

## Selective Corticostriatal Dysfunction in Schizophrenia: Examination of Motor and Cognitive Skill Learning

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It has been suggested that patients with schizophrenia have corticostriatal circuit dysfunction (Carlsson & Carlsson, 1990). Skill learning is thought to rely on corticostriatal circuitry and different types of skill learning may be related to separable corticostriatal loops (Grafton, Hazeltine, & Ivry, 1995; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999). The authors examined motor (Serial Reaction Time task, SRT) and cognitive (Probabilistic Classification task, PCT) skill learning in patients with schizophrenia and normal controls. Development of automaticity was examined, using a dual task paradigm, across three training sessions. Patients with schizophrenia were impaired at learning on the PCT compared to controls. Performance gains of controls occurred within the first session, whereas patients only improved gradually and never reached the performance level of controls. In contrast, patients were not impaired at learning on the SRT relative to controls, suggesting that patients with schizophrenia may have dysfunction in a specific corticostriatal subcircuit.

*Keywords:* schizophrenia, corticostriatal circuits, skill learning, automaticity,

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There is a longstanding hypothesis that the pathophysiology of schizophrenia is related to dysfunction of corticostriatal circuits (e.g., Kleist, 1960). There are structural abnormalities in the basal ganglia in patients with schizophrenia (Buchsbaum, 1990) as well as neurochemical imbalances in the corticostriatal circuits (Carlsson & Carlsson, 1990). In addition, corticostriatal dysfunction can account for some key neuropsychological deficits, such as impaired volition and planning, found in patients with schizophrenia (Frith, 1987; Robbins, 1990; Pantelis et al., 1997). However,

corticostriatal circuits have been relatively understudied in schizophrenia, particularly in comparison to the extensive literature on frontal and temporal functions.

Corticostriatal circuitry is characterized by several anatomically and functionally discrete loops (Alexander, DeLong, & Strick, 1986; Lehericy et al., 2004). Frontal lobe regions project to distinct regions of the neostriatum, from the neostriatum neurons project to the globus pallidus (GP), from the GP to the thalamus, and from the thalamus back to frontal regions. The same general architecture

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describes all loops, but it has been proposed that dysfunction in specific subloops may account for distinct neuropsychiatric symptoms (Mega & Cummings, 1994; Middleton & Strick, 2000). The cognitive deficits and symptoms of schizophrenia differ from those observed in other conditions known to affect corticostriatal function, such as Parkinson's and Huntington's diseases, and a different pattern of corticostriatal deficits would be expected in patients with schizophrenia. If particular corticostriatal loops were selectively impaired in schizophrenia (e.g., Pantelis et al., 1997), various tasks that depend on different loops would be differentially affected in schizophrenia. For example, learning motor skills and learning cognitive skills appear to rely on different corticostriatal loops, and may not be affected to the same degree in schizophrenia.

The circuit primarily involved in motor behavior originates in motor areas and includes the supplementary motor area (SMA), putamen, GP, and thalamus. Damage to this circuit is associated with akinetic rigidity in Parkinson's disease (Jellinger, 2002) and neuroimaging studies using the Serial Reaction Time task (SRT, Grafton, Hazeltine, & Ivry, 1995; Poldrack et al., 2005) or Rotor Pursuit tasks (Grafton et al., 1992) have implicated this loop in motor skill learning. In several studies using Pursuit Rotor and Mirror Tracing tasks, patients with schizophrenia and controls show similar learning (Huston & Shakow, 1949; Goldberg et al., 1993; Granholm, Bartzokis, Asarnow, & Marder, 1993; Clare, McKenna, Mortimer & Baddeley, 1993; Kern, Green, & Wallace, 1997; Weickert et al., 2002; Scherer, Stip, Paquet & Bedard, 2003; Bedard et al., 2000; but see Schwartz, Rosse, Veazey, & Deutsch, 1996; Bedard, Scherer, Delorimier, Stip, & Lalonde, 1996). Results from studies using the SRT are more mixed. Patients with schizophrenia, mainly treated with atypical antipsychotics, show rates of motor sequence learning similar to controls on SRT-like tasks (Perry, Light, Davis, & Braff, 2000; Stevens et al., 2002), whereas patients treated with typical antipsychotics show impairment relative to controls and olanzapine treated patients (Stevens et al., 2002). Schwartz, Howard, Howard, Jr., Hovaguimian, and Deutsch (2003) used an Alternating Serial Reaction Time (ASRT) task and found that patients learned a repeating pattern, but learned less than controls. Furthermore, there was a relationship between working memory and pattern acquisition on this task in controls. We predict that patients with schizophrenia should be able to perform normally on the SRT task used here unless treatment with typical antipsychotics compromises striatal functioning.

Cognitive skill learning, as measured by tasks such as the Probabilistic Classification Task (PCT), involves activity in cognitive corticostriatal circuits including the caudate nucleus/dorsolateral prefrontal cortex (DLPFC) and ventral striatum/orbitofrontal cortex (VS/OFC) (Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Poldrack et al., 2001; Aron et al., 2004). Studies with brain damaged patients have shown that PCT performance depends critically on the neostriatum; patients with medial temporal lobe (MTL) damage are able to learn, whereas patients with basal ganglia damage are impaired (Knowlton, Squire, & Gluck, 1994; Knowlton, Mangels, & Squire, 1996; Knowlton, Squire, Paulsen, Swerdlow, & Swenson, 1996).

The tasks most commonly used to assess cognitive skill learning in psychiatric patients are the Tower of Toronto or Tower of Hanoi tasks. Generally, patients with schizophrenia show deficits on these tasks (Gimenez et al., 2003; Schroder, Tittel, Stockert, & Karr, 1996; Purdon, Woodward, Lindborg, & Stip, 2003). How-

ever, these tasks require substantial executive control resources and may therefore be poor measures of cognitive procedural learning, per se (Winter, Broman, Rose, & Reber, 2001, but see Goldberg, Saint-Cyr, & Weinberger, 1990). Due to its simpler task demands, the PCT may be a better task for assessing striatal dysfunction. As with the SRT, prior studies of PCT performance in patients with schizophrenia have been mixed, with variations in task structure and the medication status of patients playing a role in the findings (Beninger et al., 2003; Keri et al., 2000; Weickert et al., 2002).

One difficulty in comparing cognitive and motor skill learning directly in schizophrenia is the large variations in patient groups across studies. Almost all prior studies of corticostriatal functioning in schizophrenia have assessed only one type of skill learning. Only a few prior studies have attempted to determine if specific corticostriatal circuits are impaired in schizophrenia by assessing performance on several different striatal-dependent tasks. In the present study, we examined motor and cognitive skill learning in the same group of patients with schizophrenia and healthy control participants. In addition, we examined the ability to automate skills. Extended practice of skills typically leads to automaticity, often defined as a level of skill performance where concurrent performance of a secondary task does not interfere with primary task performance (Posner & Snyder, 1975). In a prior study, it was found that with sufficient practice, patients with schizophrenia performed normally on the Multiple Frame Search Task, but still showed deficits relative to controls in a dual task condition, suggesting that they had not automated the task as well as controls (Granholm, Asarnow & Marder, 1996). Therefore, the dual task provides an important complement to more traditional methods for characterizing the degree of skill learning.

The present study tested the hypothesis that patients with schizophrenia would show impaired cognitive skill learning because it relies more upon corticostriatal circuits involving the caudate nucleus/DLPFC and VS/OFC that are dysfunctional in schizophrenia. In contrast, the same patients should be unimpaired at motor skill learning because it relies more on the motor (motor cortex/putamen) circuit, predicted to be relatively functional in schizophrenia. These hypotheses were tested using two tasks, the PCT and the SRT, to assess cognitive and motor skill learning ability. These tasks have been used extensively in other patient groups and with neuroimaging, and they were amenable to creating identical training conditions across tasks. Additionally, we examined the extent to which skill learning was automated after extensive practice by comparing performance under single and dual task conditions.

## Method

### Participants

Thirty-five participants, 18 outpatients meeting *DSM-IV* criteria for chronic schizophrenia and 17 healthy controls, participated in the study. All participants provided informed consent in accordance with UCLA's Office for the Protection of Research Subjects. Twelve patients were recruited from the UCLA Aftercare Research Clinic (see Nuechterlein et al., 1992 for details) and six patients were recruited from outpatient clinics at the West Los Angeles VA Medical Center (see Marder et al., 2003 for details). A diagnosis of schizophrenia was established using the Structured

Clinical Interview for *DSM-IV* (SCID, First, Gibbons, Spitzer, & Williams, 1996). Patients with a history of drug abuse were excluded from study. Control participants were recruited with fliers posted at UCLA, local community centers, and area community colleges. Controls were screened for reports of treated psychiatric disorders including psychosis, attention deficit disorder and learning disabilities, traumatic brain injury, drug abuse, and neurological disorders that affect cognitive functioning. All participants were paid \$15/hour for participation and reimbursed for transportation costs.

The control group was selected to match the patient group on age and education (see Table 1). *T* tests confirmed that the groups did not differ significantly in age and education. In addition the groups did not differ on an estimate of general level of intellectual function, based on a test of receptive vocabulary, the Peabody Picture Vocabulary Test (PPVT-III; Dunn & Dunn, 1997 –3rd ed.; see Table 1). The schizophrenia group had more males than the control group (see Table 2 for detailed patient characteristics).

### Apparatus

The SRT and PCT were administered on a Macintosh PowerBook G4 and the tasks were programmed in the MatLab environment using the Psychophysics Toolbox (Brainard, 1997). Responses were made on a custom button box containing a row of four buttons.

### Design

Participants completed three training sessions for each skill learning task. Performance of the two tasks alternated, and the order of performance was counterbalanced across participants (except for one participant who completed three of one, then three of the other task due to computer problems). The PPVT-III was administered after completion of the skill learning tasks. Each training session lasted approximately one hour, and the six hours of training were completed within one week and distributed over two or three days.

### Serial Reaction Time Task

In the SRT (Nissen & Bullemer, 1987), participants are presented with a 4-alternative spatial choice reaction time task. A

visual target ('X') was presented in one of four screen locations for 1 sec, with a 0.25 sec interstimulus interval. Participants were asked to respond as quickly and accurately as possible to the target by pressing one of four spatially compatible buttons. On some sets of trials, unbeknownst to participants, the locations occurred in a particular sequence, whereas locations were presented in a pseudorandom order on other sets of trials. With practice, participants generally respond more quickly on sequence than pseudorandom trials, and the amount of improvement afforded by the implicit sequence is a measure of motor skill learning. On sequence trials, stimulus locations followed a second-order conditional sequence, meaning that every individual location and every first-order transition appeared equally often. The specific order used was 324123143421. On trials following a pseudorandom order, target orders were random, but constrained such that all individual targets appeared as often as in the sequence blocks (Reed & Johnson, 1994). This design ensured that differences in behavior between sequence and random blocks reflected the learning of higher-order sequential knowledge. Each block included 60 consecutive sequence trials and 60 consecutive pseudorandom trials. Whether sequence or random trials were presented first in a block was counterbalanced across participants. During each SRT session, participants performed 12 120-trial blocks of the SRT task.

### Probabilistic Classification Task

In the PCT, participants gradually learn cue-outcome associations. On each trial a stimulus is presented, and the participant must select one of two possible outcomes. The feedback provided is probabilistic, so no stimulus always predicts an outcome. In the PCT version used here, participants were told to pretend they worked in an ice cream shop and that they would learn to predict whether each "customer" preferred chocolate or vanilla ice cream (Shohamy et al., 2004; Aron et al., 2004). On each trial a toy figure (Mr. Potato Head, Playskool/Hasbro), wearing one, two, or three out of four features (bowtie, mustache, glasses, and hat) was presented. This resulted in 14 stimulus combinations. Stimulus presentation lasted 3 seconds, during which participants indicated whether they predicted a chocolate or a vanilla ice cream preference with a key press. Feedback was given in the form of the figure appearing with a chocolate or vanilla ice cream cone in its hand.

Table 1  
*Characteristics of Controls and Schizophrenia Patients*

	Schiz pts	Controls	t-stat
<i>N</i>	18	17	
Male/female	13/5	8/9	
Age	26.72 (4.34)	27.24 (6.92)	$t(33) = .264, p = .793$
Education	14.03 (2.15)	13.88 (2.85)	$t(33) = -.171, p = .865$
PPVT-III score	101.83 (13.76)	105.80 (14.71)	$t(31) = -.799, p = .430^\dagger$
Chlorpromazine 100 mg/d Dose Equivalence	294.12 (258.38)		
BPRS scores <sup>‡</sup>			
Positive	10.28 (4.65)		
Negative	6.33 (1.88)		
Manic-excitement	8.61 (4.84)		
Depression-anxiety			

*Note.* Table displays means. Standard deviations are in parentheses.

<sup>†</sup> PPVT-III scores were not obtained for two controls.

<sup>‡</sup> BPRS scores for one patient were from the 18-item scale instead of the 24-item scale.

Table 2  
Patient Characteristics and Medication

Pt.	Test date	Age	Sex	Dose	Medication	BPRS					SANS			SAPS		
						Date	P	N	ME	DA	Date	N	Sum	Date	P	Sum
5	12/10/02	22	M	300	Risperidone 6 mg Benztropine 4 mg Divalproex 250 mg tid	12/17/02	15	10	9	4	11/18/02	15	16	3/11/03	8	13
6	12/13/02	24	M	375	Risperidone 7.5 mg Benztropine 2 mg Hydroxyzine 50 mg qhs	1/13/03	8	6	6	11	1/31/02	3	4	7/28/04	0	0
7 <sup>a</sup>	12/16/02	21	M	150	Risperidone 3 mg	12/4/02	8	7	7	7	3/7/03	11	11	3/2/03	2	4
9	12/19/02	29	F	0	Bupropion 200 mg bid Diphenhydramine 25 mg	1/8/03	16	4	24	12	1/14/02	5	5	7/12/05	0	0
10	12/27/02	26	M	1200	Clozapine 600 mg	2/13/03	10	8	6	13	11/29/04	7	10	11/29/04	2	2
17	02/27/03	25	M	375	Risperidone 7.5 mg	3/13/03	9	6	8	7	3/13/03	8	9	3/13/03	4	5
19	03/18/03	26	M	300	Risperidone 6 mg Benztropine 2 mg Fluoxetine 60 mg qhs Bupropion 100 mg bid Diphenhydramine 25 mg Prochlorperazine 10 mg	3/25/03	13	9	7	18	2/24/03	2	2	7/1/05	7	8
21 <sup>a</sup>	03/27/03	30	F	200	Ziprasidone 120 mg Sertraline 150 mg qhs Propranolol	4/3/03	6	6	6	8	3/4/03	4	4	6/9/03	1	1
22	03/31/03	24	M	200	Olanzapine, 10 mg Venlafaxine, 75 mg	3/1/04	5	5	6	5						
23	04/07/03	33	M	50	Risperidone 1 mg Citalopram, 40 mg	2/26/03	12	5	8	8	3/19/03	6				
24 <sup>b</sup>	04/11/03	31	M	400	Olanzapine 20 mg Lithium, Lipitor, Albertol	4/15/03	11	6	12	8	4/15/03	6				
25	04/14/03	34	M	200	Ziprasidone 120 mg Trazodone 100 mg	8/14/02	4	4	3	5	8/14/03	8				
26 <sup>ab</sup>	04/28/03	32	M	200	Olanzapine 10 mg Lolostatin, Quetiapine	4/1/03	17	10	8	14	4/1/03	10				
29	07/07/03	31	M	100	Olanzapine 5 mg	8/20/03	13	4	8	5	8/20/03	6				
30	07/15/03	27	F	150	Risperidone 3 mg Benztropine 2 mg	8/19/03	7	7	6	12	10/7/02	3	7	10/13/04	2	3
32 <sup>b</sup>	06/24/03	23	F	100	Risperidone 2 mg	6/23/03	6	6	6	8	10/21/03	3	3	10/21/03	1	1
33	09/02/03	23	M	400	Risperidone 8 mg	8/21/03	20	6	17	13	6/24/03	12	13	11/13/03	6	11
34	09/08/03	20	F	300	Risperidone 6 mg Citalopram 20 mg qhs Benzotropine 4 mg	9/8/03	5	5	8	4	9/12/03	4	6	9/12/03	0	1

Note. Dose is Chlorpromazine equivalent dose. For BPRS scores: P = positive symptom, N = Negative symptom, ME = Manic-Excitement, DA = Depression-Anxiety subscales. For SANS and SAPS: N = Negative symptom score, P = positive symptom score, Sum = Summary scores for each scale.  
<sup>a</sup> Excluded from PCT. <sup>b</sup> Excluded from SRT.

The interval between trials was 500 ms. Cue strengths were such that the overall probability associating each feature with chocolate was .756, .575, .425, and .244 across 100 trials (See Table 3 for details). A correct answer was predicting the outcome most strongly associated with a figure. Because the association was probabilistic, a participant could make a correct prediction and receive feedback inconsistent with that prediction. During each PCT session participants performed 12 50-trial blocks.

### Secondary Task

Participants performed both tasks under single-task and dual-task conditions. Under single-task conditions, only the SRT or PCT was performed. Under dual-task conditions, the SRT or PCT was performed concurrently with a tone-counting task. Participants counted the number of high-pitched (1000 Hz) tones occurring among low-pitched (500 Hz) tones during each dual-task block

and reported the counts by entering the number using a keyboard. During the SRT, a single tone was presented each time a visual target appeared; across participants, 50–70% of the tones were high-pitched. For the PCT between one and three tones were played during each stimulus presentation and across participants, 30–70% of the tones were high-pitched. For both tasks, blocks 3, 4, 9 and 10 in each session were performed under dual-task conditions and all other blocks were performed under single task conditions.

### Psychometric Matching

A differential deficit on the PCT and SRT is predicted in this study. However, apparent differential deficits observed in patients with schizophrenia frequently reflect the relative psychometric discriminating power of tasks rather than true differences between abilities (Chapman & Chapman, 1978, 1989, 2001; Miller, Chap-

Table 3  
*Relation Among Stimuli, Features, and Outcomes*

Stimulus	Hat	Glasses	Mustache	Bowtie	Frequency	P(Choc)
1	0	0	1	1	9	0.889
2	0	0	0	1	14	0.857
3	0	1	0	1	6	0.833
4	0	1	1	1	4	0.75
5	1	0	1	1	3	0.667
6	0	0	1	0	8	0.625
7	0	1	1	0	6	0.5
8	1	0	0	1	6	0.5
9	0	1	0	0	8	0.375
10	1	1	0	1	3	0.333
11	1	1	1	0	4	0.25
12	1	0	1	0	6	0.167
13	1	0	0	0	14	0.143
14	1	1	0	0	9	0.111
	0.244	0.425	0.575	0.756	100	0.5

*Note.* 1 denotes the presence of a cue. The 14 stimuli were composed of one to three of four features: bowtie, mustache, glasses, and hat, and each stimulus occurred with a certain frequency and probability across each set of 100 trials. The bottom row lists the overall  $P(\text{Choc})$  for the four features across all stimuli.

man, Chapman, & Collins, 1995). Demonstrating a differential performance deficit requires proving that the control task (the one predicted not to produce deficits in patients) has adequate distributional properties (e.g., no attenuated range) and reliability comparable to the task hypothesized to detect performance deficits in patients. Specifically, we attempted to confirm that performance differences on the PCT and absence of performance deficits on the SRT would not merely reflect superior psychometric properties of the PCT. Because the SRT and PCT use different measurement units (response latency vs. accuracy), a method of comparing the psychometric properties of these two tasks “in which manipulated variables are matched rather than task themselves” (Strauss, 2001, p. 8) was used. This approach requires identifying a manipulation that produces equivalent effects on performance and reliability across the two tasks in a standardization sample. If a manipulation produces equivalent effects on both tasks, the net effect of distributional properties of the two tasks is comparable. In this study, the manipulated variable was the amount of practice on each task.

To operationalize the practice benefit, a series of within subject  $t$  tests were conducted, comparing the performance of the healthy controls on the initial trial block and later trial blocks for both the SRT and PCT.  $T$  scores were used as standardized estimates of effect sizes. Next, estimates of the reliability of the trial blocks used to assess learning effects were obtained to rule out the possibility that one manipulated variable was more reliable than the other. Coefficient alphas were used to estimate the reliability of PCT and SRT performance on the trial blocks that were comparable in learning effects. Because the dependent variable for the PCT is dichotomous, coefficient alpha was computed by dividing the 50 trials in each trial block into subsets of 10 trials. Each subunit could have scores from 0–10. Coefficient alpha was computed for the five subunits within each trial block. For the SRT coefficient alpha was computed in an equivalent fashion, by chunking trial blocks into five subunits and using the median RT

for each subunit. Given the respective structures of the tasks, the reliability of the SRT was expected to be greater than that of the PCT. Trials on the SRT are quite homogeneous, whereas the number of cues varies from trial to trial on the PCT. In addition, on the PCT there are both floor and ceiling effects that attenuate the variance because participants will get 50% of the trials correct by chance, and the maximum level of performance is 100% correct. In contrast, on the SRT the response latency scores are continuous, but skewed.

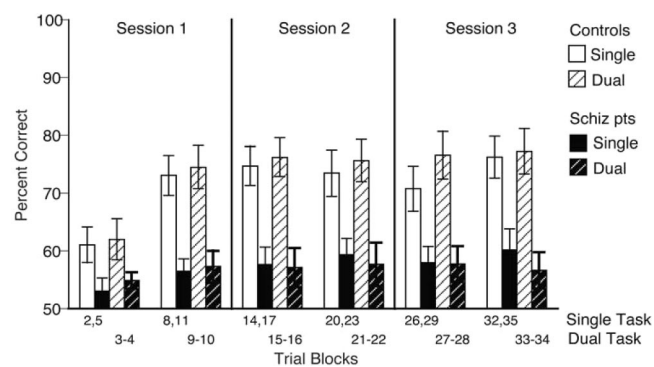
### Exclusion of Participants

One control participant was excluded from all data analysis due to possible language impairment (suggested by an Estimated Verbal IQ of 74.4 ( $>2 SD$  below mean) from the PPVT-III). Three controls and two patients were excluded from analyses of the SRT and one control and three patients were excluded from the PCT analyses because of equipment failures. One additional patient was excluded from analysis of the SRT due to low accuracy (34% across the third session; see Table 2).

### Results

PCT and SRT data were analyzed using a mixed-effects general linear model, with computations performed by SAS PROC MIXED. The experimental design included unequal numbers of single and dual task trial blocks, as well as training across multiple days, allowing between- and within-session improvement. Therefore the statistical model included a between-subject factor representing group membership, and within-subject factors for session (fixed effect, modeled categorically) and trial block (random effect per subject, modeled linearly). The session factor modeled session differences; its interaction with the block factor modeled differing change rates across sessions; the interaction of these factors modeled their differing patterns between patients and control participants. An additional intersubject factor modeled the differences between single and dual trials, as did its interaction with other factors.

Figure 1 illustrates the performance of the patients with schizophrenia and control participants across PCT trials. As expected



*Figure 1.* PCT performance of controls and schizophrenia patients. A subset of training blocks is shown. Each bar represents performance collapsed across two blocks. The two dual task blocks at the beginning and end of each training session are collapsed, and the two single task blocks surrounding dual task blocks are collapsed as well. Error bars represent the standard error of the mean.

from the figure, percent correct on the PCT showed significant main effects for group,  $F(1, 1028) = 97.82, p < .0001$  and session,  $F(2, 1028) = 27.66, p < .0001$ ; there were significant two-factor interactions between group and session,  $F(2, 1028) = 8.99, p < .001$  and block and session ( $F(2, 1028) = 11.42, p < .0001$ , and a significant three-factor interaction among group, session, and block,  $F(2, 1028) = 5.48, p = .004$ . Inspection of estimated effects confirmed the pattern evident in Figure 1, rapid and diminishing growth within and across the sessions for the control participants, and slower growth for the patients accounted for the significant interactions. The three-way interaction was further investigated with separate ANOVAs for each session. In session 1, there was an interaction between group and block ( $F[1, 308] = 2.86, p = .006$ ), whereas only the main effect of the group was significant in Sessions 2 and 3. A series of  $t$  tests confirmed that the interaction in Session 1 was due to a difference between groups that emerged midway through Session 1 [ $p > .1$  on blocks, 1,2,3;  $p < .05$  on blocks 5,7,8,9,10,11,12;  $p < .1$  on blocks 4,6]. There was no significant effect of the secondary task on performance, and no interaction between group and single versus dual task conditions. A similar analysis of PCT response latency showed significant main effects of session,  $F(2, 1028) = 3.93, p = .02$ , with response times decreasing across training, and of the single versus dual task factor,  $F(1, 1028) = 9.84, p = .0018$  due to a decrease in response times during dual task conditions. There was a significant two-factor interaction between session and the single-dual factor,  $F(2, 1028) = 3.36, p = .035$ . In the single task, condition response times exhibited the greatest decrease between session one and two, whereas response times in the dual task conditions decreased gradually across all three sessions.

Figure 2 illustrates performance on the SRT task. SRT data were analyzed by computing the difference between participants' response time performance (median RT) on the random and patterned sequences, and applying the same mixed linear model described above. There was a significant main effect for trial

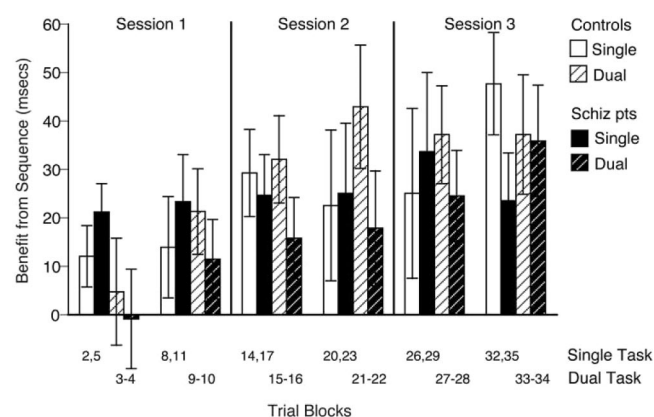


Figure 2. SRT performance of controls and schizophrenia patients. Benefit from sequence is the difference between response times on trials where the order is pseudorandom and trials where there is an ordered sequence. A subset of training blocks is shown. Each bar represents performance collapsed across two blocks. The two dual task blocks at the beginning and end of each training session are collapsed, and the two single task blocks surrounding dual task blocks are collapsed as well. Error bars represent the standard error of the mean.

block,  $F(1, 26) = 16.58, p < .001$ ; together with the absence of other significant effects or interactions, this suggests that the advantage of patterned versus random sequences increased over trial blocks consistently across the subject groups and single and dual task trials, and through sessions. There was no effect of the secondary task on performance. Accuracy was generally high for both controls and patients, but controls were significantly more accurate,  $F(1, 26) = 6.530, p = .017$ , [Controls:  $M = 97.9\%$ ,  $SD = 2.9\%$ , Patients:  $M = 94.5\%$ ,  $SD = 7.3$  across all blocks].

### Evaluating Differential Deficit

In order to confirm that the presence of performance differences on the PCT and absence of performance differences on the SRT were not the result of superior psychometric properties of the PCT, we compared the psychometric properties of the tasks as described in the Methods section. For each task, an amount of practice that produced slightly greater learning effects for the SRT than for the PCT in normal controls was identified (12 trial blocks, as reflected in  $t$ -scores; please see methods for details about this approach). Table 4 reveals that the reliability of the SRT appears to be greater than that of the PCT; coefficient alpha was greater for the SRT for all single task blocks. The effect of practice for the patients with schizophrenia was computed over the same number of practice trials. Patients with schizophrenia showed about the same learning effect as healthy controls on the SRT, but a significantly smaller learning effect than healthy controls on the PCT (see Figure 3). The finding that patients with schizophrenia benefit less from practice on the PCT (the less reliable task), but show about the same learning effect on the SRT (the more reliable task), is not merely a reflection of the poorer psychometric properties of the trial blocks used to assess learning effects on the SRT because: 1) the trial blocks used to assess learning effects across the two tasks were selected to produce equivalent learning effects in healthy control participants, thereby producing comparable distributional properties, and 2) the reliability of the trial blocks used to assess the SRT learning effect was greater than the reliability of the trials used to assess the PCT learning effect.

### Gender Differences

The patient group included more males than the control group (see Table 1). To ensure that gender did not contribute to the results, we included gender as a factor in a  $2$  (male/female)  $\times$   $2$  (patient/control)  $\times$   $2$  (single/dual task)  $\times$   $6$  (block) ANOVA. The block factor consisted of 2 time points within each session: the early and late dual task blocks or the single task blocks surrounding the early and late dual task blocks. In this analysis there was no main effect of gender or any interaction with gender (all  $ps > .1$ ). There was a significant effect of group,  $F(1, 26) = 11.11, p = .003$ , of block,  $F(1, 5) = 8.94, p < .005$ , and a block  $\times$  group interaction,  $F(1, 5) = 3.46, p = .02$ .

### Medication Effects

All but one patient received antipsychotic medications at the time of testing. The medications and dosages for each patient are summarized in Table 2. Because prior studies have found that medications affect some skill learning tasks, we calculated corre-

Table 4  
Coefficient Alpha for SRT and PCT Trial Blocks

Task	Trial Block		All single task blocks		
	1	12	Range	<i>M</i>	<i>SD</i>
PCT	0.712	0.899	0.659–0.904	0.815	0.066
SRT-Random	0.940	0.933	0.870–0.962	0.929	0.019
SRT Sequence	0.929	0.923	0.857–0.977	0.937	0.027

lations between medication dose and PCT performance (where patients were impaired). Patients were receiving a variety of atypical antipsychotic medications and dosages were converted to chlorpromazine equivalent doses (Woods, 2003). The correlation between chlorpromazine equivalence dose and a learning score on the PCT (last—first trial block) was  $-.230$ . Perhaps due to the small sample ( $n = 15$ ), this correlation did not attain statistical significance.

### Discussion

In the present study, patients with schizophrenia were unimpaired at acquiring a motor skill, but were impaired at acquiring a cognitive skill. Patients with schizophrenia acquired sequence learning on the SRT equivalent to controls. In contrast, patients were impaired on the PCT task. Controls reached asymptote by the end of the first session and showed little improvement in the two subsequent sessions, whereas patients only showed slight improvement across three sessions and never reached the level of performance that controls reached. The current pattern of results was not due to greater psychometric discriminability of the PCT. In a comparison of the psychometric properties of the two tasks, we found that the SRT had greater discriminability than the PCT, ruling out a lack of sensitivity of the SRT as the reason for finding a differential deficit. These results suggest that separate corticostriatal loops are differentially impaired in schizophrenia: striatal loops that are more involved in supporting motor functioning are relatively intact, whereas striatal loops with greater involvement in cognitive skill learning are functionally impaired.

The lack of a dual task effect on the PCT and SRT suggests that learning of these two tasks, even in the early stages, is relatively automated in both patients and controls. On dual task blocks in the PCT, RTs decreased more gradually than across single task blocks, but this effect was equivalent in both groups. Previous research has shown that performance of these tasks does not necessarily demand attentional resources (Foerde, Knowlton, & Poldrack, 2006; Hsiao & Reber, 2001). The present study suggests that this may also be true for patients with schizophrenia.

The lack of significant impairment in patients with schizophrenia on the SRT observed in this study is consistent with several previous studies. Perry et al. (2000) found normal learning on a SRT variant in a group of patients with schizophrenia mainly treated with atypical antipsychotic medication. Stevens et al. (2002) found that patients with schizophrenia treated with olanzapine learned a probabilistic sequence task at a similar rate as controls. However, patients treated with typical antipsychotics were impaired relative to controls and olanzapine treated patients. Schwartz et al. (2003) used an Alternating Serial Response Time

test, where elements constituting a sequence were alternated with random elements. Patients with schizophrenia learned the sequence, but controls showed greater sequence learning in both accuracy and response times. Almost 40% of these patients were treated with typical antipsychotic medication. One major difference between typical and atypical antipsychotics is the higher incidence of extrapyramidal side effects, commonly observed with administration of typical antipsychotics. Some studies have pointed to a link between striatal  $D_2$  occupancy of typical antipsychotics and procedural learning deficits (Paquet et al., 2004). It is possible that the studies finding impaired learning on SRT tasks are doing so because of effects due to treatment with typical antipsychotics. In a study of healthy controls, impaired sequence learning was seen after haloperidol administration, whereas d-amphetamine administration improved sequence learning (Kumari et al., 2000), further suggesting that antipsychotics with high  $D_2$  occupancy may cause motor skill learning deficits in patients with schizophrenia, rather than a primary dysfunction of the putamen and motor cortex.

In contrast to the results on the SRT, we found that patients with schizophrenia were severely impaired on the PCT compared to controls. The results of previous studies using the PCT are mixed. Keri et al. (2000) found that patients with schizophrenia performed as well as controls on the PCT. However, the task used in that study included a high proportion of deterministic cues leading to possible ceiling effects. The task was also administered by hand and allowed more time for responding than the present study. Three other studies have used computerized versions of the PCT without including deterministic cues (as in Knowlton et al., 1994, 1996). In two of these studies (Weickert et al., 2002; Keri et al., 2005), patients with schizophrenia performed worse than controls. In both studies the learning rates of controls and patients were equivalent and it was therefore concluded that patients with schizophrenia were not impaired in learning. However, patients with schizophrenia never reached the same levels of performance as controls. In the study by Weickert et al. (2002), controls

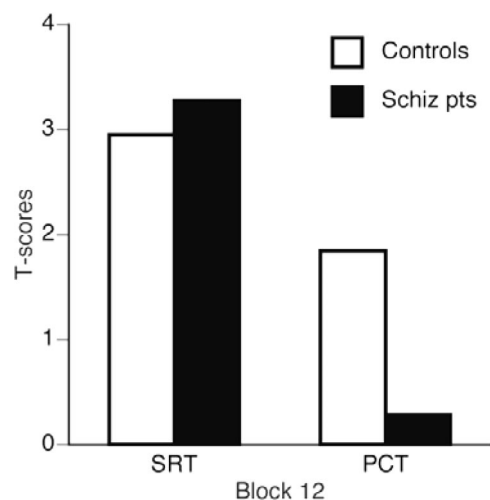


Figure 3. Learning effects on PCT and SRT on block 12. An amount of practice that produced slightly greater learning effects (as reflected in t-scores) for the SRT than for the PCT was identified.

performed above chance after 20 trials, whereas patients with schizophrenia did not get above chance until Trial 80, and neither group appeared to improve after Trial 90. Thus, patients with schizophrenia never “caught up” to controls, and overall a pattern similar to that observed in our study was found where patients improved less than controls over a longer period of training. Weickert et al. (2002) concluded that learning was intact and that performance decrements were due to primary prefrontal cortex dysfunction. However, the same result was seen in a subset of patients and controls matched on a putative measure of prefrontal function (Wisconsin Card Sort Test), leaving it unclear how prefrontal deficit could explain the group difference.

As with the SRT, the mixed results on the PCT could be related to treatment with antipsychotic medications. Beninger et al. (2003) compared performance of controls to that of patients with schizophrenia treated with typical or atypical antipsychotic medication. Patients with schizophrenia treated with typical antipsychotic medication were impaired on the PCT, whereas no significant difference was found between patients treated with atypical antipsychotics and controls. In that study, patients were not randomly assigned to medication groups but assigned according to which medication they were currently taking. In two other studies where patients were mainly treated with atypical antipsychotic medication, equivalent learning rates in controls and patients were reported, but in both studies there were overall performance decrements in patients (Weickert et al., 2002; Keri et al., 2005). In the current study, where patients with schizophrenia show severe learning impairment, all were treated with atypical antipsychotic medication. Furthermore, the negative correlation between dose and performance on the PCT, although not significant, could suggest that any relation between medication and performance may not be limited to typical antipsychotic medication. Unfortunately, it is not possible to dissociate the effects of medication and disease severity on striatal dysfunction in studies where schizophrenia patients are treated clinically with antipsychotic drugs. The poorer performance of schizophrenia patients on skill learning tasks may be due to dose related effects on performance, or patients with the most severe symptoms (possibly reflecting more severe striatal dysfunction) may receive higher doses of antipsychotic medications. Future studies in drug naïve populations will be necessary to dissociate these factors.

Corticostriatal dysfunction is implicated in a number of psychiatric conditions. The results of our study suggest a relative sparing of circuits supporting motor skill learning in patients with schizophrenia and highlight the utility of targeted behavioral tests to pinpoint underlying impairments. A dissociation between motor and cognitive loops has been shown in Gilles de la Tourette syndrome patients, suggesting that disorders that affect the corticostriatal system may do so selectively (Marsh, Alexander, Packard, Zhu, & Peterson, 2005). Middleton and Strick (2000) have suggested that impairments in selective output channels of the striatum may account for a variety of psychiatric conditions. Future studies comparing the integrity of functioning of specific loops should further clarify neuroanatomical underpinnings of specific deficits. Further development and validation of behavioral tests are necessary and might lead to discovery of endophenotypes, which will be useful in understanding and developing treatments for complex diseases such as schizophrenia (e.g., Cannon, 2005). Integration of targeted behavioral testing in clinical populations

and neuro-pharmacological investigations in experimental animals are promising venues for progress in developing targeted treatment of disorders such as schizophrenia.

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PS Form 3526, September 2006 (Page 2 of 3)

### **Correction to Foerde et al. (2008)**

In the article, “Selective Corticostriatal Dysfunction in Schizophrenia: Examination of Motor and Cognitive Skill Learning,” by Karin Foerde, Russell A. Poldrack, Barbara J. Knowlton, Fred W. Sabb, Susan Y. Bookheimer, Robert M. Bilder, Don Guthrie, Eric Granholm, Keith H. Nuechterlein, Stephen R. Marder, and Robert F. Asarnow (*Neuropsychology*, 2008, Vol. 22, No. 1, p. 100), the DOI for the supplemental materials was printed incorrectly. The correct DOI is as follows: <http://dx.doi.org/10.1037/0894-4105.22.1.100.supp>