Deficits in probabilistic classification learning and liability for schizophrenia

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ABSTRACT

Patients with schizophrenia show deficits in skill learning. We tested the hypothesis that impaired skill learning is associated with liability for schizophrenia by determining if it is present in non-affected siblings of patients. This study examined cognitive skill learning in adolescent siblings of patients with childhood onset schizophrenia (COS), who are at high genetic risk for the disorder, and age-matched controls. A probabilistic classification task was used to assess cognitive skill learning, which has been shown to be impaired in patients with striatal dysfunction or schizophrenia. Differences between the groups emerged within the first 50 trials of training: the controls showed significant learning while the COS siblings did not. Furthermore, after extended training over 800 additional trials the siblings of COS probands reached a lower level of asymptotic performance than controls. These results suggest that a behavioral impairment in probabilistic classification learning in healthy, unaffected siblings mirrors the deficits seen in patients and thus may reflect genetic liability for the disease

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1. Introduction

There are abnormalities in striatal structure and function in patients with schizophrenia. Patients with schizophrenia have structural abnormalities in the basal ganglia (Buchsbaum, 1990) and neurochemical imbalances in corticostriatal circuits (Carlsson and Carlsson, 1990). The corticostriatal system plays an important role in skill learning (Heindel et al., 1989; Knowlton et al., 1996a; Doyon et al., 2009; Peigneux et al., 2000).

Consistent with the hypothesis that schizophrenia is associated with striatal abnormalities (Buchsbaum, 1990; Buchanan et al., 1993) patients with schizophrenia show impaired performance on cognitive skill learning tasks, including the weather prediction task (WPT; Weickert et al., 2002; Keri et al., 2005; Foerde et al., 2008; Horan et al., 2008). The WPT requires participants to learn the probabilistic associations between visually presented cues and binary outcomes (sunny or rainy weather). On each trial, participants select one of the outcomes based on the cues presented, followed by feedback as to whether they chose the correct outcome.

The patients with schizophrenia included in the above studies were treated with anti-psychotic medications. Alterations in striatal dopamine neurotransmission are a major mechanism of anti-psychotic drugs (Berke and Hyman, 2000). It is possible that the anti-psychotic medications patients with schizophrenia received resulted in impaired striatal function reflected in cognitive skill learning deficits. In prior studies of striatal function in patients with schizophrenia, the effect of schizophrenia on striatal functioning was inextricably confounded with the effects of the anti-psychotic medications used to treat schizophrenia. One way to address this issue is to study the non-psychotic first degree relatives of patients with schizophrenia. These relatives share some of the familial liability to schizophrenia with patients with schizophrenia but since they are not psychotic they are not receiving anti-psychotic medications. Thus, if they show cognitive skill learning deficits those deficits would appear to reflect familial liability to schizophrenia, not the effects of anti-psychotic medication. The present study tests the hypothesis that corticostriatal dysfunction is associated with liability to schizophrenia by testing the non-psychotic siblings of patients with childhood onset of schizophrenia using the WPT. These children were never treated with antipsychotic drugs.

While several studies have found a substantial performance deficit on the WPT in patients with schizophrenia (Weickert et al., 2002; Keri et al., 2005), other studies have demonstrated that the

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rate of learning is reduced as well. Within 100 and 600 trials of training (Horan et al., 2008; Foerde et al., 2008), there is a diminished rate of learning in patients with schizophrenia during acquisition. In a recent study (Weickert et al., 2010), the performance of patients with schizophrenia was compared to their siblings and controls on the WPT. While the patients exhibited a severe learning deficit consistent with previous work, there were no statistically significant performance differences between the controls and siblings of patients with schizophrenia. However, further analysis revealed that when subjects were divided into good and poor learners, the siblings of schizophrenia patients were disproportionately represented in the poor learner group, suggesting that a subset of the siblings were impaired on this task.

Consistent with Weickert et al. (2010), fMRI studies have revealed an underactivation of striatal regions in non-psychotic first-degree relatives of patients with schizophrenia that are similar to those seen in patients with schizophrenia, suggesting that striatal abnormalities may be associated with liability to schizophrenia (Vink et al., 2006; Raemaekers et al., 2005).

In the present study, we tested siblings of individuals with childhood onset schizophrenia (COS). COS is a severe form of schizophrenia that appears clinically continuous with the adult onset form (Asarnow and Asarnow, 1994; Nicolson and Rapoport, 1999). COS may represent a more homogenous disorder than adult-onset schizophrenia, with a more pronounced genetic risk (Asarnow et al., 1977). Patients with COS tend to show the same cognitive deficits, but to a greater extent than patients with adult onset of schizophrenia (Asarnow and Kernan 2009). Relatives of patients with COS may have greater genetic liability for schizophrenia than relatives of adult onset patients, and thus may be more likely to show the cognitive skill learning deficit present in patients with schizophrenia (Asarnow et al., 2001).

Patients with schizophrenia show deficits on other cognitive skill learning tasks such as the Tower of Toronto and the Tower of Hanoi (Gimenez et al., 2003; Purdon et al., 2003). However, these tasks demand considerable executive control, and thus impairments may reflect additional, non-striatal deficits in these patients. Because of its relatively simple task demands, the WPT may be a more specific measure of cognitive skill learning that taps corticostriatal dysfunction. Previous studies have shown that reinforcement learning driven by rewards is impaired in patients with schizophrenia, consistent with corticostriatal dysfunction (Waltz, et al., 2007; see Barch and Dowd, 2010 for a review).

The WPT depends on the integrity of the neostriatum (Knowlton et al., 1996a; Knowlton et al., 1996b) and will be used to assess corticostriatal function. In fMRI studies, performance of this task activates striatal regions (Poldrack et al., 1999, 2001; Foerde et al., 2006) that are part of cognitive corticostriatal circuits including the caudate nucleus/dorsolateral prefrontal cortex (DLPFC) and ventral striatum/orbitofrontal cortex (VS/OFC) (Poldrack et al., 1999, 2001; Aron et al., 2004).

In healthy controls, the WPT can be learned explicitly using medial temporal lobe circuitry or implicitly using basal ganglia circuitry (Foerde et al., 2006). To probe whether the WPT was learned implicitly, we inserted dual-task tone-counting probe trials to test whether performance was automatic at different points during training. Automatization of a skill refers to the ability to execute a task without the demand for effortful control. If performance does not decline when a concurrent task is performed, it would suggest that performance on the WPT is relatively automatic and is based on stimulus–response habits involved in automatic skills rather than declarative memory.

To our knowledge this is the first study to investigate the performance of adolescent siblings of COS probands on an implicit learning task. A previous study has demonstrated that healthy young, adolescent control performance on a PCT is comparable to that of healthy young adult controls (Marsh et al., 2004; accuracy for both groups was in the 65–67% range). Based on studies that have compared schizophrenic patients and their first-degree relatives to healthy controls, we hypothesize that the unaffected siblings of COS patients will have an impairment in performance during early learning and after extended training. We also hypothesize that the siblings of COS patients will show a deficit in automaticity revealed by a decrement in dual-task performance after extended training.

2. Method

2.1. Participants

Sixteen siblings of COS patients and 87 control participants who were matched in age, education, and gender to the COS siblings participated in the experiment (Table 1). Eight controls and four siblings were excluded from analysis based on computer malfunction or not responding on more than 10% of the trials. All participants provided informed consent according to the procedures approved by the University of California, Los Angeles (UCLA) Human Subjects Committee and were paid for their participation. Siblings of COS probands were recruited based on their previous participation in family studies of COS at UCLA. Families of potential control participants were recruited through online advertisements, flyers, and by randomly calling families found through a commercially available list of households within a 25-mile radius of UCLA (Survey Sampling Inc., Fairfield, CT, USA). All participants were screened and were excluded if there was a history of prior treatment of psychiatric disorders (including psychosis, attention-deficit hyperactivity disorder, learning disabilities, Tourette's Syndrome) traumatic brain injury, drug or alcohol abuse, or neurological disorders that affect cognitive functioning. Control participants were excluded if a first-degree relative was reported to have been diagnosed with psychosis.

2.2. Experimental design

Subjects practiced the WPT for a total of 1.5 h, spanning 2 days. The second session took place within 8 days of the first, and the interval between the first and second session did not differ between groups (Mean interval for control participants = 5.0 days, Mean interval for COS siblings = 7.3 days ($t(88) = 1.57$, $P > 0.1$)). On the 1st day, subjects were assessed for any neurological disorder or psychotic symptoms by a psychiatrist, underwent a neuropsychological battery by completing the Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Block Design subtests (Table 1). All COS siblings and 42 of the control participants then completed 50 trials of the WPT inside an MRI scanner. The other 37 control subjects performed the WPT outside the scanner. On the 2nd day, all subjects were trained for an additional 800 trials outside the scanner occurring in two sets with an intervening break of 30 min where another task (the serial reaction time task) was performed. At the end of training, subjects' declarative knowledge of cue-outcome associations were tested by asking them to estimate how frequently each outcome occurred for each of the cue combinations.

In the WPT used here (Knowlton et al., 1994) participants are told that they have to predict the weather (sun or rain) based on cues (Fig. 1). These cues are probabilistically related to the outcomes. On every trial between one and three cues (out of four possibilities) can appear, yielding 14 possible combinations. The association of the different cues with different probabilities was randomized across participants. The cue strength of each of the 14 resulting stimuli were such that the overall probability associating each cue with sun or rain is 0.756, 0.575, 0.425, and 0.244 across the trials. A response was counted as correct if it matched

Table 1
Demographics of the controls and siblings.

Variable	Controls ($n=79$)		Siblings ($n=12$)	
	M	S.D.	*M*	S.D.
Age	12.76	2.39	12.58	2.19
Education	6.00	2.49	6.75	2.38
Gender[a]	40/39		6/6	
Vocabulary[b]	60.53	8.62	45.00	9.44
Blocks[c]	56.91	7.87	45.00	9.82

[a] Men/Women.
[b] WASI Vocabulary subtest (missing one sibling).
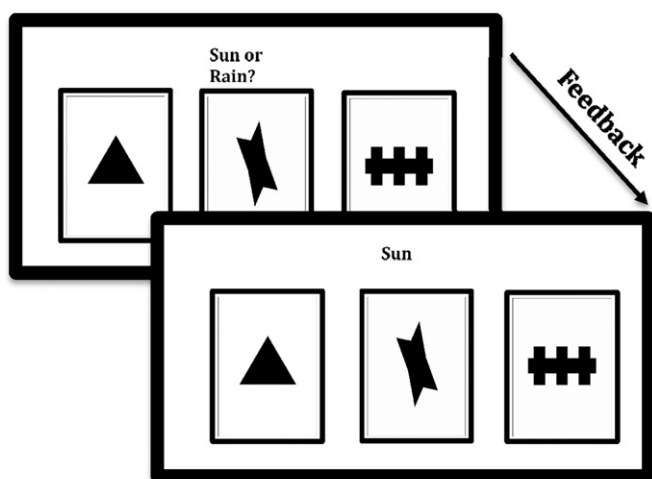[c] WASI Blocks subtest (missing two controls and one sibling).

Fig. 1. The WPT task. Participants were told to predict the weather (sun or rain) based on cues. On every trial between one and three cues (out of four possibilities) could appear, yielding 14 possible combinations. The cues were probabilistically related to the outcomes. The association of the different cues with different probabilities was randomized across participants. The cue strength of each of the 14 resulting stimuli were such that the overall probability associating each cue with sun or rain was 0.756, 0.575, 0.425, and 0.244 across the task. Since feedback was probabilistic, a response was considered correct if it matched the outcome most strongly associated with a stimulus, regardless of feedback. Thus, a response could be "correct" even if feedback reported an incorrect answer. Therefore, the percentage correct score reflected how well the subjects learned the cue-outcome associations (Marsh et al., 2004). The cues are shown on the screen for a maximum of 3 s, the feedback is shown on the screen for 1 s, and the time between trials is 0.5 s. During the secondary task, a subject hears a series of high and low pitch tones during the task and has to count the number of high pitch tones while completing the WPT. Between one and three tones are heard during each trial of the secondary task.

the outcome most strongly associated with a stimulus; thus, a response could be counted as correct even if feedback reported an incorrect answer. It is important to note that in the WPT the cues are *probabilistically* associated with outcomes. For example, a particular cue is associated 75.6% of the time with sun. This means that 24.4% of the time the cue will be associated with rain. On this task there is not a one–one association between a cue and an outcome. A response was counted as correct if it matched the outcome *most strongly associated* with a stimulus; thus, a response would be counted as correct if the subject responded with "sun" for a cue associated with sun 75.6% of the time even when the feedback was rain. The response "sun" is correct in this situation, as it is the most likely outcome. Therefore, the percentage correct score reflects how well the subjects learned the cue-outcome associations (Marsh et al., 2004). Because of the probabilistic nature of the cue-outcome associations, memory for individual trials is not as important as information accrued across multiple trials.

2.2.1. Secondary task

On the 2nd day, a secondary task was introduced during trials 81–160 and 641–720. These probe trials were inserted to assess whether WPT performance was unaffected by the addition of a concurrent task and was thus relatively automatic (Foerde et al., 2008). For the secondary task, participants heard high (1000 Hz) and low (500 Hz) pitched tones during the task and had to count the number of high-pitched tones. At the end of each dual task block the subject reported the number of high-pitched tones they counted by entering the number into the computer.

2.3. Data analysis

The WPT data were analyzed using 2-way (group x block) multivariate ANOVA. To correct for violations of sphericity, the Huynh–Feldt test was used. In addition, to examine how robust the ANOVA findings were the group data were also analyzed using a non-parametric test (Mann–Whitney U-test) that made no assumptions about the distribution of the data. We tested a directional hypothesis: the COS siblings would perform worse than healthy, age-matched controls.

The effect of the secondary task was assessed by computing the differences between the average of the trial block immediately before and after the two dual task blocks and the average of the two dual task blocks.

Performance on the declarative knowledge test was assessed by computing the average of the difference between the true and the participant's estimated probability of each outcome for each cue combination. Thus, a lower score would

reflect more veridical declarative knowledge of the cue-outcome associations. Chance performance would equal the difference between 50% and the veridical probability for each cue combination.

3. Results

We examined performance on the WASI subtests and found significant differences between the groups with the controls performing better on both tests, Vocabulary $t(88)=5.537$, $P < 0.00$, Blocks $t(86)=4.550$, $P < 0.00$. For these analyses, one of the COS siblings was not tested on the WASI subtests and two control participants were not tested on the Blocks subtest due to time constraints.

3.1. Early learning

We first examined learning by analyzing accuracy during early learning, which we defined as learning on Day 1 (50 trials) and the first block of Day 2 (80 trials). The greatest improvement in accuracy occurred during these periods. Comparing control participants tested inside and outside the scanner on Day 1, we found no significant difference (main effect, $F(1, 77)=3.08$, $P > 0.05$, interaction between group and block, $F < 1$), and thus we combined these two subgroups for further analyses. Fig. 2 presents accuracy of the control and COS sibling groups during this early learning phase. During the 50 trials of training on Day 1, there was a main effect of group ($F(1, 89)=3.606$, $P=0.031$, $MSE=0.104$, $\eta_p^2=0.039$) with significantly better performance by the controls. There was no main effect of block, ($F < 1$), but there was a trend for an interaction between group and block ($F(4, 356)=1.743$, $P=0.071$, $\eta_p^2=0.019$) due to the better learning in the control group. During blocks 2–5 of Day 1, control performance was significantly above chance, t's$(78) > 3.3$, $P < 0.001$, while COS sibling performance did not improve during Day 1 and remained at chance levels, . Within eight blocks of 10 trials in the first 80 trials on Day 2, there was a trend for a main effect of group ($F(1, 89)=1.986$, $P=0.081$) and a trend for a main effect of trial blocks ($F(7, 623)=1.548$, $P=0.074$, $MSE=0.036$, $\eta_p^2=0.017$). There was no significant interaction between trial blocks and group, ($F < 1$) suggesting that early during the 2nd day both groups showed learning, although the control group appeared to maintain a higher level of accuracy.

In order to examine how robust the findings were for the ANOVA analysis, we conducted a non-parametric test that made
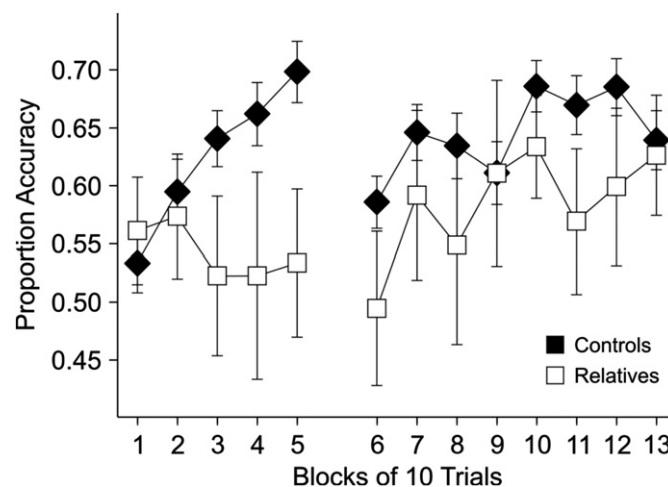

Fig. 2. WPT accuracy of the controls and COS relatives in early training (Day 1 and the first 80 trials of Day 2 (blocks 6–13 in this graph)). Error bars represent the standard error of the mean.

no assumptions about the distribution of the data. For early learning in the first 50 trials on Day 1, the original scores, measured in proportion accuracy, were rank ordered and a Mann–Whitney U-test was used to compare the ranks for the $n=12$ siblings versus the $n=79$ controls. The results indicated a significant difference between the groups, with the controls having much better performance than the siblings, $U=328$, $P=0.0435$, with the sum of the ranks equal to 406 for the siblings and 3780 for the controls.

There was a significant main effect of block ($F(4, 356)=2.911$, $P=0.014$, $MSE=54740.379$, $\eta_p^2=0.032$) for reaction time during the early training on Day 1 (blocks 1–5 of Fig. 2), with reaction times decreasing over trials. The main effect of group and the interaction between block and group were not significant.

3.2. Performance after extended training

We next analyzed accuracy during the second day of training. Fig. 3 presents accuracy for the two groups during extended training. We did not include the dual task trials in these analyses. We analyzed the Day 2 performance broken into two sessions (the 320 single-task trials before and after a 30 min break). For the first session, there was no main effect of group ($F<1$), block ($F(3, 267)=1.369$, $P=0.127$, $MSE=0.006$, $\eta_p^2=0.015$), or a significant interaction between block and group, ($F<1$). For the second session, there was a main effect of group, ($F(1, 89)=3.019$, $P=0.043$, $MSE=0.063$, $\eta_p^2=0.033$). The COS sibling group performed significantly more poorly than controls. There was no main effect of block, or a significant interaction between block and group, (F's <1). In addition, within group t-tests revealed that there was no difference in accuracy for the controls or in the siblings of COS probands between sessions 1 and 2. Table 2
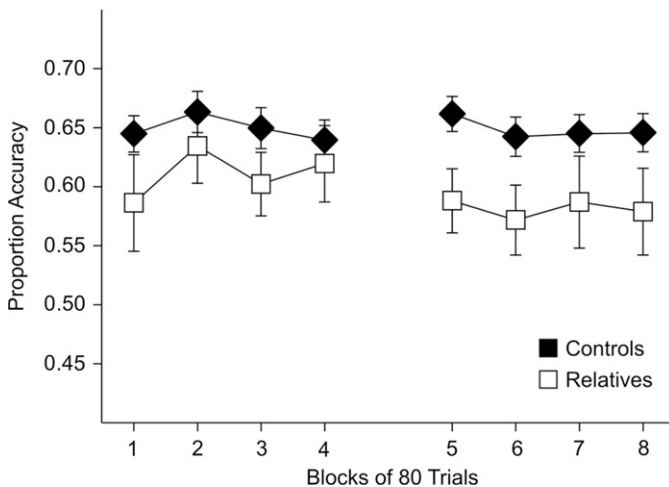

Fig. 3. WPT accuracy of the controls and COS relatives During Day 2. Only single task trials are depicted. Error bars represent the standard error of the mean.

presents the group means and standard deviation for every trial block.

We also conducted a non-parametric Mann–Whitney U-test for late learning during the second session where the group differences were the most striking. The results indicated a significant difference between the groups, with the controls having better performance than the siblings, $U=321.5$, $P=0.037$, with the sum of the ranks equal to 399.50 for the siblings and 3786.50 for the controls.

Reaction time was also analyzed for session one and session two on the 2nd day. There was no significant main effect of group ($F<1$) or block ($F(3, 267)=1.492$, $P=0.115$, $MSE=29209.533$, $\eta_p^2=0.016$), and no interaction between block and group ($F<1$), for the first session. During the second session, there was no main effect of group, or an interaction between block and group (F's <1). There was a main effect of block ($F(3, 267)=2.969$, $P=0.020$, $MSE=20228.810$, $\eta_p^2=0.032$), with reaction times decreasing across the session for both groups.

The effect of the secondary task was assessed by computing the differences between the average of the trial block immediately before and after the two dual task blocks and the average of the two dual task blocks. For both groups, there was little cost associated with performing the concurrent task. There was no effect of the dual task on accuracy in either the first session (Mean of controls=0.64, Mean of siblings=0.58, $t(89)=0.051$, $P=0.480$), or the second session, (Mean of controls=0.66, Mean of siblings=0.61, $t(89)=0.537$, $P=0.296$). This lack of any cost associated with performance of the secondary task suggests that performance of the PCT was relatively automatic, at least by the 130 trials of training that occurred before the first dual task probe. For reaction time, we calculated difference scores for the dual task trials and the single task trial immediately before and after the two dual surrounding single task trials. When comparing reaction times for single and dual task blocks, there was a nonsignificant trend for subjects in both groups to perform faster during dual task blocks during both the first session ($t(89)=1.511$, $P=0.067$) and for the second session ($t(89)=1.420$, $P=0.080$).

On the declarative cue estimation test, there was a significant difference between the controls and siblings in terms of the deviation of the subjects' estimates from the true probabilities ($t(85)=1.738$, $P=0.043$), revealing that the controls had more explicit knowledge of the cue-outcome associations. In addition, it was not the case that the siblings did not understand the declarative knowledge assessment; further analysis revealed that the siblings performed above chance ($t(8)=4.296$, $P<0.01$).

4. Discussion

In the present study, siblings of COS patients were impaired on a cognitive skill learning task compared to controls. At the beginning of training, both groups began at chance levels of accuracy. However, controls showed clear learning over the first

Table 2
Group mean of performance of proportion accuracy on the WPT and standard deviation (SD) at each block.

Variable		Blocks												
		Day 1					Day 2							
		1	2	3	4	5	1	2	3	4	5	6	7	8
Mean	Controls	0.53	0.59	0.64	0.66	0.70	0.64	0.66	0.65	0.64	0.66	0.64	0.65	0.65
	Relatives	0.56	0.57	0.52	0.52	0.53	0.59	0.63	0.60	0.62	0.59	0.57	0.59	0.58
SD	Controls	0.22	0.25	0.22	0.24	0.24	0.14	0.16	0.15	0.15	0.13	0.15	0.14	0.14
	Relatives	0.16	0.19	0.24	0.32	0.19	0.14	0.11	0.09	0.11	0.09	0.10	0.14	0.13

50 trials, while the siblings of COS probands did not, and a significant group difference in accuracy emerged during this early training. While the groups did not differ significantly during the first session of Day 2 the siblings of COS probands were significantly less accurate than controls during the second session of Day 2. During this second session, both groups appeared to reach asymptote. There was no evidence of further learning, indicating that the groups differed in their level of asymptotic performance. Even after hundreds of trials, the siblings of individuals with COS were not performing significantly above chance.

By the 130th trial, when the first dual task trials were inserted, there was no dual task effect. The performance of a secondary task had no significant effect on WPT accuracy for either group after 130 trials. Because the concurrent task decreases declarative memory retrieval by occupying working memory, the lack of a dual task effect suggests that subjects were not explicitly recalling information about the associations to perform the task when the probe trials were presented. However, other evidence suggests that learning on the WPT in early trials can be supported by declarative memory. Data provided by computational modeling, studies of patients with amnesia or Parkinson's disease, and pharmacological manipulations suggest that "multiple, distinct cognitive processes contribute to how people predict outcomes" on the WPT (Shohamy et al., 2008). Early in practice healthy subjects can use simple, easily verbalizeable, non-optimal rules, which can be learned in a single episode. This type of learning is impaired in patients with amnesia with medial temporal lobe damage but preserved in patients with mild Parkinson's disease. As practice continues, subjects use a more optimal, incremental strategy based on error prediction. This strategy is supported by the basal ganglia (Shohamy et al., 2008). The degree to which subjects rely on declarative vs. habit strategies likely depends on the ability to memorize the outcomes of specific trials (Foerde et al., 2006). Prior research shows that patients with schizophrenia have impaired medial temporal lobe function, and in the present study, the siblings of COS probands exhibited impaired declarative memory for the cue-outcome associations, raising the possibility that the poor performance of the siblings of COS patients early in practice reflects medial temporal lobe dysfunction while their poor performance later in practice reflects basal ganglia dysfunction. We are currently processing fMRI data to see if early in practice there are differences in MTL activation and later in practice differences in basal ganglia activation in siblings of COS patients on the WPT.

Consistent with other studies of first degree relatives of patients with schizophrenia (Hill et al., 2008) in the present study adolescent siblings of patients with COS with schizophrenia performed significantly more poorly than controls on the WASI, a measure of intellectual functioning. The poor performance of relatives of patients on intelligence tests has been interpreted as indicating that poor intellectual function may reflect liability to schizophrenia (Hill et al, 2008). However, it is unlikely that this impairment can explain the deficits in this group on the WPT, in that patients with Alzheimer's disease, who also exhibit impairments on tests of intellectual function, nevertheless perform as well as age-matched control subjects on the WPT (Eldridge et al., 2002). Consistent with these findings, in our study, there was little relationship within each group between measures of intellectual function and learning or asymptotic level of performance on the WPT. There was no significant correlation within either group for scores on Vocabulary Subtest of the WASI and either early or late performance (r's < 0.15). For the COS sibling group, there was no relationship between scores on the Block Design subtest of the WASI and either early or late performance (r's < 0.14). For the control participants, there was a small correlation between scores on the Block Design subtest and

WPT performance, which achieved significance for the amount of early learning ($r(77) = 0.24$, $P < 0.05$) and was trending towards achieving significance for the level of asymptotic performance ($r(77) = 0.22$, $P < 0.1$). Based on the lack of a strong relationship between either measures of verbal or performance IQ and WPT performance, it is unlikely that differences in general intellectual function between the groups could account for the findings of our study.

It was also not the case that the WPT task was too difficult for the adolescent participants in the present study. The WPT task has been shown to be learned relatively well in patients in this age group (Marsh et al., 2004). Moreover, performance in the healthy control group in our study was comparable to the performance of healthy young adolescent and adults in the Marsh et al. study and in healthy adults in previous work (Knowlton et al., 1994).

We observed a greater deficit in WPT performance in siblings of individuals with schizophrenia than that seen by Weickert et al. (2010). The major difference between the studies is that we tested siblings of patients with COS, while in Weickert et al. (2010) siblings of adult onset patients were tested. The COS siblings may have a greater genetic liability for schizophrenia, and thus cognitive endophenotypes associated with this liability may be more apparent. Another difference between the present study and the study conducted by Weickert et al. (2010) is that we tested adolescents rather than adults. It may be that this type of habit learning is at the cusp of development, and thus may be more sensitive to individual differences.

The impairment exhibited by siblings of patients with COS in this study contrasts with the relatively good performance of patients with amnesia or Alzheimer's disease on this task. Although these patient groups exhibit severe deficits in declarative memory, they are able to perform well on the WPT (Knowlton et al., 1994; Eldridge et al., 2002). The performance of the COS siblings seems similar to that of patients with basal ganglia disorders. Similar to the COS siblings in the current study, patients with Huntington's disease exhibit impaired learning and a very low level of asymptotic performance (Knowlton et al., 1996b). The siblings of patients with COS perform comparably to patients with schizophrenia, who also have impaired performance in the WPT and similar tasks. In patients with schizophrenia, there are performance gains early on by the controls and the patients never catch up to the same level even after extended training (Foerde et al., 2008). This close correspondence between the performance of patients with schizophrenia and the unaffected siblings of COS patients supports the hypothesis that deficits in probabilistic classification are associated with liability to schizophrenia and not a consequence of expression of the disease or medication history.

Genetic liability for schizophrenia involves cognitive impairments as well as functional brain abnormalities. The present results suggest that dysfunction in specific corticostriatal loops may reflect liability for schizophrenia. An important direction for future work is the analysis of striatal function during performance of the WPT using fMRI in first-degree relatives of patients with schizophrenia.

analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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