to act that typically precede compulsive behaviors. In fact, patients with TS are often affected with comorbid obsessive-compulsive disorder (OCD). Evidence from family-genetic and twin studies indicate that the disorders are genetically related,<sup>15,16</sup> and neuroimaging studies suggest that the neural bases of TS and OCD are related as well.<sup>17</sup> The phenomenological similarities between tics and compulsions and their common genetic and neural basis suggest that they might lie on a continuum of semi-involuntary or habitual behaviors. On one end of this spectrum are those behaviors with a strong ideational component belonging to OCD, on the other end are those with little or no ideational component belonging to simple tics, and in between are the complex tics of patients with TS and comorbid OCD.<sup>15</sup> Tics are therefore similar in their appearance and subjective experience to habits. Parents of children with tics and OCD symptoms in fact often describe the behaviors as habits or mannerisms. This phenomenological similarity of tics and compulsions to hab-

its, together with both the documented striatal abnormalities in TS and the role of the striatum in habit learning, has prompted others and us to suggest that tics could represent habit learning gone awry.<sup>3,4,15,18,19</sup> In fact, impairments in habit learning have recently been reported in a preliminary study of 10 children with TS.<sup>20</sup> Thus, deficient habit learning in persons with TS could contribute to their habit-like, stereotyped behaviors.

We report herein a study in which we used the weather prediction task to study habit learning in 55 children and 68 adults, both subjects with TS and healthy controls. We tested our hypothesis that children with TS would differ from healthy control children in habit learning. We then sought to replicate this finding in an independent sample of adults with TS. In exploratory analyses, we assessed whether measures of habit learning were associated with the severity of tic symptoms across individuals with TS. Finally, we measured performance on 3 tasks that require intact functioning of declarative memory systems to assess whether learning impairments are specific to the habit-learning system.

## METHODS

### SUBJECT RECRUITMENT AND CHARACTERIZATION

Subjects were recruited to participate in 1 or more studies of childhood neuropsychiatric disorders. The TS sample was ascertained through the Tic Disorder Clinic of the Yale Child Study Center, New Haven, Conn, and through the local chapter of the Tourette Syndrome Association. The unaffected control children and adults were recruited from randomly selected names on a telemarketing list of approximately 10 000 families in the local community. These families received introductory letters, which were then followed by screening and recruitment telephone calls. Approximately 10% of the families who were contacted ultimately participated. Control subjects were group matched with the patients by age, sex, and socioeconomic status. Those with a history of neurological illness, past seizures or history of head trauma with loss of consciousness, mental retardation, pervasive developmental disorder, psychosis, or major depression were excluded. Written informed consent was obtained from adult subjects and the parents of participating children, and assent was obtained from the children. Subjects were paid for their participation.

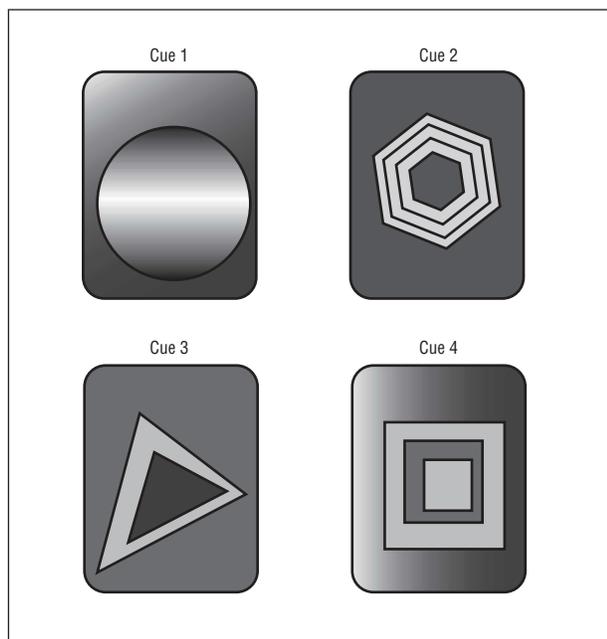
Neuropsychiatric diagnoses were established through clinical evaluation and administration of the Schedule for Tourette and Other Behavioral Syndromes.<sup>21</sup> This diagnostic interview includes the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version for diagnoses in children,<sup>22</sup> the Schedule for Affective Disorders and Schizophrenia for diagnoses in adults,<sup>23</sup> and more detailed sections on TS and OCD for both age groups. Using all available clinical and investigational materials, 2 child psychiatrists performed a best-estimate procedure to establish diagnoses.<sup>24</sup> The Yale Global Tic Severity Scale,<sup>25</sup> the Yale-Brown Obsessive Compulsive Scale,<sup>26-28</sup> and the DuPaul-Barkley attention-deficit/hyperactivity disorder (ADHD) rating scale<sup>29</sup> were used, respectively, to obtain ratings of current and worst ever severity of tic, OCD, and ADHD symptoms. Intraclass correlation coefficients<sup>30</sup> for clinicians who administered the Yale Global Tic Severity Scale and the Yale-Brown Obsessive Compulsive Scale were greater than 0.90 on videotaped training interviews. Estimates of full-scale IQs were made using the Wechs-

**Table 1. Demographic and Clinical Characteristics of Subjects\***

Characteristic	Subjects					
	Children			Adults		
	TS (n = 32)	NC (n = 23)	Test Statistic	TS (n = 24)	NC (n = 44)	Test Statistic
Age, y	12.38 (2.7)	12.65 (3.2)	$t_{53} = -0.34; P = .73$	35.28 (11.3)	35.37 (12.1)	$t_{66} = 0.03; P = .98$
Sex, M:F	22:10	13:10	$\chi^2 = 1.02; P = .31$	13:11	21:23	$\chi^2 = 0.26; P = .62$
SES	49.90 (10.3)	53.85 (9.3)	$t_{49} = -1.38; P = .17$	47.69 (10.4)	49.00 (11.3)	$t_{38} = 0.37; P = .71$
WASI IQ score						
Full-4	105.41 (15.9)	111.91 (11.3)	$t_{53} = -1.68; P = .10$	113.1 (11.5)	115.32 (13.6)	$t_{56} = 0.63; P = .53$
Verbal	109.21 (11.0)	114.20 (11.0)	$t_{32} = -1.31; P = .20$	104.55 (20.7)	114.44 (15.3)	$t_{36} = 1.63; P = .11$
Performance	100.21 (18.6)	109.33 (14.3)	$t_{32} = -1.57; P = .12$	111.50 (7.8)	113.89 (14.3)	$t_{35} = -0.50; P = .62$
YGTSS score						
Motor/phonic W/E	33.19 (7.2)	NA		31.82 (9.2)	NA	
Motor W/E	18.19 (3.7)	NA		18.26 (4.6)	NA	
Phonic W/E	15.03 (4.1)	NA		13.56 (6.4)	NA	
Comorbidity, No. (%)						
OCD	7 (21.8)	NA		6 (25)	NA	
ADHD	7 (21.8)	NA		2 (8)	NA	
OCD/ADHD	6 (18.7)	NA		4 (16.6)	NA	
Depression	3 (9.3)	NA		0	NA	
ODD	8 (25)	NA		NA	NA	
Medication, No. (%)	24 (75)	NA		15 (62)	NA	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NA, not applicable; NC, normal controls; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SES, socioeconomic status; WASI, Wechsler Abbreviated Scale of Intelligence; W/E, worst ever; YGTSS, Yale Global Tic Severity Scale.

\*Data are presented as mean (SD) unless otherwise indicated.



**Figure 1.** Cues in the weather prediction task. The probabilities of each possible combination of cues that appear together are provided in Table 2.

ler Abbreviated Scale of Intelligence.<sup>31</sup> Socioeconomic status was quantified using the Hollingshead Four-Factor Index of Social Status.<sup>32</sup> Sample characteristics are given in **Table 1**.

### THE WEATHER PREDICTION TASK

This measure of probabilistic learning was administered on a laptop computer (Macintosh iBook). The task required subjects to learn which of 2 outcomes, rain or sunshine, would oc-

**Table 2. Probability Structure of the Weather Task\***

Cue 1	Cues				G(n)	H(n)	P(G)
	Cue 2	Cue 3	Cue 4				
0	0	0	1	10	2	.83	
0	0	1	0	4	3	.57	
0	0	1	1	7	1	.88	
0	1	0	0	3	4	.43	
0	1	0	1	5	1	.83	
0	1	1	0	2	2	.50	
0	1	1	1	3	1	.75	
1	0	0	0	3	10	.23	
1	0	0	1	2	3	.40	
1	0	1	0	1	5	.17	
1	0	1	1	2	1	.67	
1	1	0	0	1	7	.13	
1	1	0	1	1	2	.33	
1	1	1	0	1	3	.25	

\*Each row represents 1 of 14 possible different combinations of 4 cue types that appear with probability P(G). G(n) is the number of times the combination predicts sunshine, and H(n) is the number of times it predicts rain.

cur on each trial based on 1, 2, 3, or 4 different cues (**Figure 1**) that occurred on each presentation in 1 of 14 possible combinations (**Table 2**). The sequence of cue combinations appearing on each trial was randomized for each participant, with the constraints that the same cue combination could not appear twice in succession and that each outcome did not occur more than 5 times in succession.

Each cue was independently associated to each outcome (rain or sunshine) with a fixed probability, and the 2 outcomes occurred equally often. Across all 14 cue combinations, each cue-outcome association occurred at a consistent frequency; ie, cue 1 was associated 26.2% of the time with sun and 73.8% of the

time with rain, cue 2 was associated 44.4% of the time with sun and 55.6% of the time with rain, cue 3 was associated 55.6% of the time with sun and 44.4% of the time with rain, and cue 4 was associated 73.2% of the time with sun and 26.8% of the time with rain. These percentages were calculated from Table 2 by adding, for example, the number of times that cue 1 was associated with sun (column G) and dividing that number by the total number of times that cue 1 appeared ( $11/42 = 26.2\%$ ). The probability structure of this task (determined by the cue-outcome association strengths and cue patterns) was more difficult than those used in other studies to minimize the likelihood that subjects would gain conscious, declarative knowledge of the S-R contingencies in this task.<sup>6,7,13,20</sup>

Subjects were asked to read the instructions on the computer screen and to look up when finished. These instructions explained that they would be seeing 1 to 3 cues on each trial and their task would be to decide whether the cues predicted sunshine or rain. The experimenter informed the subjects that predicting the outcome would feel like guessing but that their performance would gradually improve. On each trial, 1, 2, or 3 of the 4 cues appeared vertically on the computer screen (in 1 of the 14 possible combinations), and subjects predicted sunshine or rain by pressing either the G or the H key, respectively. To minimize confusion, the G key was covered with a sticker of a sun and the H key was covered with a sticker of a rain cloud. Feedback was provided immediately to signal a correct or incorrect response. For each trial, correct responses were followed by the appearance of a smiling face along with the sound of a bell. Incorrect responses were followed by a frowning face and the sound of a groan. The task consisted of 90 trials with a short, 1-minute break after the first 40 trials.

A response was considered correct on a particular trial if the outcome selected was more strongly associated with the cue combination that appeared on that trial. Because of the probabilistic nature of the task, a cue combination was sometimes followed by the less strongly associated outcome. Thus, subjects could have been scored as making a correct response (because they selected the most likely outcome) even though the feedback they received on that particular trial suggested to them that their response was incorrect. In this way, the percentage-correct score reflected how well subjects learned the cue-outcome associations. Because the 2 outcomes occurred equally often, chance performance was 50% correct. The data were not analyzed for trials on which the 2 outcomes were equally associated with the cue combination and on which there was therefore no correct answer (combination 6) (Table 2). Percentage-correct and latency scores were analyzed by averaging across 10 trials in each of 9 successive blocks.

## DECLARATIVE LEARNING AND MEMORY TASKS

### Weather Task Questionnaire

Each subject was administered a 5-item, 4-alternative multiple-choice questionnaire that explicitly inquired about the nature of the cues and feedback, the layout of the screen, and the testing procedure. Proportion-correct scores were derived for each subject.

### Silverman and Eals Location Memory Task<sup>33</sup>

This measure consisted of 1 stimulus card and 2 response cards, each depicting a spatial array of common objects. The stimulus card depicted an array of 27 common objects, including nature items (ie, cat, elephant, bird, and flower), household items (ie, telephone, iron, teapot, and plant), and work-related items (ie, briefcase, hat, and cane). The first response card measuring

memory for object identities depicted an array of the original 27 objects in their original locations and 20 added objects. The second response card measuring memory for object location depicted the original 27 objects, with an exchange between positions of 7 pairs of objects. For the purposes of this study, we focused on the first response card. Subjects were presented with the stimulus card for 1 minute and were given the explicit instruction to try to remember the objects on the page because they would be asked to identify them later. After 1 minute, the stimulus card was removed from sight and subjects were presented with the first response card. The response card was removed after they marked the added objects. Proportion-correct scores were derived for each subject. Errors included total omissions (false negatives) and total commissions (false positives); thus, scores were defined as  $1 - (\text{omissions} + \text{commissions}) / \text{total number of objects}$ .

## Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence<sup>31</sup> was used to estimate full-scale IQ in the children and adults. It is a short and reliable measure of intelligence, consisting of 4 subtests: vocabulary, block design, similarities, and matrix reasoning. It was considered an indirect measure of declarative memory functioning because each subtest requires an intact, flexibly accessible, and relational memory for the facts learned, and these are the defining characteristics of declarative memory functions.<sup>8,34</sup> Administration of the 4 subtests yields verbal, performance, and full-scale IQ scores for each subject. The full-scale scores were used in our statistical analyses.

## A PRIORI HYPOTHESIS TESTING: WEATHER PREDICTION TASK

The following statistical procedures were performed in SAS version 8.0 (SAS Institute Inc, Cary, NC). A priori hypotheses were tested using mixed models analysis (PROC MIXED) with repeated measures over blocks of trials. Percentage-correct scores were entered as the dependent variable in a linear mixed model. Analyses were performed first in children (age, <18 years) and then in adults (age, 18-59 years) in an attempt to replicate findings from the children. For both models, diagnosis (TS or healthy control) was a between-subjects factor. Covariates included age, sex, and current diagnosis of OCD or ADHD. We entered block as an ordinal variable from 1 to 9 to ensure that performance was modeled as a linear trend across blocks. We also considered for inclusion in the model all 2- and 3-way interactions of diagnoses (TS, OCD, and ADHD), age, sex, and block. Terms that were not statistically significant were eliminated via backward stepwise regression, with the constraint that the models had to be hierarchically well formulated at each step (ie, all possible lower-order terms had to be included in the model, regardless of their statistical significance).<sup>35</sup> Habit learning for each subject in the weather prediction task was quantified by analyzing the linear trend in performance across trial blocks. The hypothesized difference in habit learning between the patients with TS and the healthy control subjects was tested by assessing statistical significance of the diagnosis-by-block interaction. Because we tested this term separately in children and adults, we protected against false positives associated with these 2 comparisons by considering  $P$  values  $< .025$  to be statistically significant in a priori testing.

## EXPLORATORY ANALYSES

### Latency to Response

Subjects who demonstrate learning on habit-learning tasks should become progressively faster at responding (ie, they should

have shorter latency scores) over blocks of trials. With latency defined as the response time for each trial, we compared the changes in latency scores for the TS and control groups by assessing the significance of the diagnosis-by-block interaction.

### Correlation Analyses

The associations of learning with the severity of symptoms, and of learning with IQ estimates, were assessed in correlation analyses. To evaluate these associations, we first quantified learning across the 9 blocks of trials by modeling the percentage-correct scores across blocks as linear trends within each subject. Learning for each subject was thus characterized by the values of the coefficients of these trends in a linear model (ie, larger coefficients indicated better learning).

### Medication and Comorbidity Effects

The effects of comorbid illnesses and medication use on the findings of a priori hypothesis testing were assessed in 2 complementary ways. First, their effects were assessed as statistical covariates in our final model for hypothesis testing, both as main effects and as interactions with trial block. Second, the stability of findings in the absence of these effects was assessed by examining the stability of parameter estimates for the effect of TS on learning in separate models that included either subjects with pure TS (ie, without OCD or ADHD) or subjects with TS who were not taking any medication. Medication effects were assessed separately for any medication use and for use of traditional neuroleptics (haloperidol or pimozide), risperidone,  $\alpha$ -agonists (clonidine or guanfacine), or selective serotonin reuptake inhibitors.

### Declarative Memory Measures

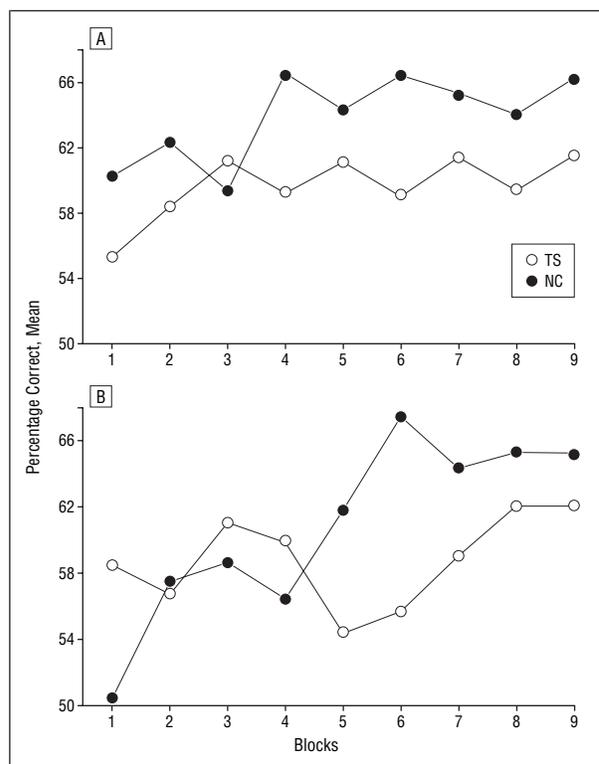
Linear regression was used to compare TS and control subject scores on the weather task questionnaire. Independent *t* tests compared IQ scores and scores from the Silverman and Eals memory task across groups.

## RESULTS

### SUBJECTS

Data were acquired from 55 children (32 subjects with TS and 23 normal control subjects) and 68 adults (24 subjects with TS and 44 normal control subjects). Among the children, the TS and control groups were of comparable ages (mean  $\pm$  SD, 12.38  $\pm$  2.74 vs 12.65  $\pm$  3.16 years;  $t_{66} = -0.34$ ;  $P = .73$ ) and had similar proportions of boys and girls ( $\chi^2 = 1.02$ ;  $P = .31$ ). In the adult sample, the groups were also similarly aged (mean  $\pm$  SD, 35.28  $\pm$  11.29 vs 31.68  $\pm$  12.10 years;  $t_{66} = -0.03$ ,  $P = .97$ ) and had a similar sex composition ( $\chi^2 = 0.26$ ;  $P = .61$ ).

Among the 32 child subjects with TS, current diagnoses included OCD in 7 (21.8%), ADHD in 7 (21.8%), both OCD and ADHD in 6 (18.7%), depressed mood in 3 (9.3%), and oppositional defiant disorder in 8 (25%). In the 24 adults with TS, current diagnoses included OCD in 6 (25%), ADHD in 2 (8%), and both OCD and ADHD in 4 (16.6%). At the time of the study, 39 (70%) of the subjects with TS (24 children and 15 adults) were taking medications. These included stimulants ( $n = 1$  [1.7%]), traditional neuroleptic agents (haloperidol or pimozide;  $n = 3$  [5.3%]), risperidone ( $n = 5$  [8.9%]),  $\alpha$ -adrenergic agonists (clonidine or guanfacine;  $n = 10$  [17.8%]), and selective serotonin reuptake inhibitors ( $n = 20$  [35.7%]).



**Figure 2.** Percentage-correct scores over trial blocks. Shown here are the percentage-correct scores of the patients with Tourette syndrome (TS) and the normal controls (NC) plotted against trial blocks in both the child (A) and the adult (B) populations.

zide;  $n = 3$  [5.3%]), risperidone ( $n = 5$  [8.9%]),  $\alpha$ -adrenergic agonists (clonidine or guanfacine;  $n = 10$  [17.8%]), and selective serotonin reuptake inhibitors ( $n = 20$  [35.7%]).

### A PRIORI HYPOTHESIS TESTING

#### Children

Analysis of the linear trend only in children revealed a significant diagnosis  $\times$  block interaction ( $F_{1,430} = 6.87$ ;  $P < .01$ ; effect size = -2.62). A plot of performance across trial blocks indicated that this effect derived from a relative impairment in learning in children with TS compared with controls (**Figure 2A**).

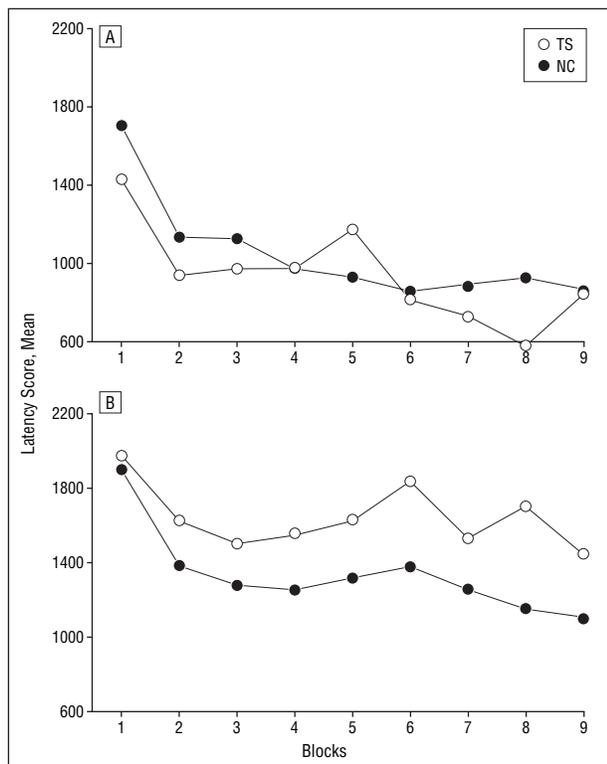
#### Adults

A significant diagnosis  $\times$  block interaction ( $F_{1,540} = 5.58$ ;  $P < .02$ ; effect size = 2.36) was confirmed in the adult sample. Similar to findings in the children, this effect derived from impaired learning in the TS group (Figure 2B).

### EXPLORATORY ANALYSES

#### Latency to Response

Because technical complications interfered with the recording of response times in 29 subjects, this analysis was performed for 94 of the 123 participating subjects. Modeling latency scores also revealed significant diag-



**Figure 3.** Latency scores over trial blocks. Shown here are the latency scores of the patients with Tourette syndrome (TS) and the normal controls (NC) plotted against trial blocks in both the child (A) and the adult (B) populations.

nosis  $\times$  block interactions in both children ( $F_{1,320}=2.16$ ;  $P<.05$ ) and adults ( $F_{8,352}=2.03$ ;  $P<.05$ ). Plots of mean latency scores against trial blocks indicated in each age group that control subjects responded progressively faster over subsequent blocks of trials than did subjects with TS, further suggesting that children and adults with TS were impaired in learning the task (**Figure 3**).

### Correlation Analyses

Pearson correlation coefficients were calculated to assess the association of tic severity in the TS group, measured with the Yale Global Tic Severity Scale score for combined motor and vocal tics, with the coefficients used to define learning. These correlations revealed a significant inverse association ( $r=-0.34$ ;  $P=.01$ ) of tic severity and learning, indicating that those who had more severe tic symptoms had the greatest deficits in habit learning. In contrast, IQ scores were not significantly associated with learning scores among the TS group ( $r=0.03$ ;  $P=.89$ ), suggesting that any individual and group differences in IQ were not confounding results of other analyses.

### Medication and Comorbidity Effects

Attention-deficit/hyperactivity disorder and OCD as comorbid illnesses were not significantly associated with learning either as main effects ( $P>.13$  and  $P>.44$ , respectively) or as interactions ( $P>.47$  and  $P>.90$ , respectively) in either the children or the adults with TS. These results did not change when the actual symptom sever-

ity scores from the Yale-Brown Obsessive Compulsive and the DuPaul-Barkley ADHD rating scales were used as covariates in the models ( $P>.31$  and  $P>.12$  for ADHD and OCD, respectively). To assess further the effects of comorbid illnesses on our findings, we examined the stability of parameter estimates and  $P$  values for the effects of TS in the models that included or excluded all subjects with comorbid OCD or ADHD. The values of these parameters did not change appreciably. In addition, correlation analyses revealed that OCD and ADHD symptom severity was not associated with habit learning in the patients diagnosed as having comorbid OCD ( $r=0.08$ ;  $P=.78$ ) or ADHD ( $r=-0.27$ ;  $P=.48$ ). Together these analyses confirmed that impaired learning in the TS group was not caused by the presence of comorbid OCD or ADHD. In addition, current oppositional defiant disorder as a comorbid illness was not significantly associated with learning as a main effect ( $P>.66$ ) or as an interaction ( $P>.93$ ), indicating that its presence in children with TS was also not the cause of their impaired habit learning.

Habit learning differed significantly in those patients with TS who were taking medications compared with those who were not taking medications (main effect for medication,  $F_{1,48}=8.49$ ;  $P<.001$ ). This effect was caused by the difference in performance between the nonmedicated patients and those taking neuroleptics ( $t_{33}=3.24$ ;  $P=.002$ ). No significant associations with habit learning were noted with the use of  $\alpha$ -adrenergic agonists or selective serotonin reuptake inhibitors. Comparing the performance of the nonmedicated patients with that of the healthy controls still produced a significant diagnosis  $\times$  block interaction ( $F_{1,91}=2.60$ ;  $P=.008$ ), indicating that medication effects were not responsible for findings of a priori hypothesis testing. Comparing the medicated patients with the healthy controls did not yield a significant diagnosis  $\times$  block interaction ( $P=.61$ ), indicating that performance of the medicated patients was similar to that of the healthy controls. Furthermore, partial correlation analyses in which medication was a covariate still revealed a significant inverse association of tic severity scores with learning coefficients ( $\beta=-.39$ ;  $P=.003$ ), indicating that patients with more severe symptoms had the greatest deficits in habit learning, regardless of medication use.

### Declarative Memory Measures

A linear regression model comparing TS patients with controls on the weather task questionnaire revealed a trend toward poorer performance in the TS group (mean  $\pm$  SD,  $70.0\% \pm 2.6\%$  vs  $77.8\% \pm 4.4\%$ ;  $F_{1,82}=3.31$ ;  $P=.08$ ). However, this trend derived from the effects of comorbid OCD or ADHD in that the trend was absent when individuals with these comorbidities were excluded from the analyses ( $t_{83}=1.03$ ;  $P=.31$ ). Independent-samples  $t$  tests comparing the TS and normal control subjects revealed no significant differences between groups on the Silverman and Eals Location Memory Task in either the children ( $t_{85}=-0.65$ ;  $P=.51$ ) or the adults ( $t_{77}=-0.98$ ;  $P=.33$ ). Similarly,  $t$  tests revealed no significant differences across groups on IQ (children:  $t_{56}=-0.63$ ;  $P=.53$ ; adults:  $t_{52}=-1.61$ ;  $P=.11$ ), which remained true when the pa-

tients with the comorbid illnesses of OCD and ADHD were eliminated from the analyses (children:  $t_{45} = -0.03$ ;  $P = .98$ ; adults:  $t_{32} = -1.63$ ;  $P = .11$ ). Taken together, these analyses suggest that adults and children with TS in general perform normally on declarative memory tasks.

## COMMENT

Both children and adults who have TS were impaired in a probabilistic classification learning task that has previously been shown to depend on the functional integrity of the neostriatal system for habit learning.<sup>6,7</sup> Compared with healthy control subjects, patients with TS did not improve in task performance, measured either by improved prediction accuracy or by improved reaction times over trial blocks. Learning was significantly and inversely associated with the severity of tic symptoms, indicating that subjects with TS who had more severe symptoms were proportionately more impaired in habit learning. Although the association of diagnosis with impaired habit learning does not prove that impairments in striatally based habit learning cause tics, the association of symptom severity with learning scores does provide strong circumstantial evidence that impaired habit learning is centrally involved in the pathophysiology of TS. Patients with TS were not impaired on measures requiring intact functioning of declarative memory, a system that requires the structural and functional integrity of the hippocampus and other medial temporal lobe structures. These findings suggest that deficits in memory functioning in patients with TS are relatively specific to the striatal learning system.

Previous habit-learning studies have employed transfer tests, such as questionnaires, as indexes of declarative memory functioning. Results of those studies have indicated that patients with Parkinson disease, Huntington disease, and TS lack awareness of the algorithm learned in the weather prediction task, but their explicit memory of the testing situation remains intact.<sup>6,7,13</sup> Few studies, however, have systematically and comprehensively assessed declarative memory functions in individuals with TS. One large study of adolescents with TS did report normal performance in declarative memory functions assessed with the Adult Memory and Information Processing Battery of story recall, the Rey Auditory Verbal Learning Test, and the Visual Reproduction Test of the Wechsler Memory Scale.<sup>36</sup> More extensive and detailed assessments of declarative memory functions are needed to determine whether the learning deficits observed among patients with TS are indeed specific to striatally based systems for habit learning.

Our findings replicate and expand on a previous preliminary report of impaired habit learning in 10 children with TS.<sup>20</sup> Ours was a much larger sample than that of the previous study, and it included adults as well as children. We found that habit learning was deficient in subjects with TS from both age groups, suggesting that impairments in habit learning are not likely to reflect simply the presence of an immature cognitive processing skill that improves later in life. In addition, we used a more difficult probability structure in the task than has been

used in previous studies to minimize the likelihood that declarative memory functions could be used to improve performance in later trials.<sup>6,7,13,20</sup>

Our behavioral findings provide a useful conceptual framework for understanding the anatomical and functional abnormalities of the basal ganglia in TS that have been reported previously.<sup>2-4,18</sup> Deficits in habit learning, for example, seem likely to be a functional consequence of the reduced caudate nucleus volumes previously reported in children and adults with TS.<sup>4,37</sup> They are also consistent with findings from a functional imaging study that demonstrated disturbances in subcortical activity during the voluntary control of tics, disturbances that were directly proportional to the severity of tic symptoms measured clinically outside of the scanner.<sup>38</sup> Based on regional patterns of activation and the known connectivity within corticostriatal-thalamocortical circuits, this functional imaging study concluded that the disturbances in controlling tics likely originated in or around the caudate nucleus.

## POTENTIAL CONFOUNDING EFFECTS

The associations of learning with both diagnosis and symptom severity persisted even when excluding medicated subjects from the analyses, suggesting that medication use did not contribute to our main findings. The use of neuroleptic agents, however, was associated with better habit learning in the subjects with TS who were taking them. This finding suggests that tic medications may improve not only tic symptoms but also habit learning. Study of habit learning before and after initiation of medication use is warranted in future clinical trials to help clarify whether neuroleptic use can improve habit learning in persons with TS. We found no evidence that the presence of comorbid OCD or ADHD affected our findings for habit learning, assessed either through statistical covariation for these diagnoses or through the analysis of subgroups of patients with TS who did not have these comorbid illnesses.

## THE NEURAL BASIS OF HABIT LEARNING

The mediation of habit learning by the basal ganglia and the independence of habit learning from declarative learning and memory functions based within medial temporal lobe structures have been demonstrated in both animal<sup>5,10-12</sup> and human studies.<sup>6,7,13</sup> Animal studies have shown, for example, that electrolytic or neurochemical lesions of the dorsal striatum impair performance of habit-learning tasks but not declarative memory tasks, whereas lesions of the hippocampal system impair performance of declarative memory tasks but not habit-learning tasks.<sup>11,39</sup> Patients with temporal lobe amnesia whose performance is impaired in declarative memory tasks tend to learn normally in probabilistic classification tasks,<sup>6,7,13</sup> whereas patients with Huntington and Parkinson diseases who perform normally on tests of declarative memory are impaired at probabilistic classification learning tasks.<sup>5,6</sup> Consistent with the implication from these behavioral findings that habit learning is based within the dorsal striatum, one human functional imaging study has demonstrated increased neuronal activity in the stri-

tum and reduced activity in the hippocampus during habit learning in the weather prediction task.<sup>40</sup> In addition, other human imaging studies of similar tasks of skill learning have also shown activation of the caudate nucleus, confirming the mediation of these tasks by the striatum.<sup>41,42</sup>

Changes in activity of dopaminergic neurons within the striatum are known to contribute to learning in response to reward. Striatal dopamine neurons are sensitive to prediction errors (the discrepancies between outcomes and their predictions). Their firing increases in the presence of unpredicted rewards and decreases in the absence of predicted rewards. These neurons do not fire when rewards occur as predicted, consistent with learning theories in which learning is induced when rewards or reinforcers occur more often than predicted and in which learning is extinguished in the absence of reward.<sup>43,44</sup> Dopamine systems therefore contribute to learning most powerfully when reward contingencies change, ie, when rewards are unpredictable. The weather task requires subjects to make predictions based on cues presented in the current trial and on the feedback, or reward, received after previous trials. However, rewarding feedback is predicated on probabilistic associations with the stimulus cue and not always consistent with the correct prediction or feedback anticipated with the current stimulus. Thus, the rewards in this task are unpredictable, and this unpredictability should provide an important role for dopaminergic firing within the striatum during learning of this task.

Electrophysiological recordings in animals have also elaborated this understanding of striatally based learning. They have shown, for example, that habit learning of complex action sequences is associated with gradual changes in the task-related firing of neural ensembles within the striatum.<sup>45</sup> The new firing patterns stabilize during subsequent performance and consolidation of the learned action sequence. The striatum thus develops a neuronal representation of the action pattern or sequence of movements. Firing is most frequent at the beginning and the end of the action sequence. This change in firing pattern is thought to indicate that each of the behavioral fragments composing the entire action sequence are chunked together within the striatum into a single, coherently executed behavior. Once a chunked action sequence is activated, it tends to execute smoothly and in entirety. Intact dopaminergic innervation seems to be important for these chunking functions of the striatum.<sup>46</sup> The long-term acquisition of memories for habit-learning tasks, similar to the acquisition of all long-term memories, presumably involves the alteration of cellular architecture within the striatum. This may include the modification of dendritic spines, dendritic arborization, or synaptic remodeling, processes that require modification of gene expression and protein production within the cell.<sup>47,48</sup> Whether these presumed ultrastructural correlates of learning are visible macroscopically in the striatum is unknown.

#### HABIT LEARNING IN THE PATHOPHYSIOLOGY OF TS

Our finding that habit learning is impaired in children with TS and the replication of these findings in adults with TS suggest that the chunking together of action se-

quences is dysfunctional in persons of all ages who have TS. It has long been noted that the sudden, repetitive, and jerking movements that constitute tics appear to be fragments of normal motor and vocal behavioral repertoires.<sup>1,17,49</sup> The presence of impaired habit learning in persons with TS suggests that these behavioral fragments are not concatenated together properly but instead occur in isolation and independently of normal S-R contingencies.<sup>50</sup> Trait-like abnormalities previously documented in the structure and function of the striatum in persons with TS<sup>2,4</sup> may impair the concatenation or chunking of these behavioral fragments into coherent action sequences that are executed smoothly as habits. The disturbances in habit learning may not produce the cellular changes within the striatum that support long-term learning; deficient habit learning might thereby produce the macroscopic hypoplasia of the caudate nucleus that has been observed *in vivo* in the brains of children and adults with TS.<sup>4</sup>

In addition, large, controlled imaging studies of individuals with TS suggest that additional disturbances in frontostriatal projections may release from regulatory control this trait-like predisposition for behavioral fragmentation that is based within the striatum.<sup>4,51,52</sup> Thus, the tics of TS seem to be the product of core disturbances in the structure and function of the striatum that predispose an individual to impairments in habit learning and to the expression of fragmented motor and vocal behaviors. These predispositions to tic behaviors may then be released from regulatory influences of the prefrontal cortex.<sup>52,53</sup>

Medication use, particularly the long-term use of dopamine receptor antagonists,<sup>1,51</sup> was associated with better performance on the habit-learning task. In apparent contrast, acute posttraining peripheral<sup>54-57</sup> and intradorsal striatal<sup>11,58</sup> administration of dopamine agonists has been shown to enhance habit-memory formation in rats. The effects of long-term administration of dopaminergic agents, however, often differ from the effects of acute administration.<sup>59</sup> Long-term use of dopamine receptor blockers, for example, decreases the overall firing rate of dopamine neurons<sup>60</sup> while increasing burst firing in response to prediction errors. Decreased background firing and increased burst firing associated with long-term dopamine blockade may together increase the signal-to-noise ratio of the information carried to the dorsal striatum by bursting dopaminergic neurons during reward-based learning. Thus, we speculate that the long-term use of dopamine antagonists may have contributed to relatively better performance in subjects with TS by enhancing the salience of dopamine bursting as these subjects learned the task. This interpretation is perhaps consistent with previously reported clinical and experimental evidence for disturbances of dopaminergic transmission in the striatum of individuals with TS,<sup>1,52,61-66</sup> and it further suggests that the impaired habit learning detected in our patients with TS may have its basis in dysfunction of the nigrostriatal dopamine system. Consistent with this suggestion, 6-hydroxydopamine lesions of the nigrostriatal pathway impair learning in lower animals.<sup>67,68</sup> Alternatively, the observed medication effect could have arisen from normal dopaminergic neurons interacting with other abnormal striatal tissues.

## FUTURE DIRECTIONS

The findings from this study have important implications for our understanding of the behavioral basis and pathophysiology of TS in children and adults. They also help us to understand better the role of the basal ganglia and frontostriatal circuits in habit learning. This line of work is the first to implicate directly in TS a deficit in a specific and discrete cognitive-behavioral system, the neostriatum-based habit-learning system. Furthermore, animal models permit study of the neural and molecular bases of habit learning. By extension, these models should permit study of the neural and molecular basis of the tic-like behavioral fragments that fail to enter the unified action sequences of S-R or habit learning. The potential availability of both animal models and human paradigms for studying habit learning therefore offers the exciting promise not only of improving our knowledge of the neurobiological origins of TS but also of developing novel therapeutics through bona fide translational research programs and methods that are not available to human clinical studies alone. Future research should evaluate the effects of medication and behavioral interventions, such as dopamine blockers and habit-reversal therapy,<sup>69</sup> on habit learning in randomized clinical trials.

Accepted for Publication: June 11, 2004.

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**Funding/Support:** This study was supported in part by grants MH01232, MH59139, and MH068318 from the National Institute of Mental Health, Bethesda, Md; the Suzanne Crosby Murphy Endowment at Columbia University College of Physicians and Surgeons, New York, NY; and the Thomas D. Klingenstein & Nancy D. Perlman Family Fund, New York, NY.

**Acknowledgment:** We are grateful to James Leckman, MD, Robert King, MD, Larry Scahill, PhD, and Diane Findley, PhD, as well as the Tourette Syndrome Association, for their help with patient recruitment.

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