Title

Impaired automatization of a cognitive skill in first-degree relatives of patients with schizophrenia

Journal

Psychiatry Research, 215(2)

ISSN

0165-1781

Authors

Wagshal, Dana
Knowlton, Barbara Jean
Cohen, Jessica Rachel
et al.

Publication Date

2014-02-01

DOI

10.1016/j.psychres.2013.11.024

Peer reviewed

Psychiatry Research 215 (2014) 294–299

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Impaired automatization of a cognitive skill in first-degree relatives of patients with schizophrenia

Dana Wagshal [a,*], Barbara Jean Knowlton [b], Jessica Rachel Cohen [c], Russell Alan Poldrack [d,e,f], Susan Yost Bookheimer [g], Robert Martin Bilder [g], Robert Franklin Asarnow [g]

[a] University of California, San Francisco, United States
[b] University of California, Los Angeles, United States
[c] University of California, Berkeley, United States
[d] Imaging Research Center at University of Texas at Austin, United States
[e] Department of Psychology at University of Texas at Austin, United States
[f] Department of Neurobiology at University of Texas at Austin, United States
[g] David Geffen School of Medicine at University of California, Los Angeles, United States

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised form
4 October 2013
Accepted 25 November 2013
Available online 4 December 2013

Keywords:
Automatization
Schizophrenia
Skill learning
Genetic liability

ABSTRACT

We studied healthy, first-degree relatives of patients with schizophrenia to test the hypothesis that deficits in cognitive skill learning are associated with genetic liability to schizophrenia. Using the Weather Prediction Task (WPT), 23 healthy controls and 10 adult first-degree Relatives Of Schizophrenia (ROS) patients were examined to determine the extent to which cognitive skill learning was automated using a dual-task paradigm to detect subtle impairments in skill learning. Automatization of a skill is the ability to execute a task without the demand for executive control and effortful behavior and is a skill in which schizophrenia patients possess a deficit. ROS patients did not differ from healthy controls in accuracy or reaction time on the WPT either during early or late training on the single-task trials. In contrast, the healthy control and ROS groups were differentially affected during the dual-task trials. Our results demonstrate that the ROS group did not automate the task as well as controls and continued to rely on controlled processing even after extensive practice. This suggests that adult ROS patients may engage in compensatory strategies to achieve normal levels of performance and support the hypothesis that impaired cognitive skill learning is associated with genetic risk for schizophrenia.

1. Introduction

Consistent with the hypothesis that the pathophysiology of schizophrenia involves dysfunction of corticostriatal circuits (e.g., Kleist, 1960; Buchsbaum, 1990; Buchanan, 1993), patients with schizophrenia perform poorly on cognitive skill learning tasks that tap corticalstriatal networks. Skill learning involves the improvement of performance with practice on a task and is demonstrated by reduced reaction time or increased accuracy. The corticostriatal system plays an important role in cognitive skill learning (Heindel et al., 1989; Knowlton et al., 1996; Doyon et al., 2009; Peigneux et al., 2000) and involves the caudate nucleus, dorsolateral prefrontal cortex, and ventral striatum/orbitofrontal cortex (Aron et al., 2004; Poldrack et al., 2001, 1999).

Several studies have lent support to the idea that patients with schizophrenia show deficits in cognitive skill learning using tasks such as the Tower of Toronto and the Tower of Hanoi (Gimenez et al., 2003; Schroder et al., 1996; Purdon et al., 2003). Another cognitive skill learning task is the Weather Prediction Task (WPT; Knowlton et al., 1994), a probabilistic classification task that requires participants to learn probabilistic associations between cues and binary outcomes by attending to visual stimuli presented on a computer screen, after which they are provided feedback about the correctness of their response (Fig. 1). Because the Tower of Toronto and the Tower of Hanoi demand considerable executive control resources and can involve learning strategies dependent on declarative cognitive processes through the application of stateable rules or algorithms (Winter et al., 2001), impairments on these tasks in patients with schizophrenia may reflect deficits in these domains. Due to its relatively simple task demands and the fact that there is no algorithm or rule that can potentially provide a solution, the WPT may be a more specific test of cognitive skill learning that is characterized by incremental learning that relies on corticostriatal function.

Performance on the WPT is impaired in patients with schizophrenia (Foerde et al., 2008; Keri et al., 2005; Horan et al., 2008;

* Corresponding author at: Department of Neurology, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158, United States. Tel.: +1 415 476 2941.
E-mail address: dwagshal@memory.ucsf.edu (D. Wagshal).

0165-1781/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2013.11.024

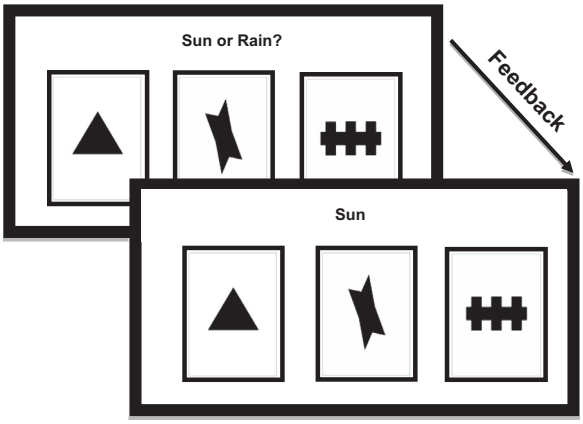

Fig. 1. The WPT. Participants were told to predict the weather (sun or rain) based on cues. On every trial between one and three cues (out of four possibilities) could appear, yielding 14 possible combinations. The cues were probabilistically related to the outcomes. The association of the different 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 0.727, 0.556, 0.409, and 0.280 across the task. 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.

Weickert et al., 2002). However, these deficits may be related to the anti-psychotic medications these patients were receiving to control their psychotic symptoms. Anti-psychotic medications have effects on striatal structure (i.e., enlargement of the volume of the basal ganglia) and alter striatal D^2 receptors (Paquet et al., 2004; Kumari et al., 2000). It is possible that these medications impair striatal function, resulting in the impaired cognitive skill learning observed in patients receiving anti-psychotic treatment. In other studies, treatment with antipsychotic medication improves performance on skill learning tasks (Harvey et al., 2000; Serper et al., 1990), and thus may mask deficits. Thus, whether impaired cognitive skill learning reflects liability to schizophrenia remains unclear because of potential medication effects.

Since schizophrenia has a strong genetic basis, findings of impaired cognitive skill learning in patients raise the possibility that genes that contribute to schizophrenia may affect striatal functioning as well. Studying healthy relatives of patients with schizophrenia eliminates the possible confounding effects of medication and can provide valuable insight into the etiology of this disease. Cognitive skill learning in relatives of patients with schizophrenia (ROS) has been less well examined than in patients themselves. Weickert et al. (2010) compared patients with schizophrenia to their healthy adult siblings and to controls on the WPT. While the patients demonstrated a severe learning deficit compared to controls, the siblings of patients generally performed in the normal range. However, the sibling group included more poor performers than the control group. Wagshal et al. (2012) compared adolescent siblings of patients with Childhood Onset Schizophrenia (COS) to adolescent controls and found significant performance differences early and late in training. Early in training siblings revealed a severe learning deficit compared to controls, and even after extensive training the COS siblings reached a lower level of asymptotic performance than controls. COS is a more severe and more familial form of schizophrenia than the adult onset form (Asarnow et al., 2001; Asarnow and Asarnow, 1994; Nicolson and Rapoport, 1999) and this may have contributed to the greater deficit found in Wagshal et al. (2012). Age may have also played a role, in that the participants in Wagshal et al. (2012) were adolescents. It is possible that the impairment in the COS siblings represents a developmental delay and not an enduring delay that is present in adulthood.

In this study we examined the performance of healthy, adult first-degree ROS patients on the WPT. Previous work suggests that there may be only subtle deficits in WPT performance in this group. To detect relatively subtle deficits in ROS patients we assessed the degree to which performance becomes automatic as training progresses. Automatization of a skill is achieved when the skill can be executed without making demands for executive control and effortful processing. A major characteristic of automaticity is when concurrent performance of a secondary task does not interfere with primary task performance of a skill (Posner and Snyder, 1975). Automaticity is important in everyday life and is critical for handling unexpected cognitive challenges, for problem-solving, and for performing concurrent activities that are required in many social and work settings (Green et al., 2000; Harvey et al., 2006). Thus, evidence of reduced automatization of cognitive skills in ROS patients may have implications for daily life activities.

There is agreement in the literature that individuals with schizophrenia or schizotypal personality disorder have diminished processing resources (Asarnow et al., 1995; Braff, 1981, 1985; Harvey et al., 1996, 2006; Holzman, 1987; Moriarty et al., 2003; Nuechterlein, 1991), and that the ability of individuals with schizophrenia to automate skills is more impaired than controls. Insufficient processing resources to handle higher processing loads can result in cognitive impairment in schizophrenia patients (Asarnow et al., 1991; Asarnow and Sherman, 1984; Gjerde, 1983; Sherman and Asarnow, 1985). Patients with schizophrenia may reach the limits of their available resources at lower processing loads and have fewer available resources than healthy controls (Asarnow, 1999). Processing resources are used when an individual is first learning a skill. With practice, learning becomes automated and makes fewer demands on available resources (Schneider et al., 1984; Asarnow, 1999; Granholm et al., 1996). Even if there are no overt impairments in the ROS patients in this study, their performance may be less automatic than that of controls and thus more sensitive to the effect of a concurrent task.

2. Methods

2.1. Participants

Ten adults who were first-degree relatives of patients diagnosed with schizophrenia (ROS) and 23 adult controls that were matched in age and gender to the relatives participated in the experiment (Table 1). Four controls and two relatives were excluded from analyses 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. Relatives of schizophrenia probands were recruited based on their previous participation in family studies 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 in both groups were screened and participants were excluded if there was a history of prior treatment of

Table 1
Demographics of the controls and relatives.

Variable	Controls ($n=19$)		Relatives ($n=8$)	
	M	S.D.	*M*	S.D.
Age	40.00	5.61	39.25	6.90
Gender[a]	5	14	2	6
Vocabulary[b]	55.32	8.50	42.20	9.20
Blocks	55.42	10.72	44.50	8.67

[a] Men/women.
[b] WASI vocabulary subtest (missing three relatives).

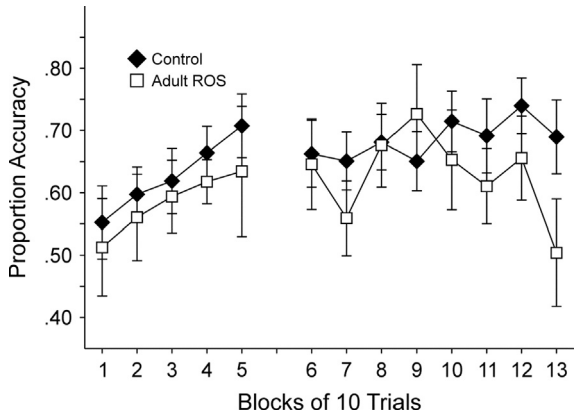

Fig. 2. WPT accuracy of the controls and adult ROS in early training [Day 1 and the first 80 trials of Day 2 (blocks 6–13 in this graph)]. Error bars represent the standard error of the mean.

psychiatric disorders (including psychosis, attention-deficit hyperactivity disorder, learning disabilities, or 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

The experimental design and data analysis were identical to those of our previous study (Wagshal et al., 2012). Subjects practiced the WPT for a total of one and a half hours, spanning 2 days. The second session took place within seven days of the first. On the first day, subjects were assessed for any neurological disorder or psychotic symptoms by a clinical psychologist, completed the Wechsler Abbreviated Scale of Intelligence (WASI) vocabulary and block design subtests (Table 1), and completed 50 trials of the WPT. In the second session, subjects were trained for an additional 800 trials occurring in two sets of 400 trials with an intervening break of 30 min, during which a sensorimotor task (the serial reaction time task) was performed. At the end of training, subjects' declarative knowledge of cue–outcome associations was tested by asking them to estimate how frequently each outcome occurred for each of the cue combinations.

In the version of the WPT used here (Knowlton et al., 1994), participants were told that they had to predict the weather (sun or rain) based on cues. These cues were probabilistically related to the outcomes. On every trial between one and three cues (out of four possibilities) could appear, yielding 14 possible combinations. The association of the different cues with different probabilities was randomized across participants. A response was counted as correct if it matched the outcome most strongly associated with a stimulus; thus, a response could be counted as correct even if feedback reported an incorrect answer (i.e., the feedback presented was associated with the less strongly associated outcome). Therefore, the percentage correct score reflects how well the subjects learned the cue–outcome associations (Marsh et al., 2004).

2.2.1. Secondary task

On the second 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 participants reported the number of high-pitched tones they counted by entering the number into the computer.

2.3. Data analysis

Based on our previous results (Wagshal et al., 2012) showing deficits early in learning and asymptotic performance late in learning in adolescent siblings of patients with childhood onset schizophrenia, we separately examined performance early in learning on the first day of training and the first block of the second day of training. To assess learning after extensive practice we compared performance of the two groups on the single-task blocks on Day 2. To assess the level of automaticity, we analyzed performance separately in the dual task blocks early and late in practice. The effect of the secondary task was assessed by computing the differences between the average of the trial blocks immediately before and after the two dual task blocks and the average of the two dual task blocks. Data were analyzed using a 2 × 2 (group × block) multivariate ANOVA. To correct for violations of sphericity, the Huynh–Feldt test was used.

Performance on the declarative knowledge test was assessed by computing the average of the difference between the true probability 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

In the present study, subjects were performing above 75% accuracy, which is higher than in our previous work using the WPT in adolescents. We also examined performance on two WASI subtests (Vocabulary and Block Design) and found significant differences between the groups with the controls performing better on both tests, Vocabulary ($t(22)=3.023$, $P=0.006$), Block Design ($t(25)=2.545$, $P<0.017$). For these analyses, three participants in the ROS group were not tested on the Vocabulary subtest due to time constraints (Table 1).

3.1. Early learning

We first examined accuracy during early learning in the single task condition (first block) of 50 trials on Day 1 and the first block of 80 trials on Day 2. Based on our previous findings (Wagshal et al., 2012), this is the period during which most learning occurs. Fig. 2 presents the accuracy of the two groups during this early learning phase. During the 50 trials of training on Day 1, there was strong trend for a main effect of block ($F(4, 100)=1.91$, $P=0.058$) with both groups improving in accuracy across blocks. There was no significant main effect of group ($F(1, 25)=0.585$, $P>0.05$) or an interaction between block and group ($F(4, 100)=0.052$, $P>0.05$). Within the eight blocks of 10 trials in the first 80 trials on Day 2, there were no significant main effects of group or block or an interaction between block and group ($Fs<1.0$, $Ps>0.05$).

There was a main effect of block ($F(4, 100)=5.327$, $P<0.001$) for reaction time during early training in the single task condition on Day 1, with reaction time decreasing for both groups and a trend for an interaction between block and group ($F(4, 100)=1.795$, $P=0.069$), with the ROS group demonstrating more of a decrease in reaction time during the later blocks of early learning. The main effect of group was not significant ($F<1$, $P>0.05$).

3.2. Performance after extended training

Fig. 3 presents accuracy for the two groups during extended training in the single task condition (the second day of training, Trials 51 through 850), excluding those trials in which the subject performed the concurrent tone-counting task). We analyzed Day 2 overall performance and Day 2 performance broken into two sessions (the 320 single-task trials before and after a 30 min break) in 80 trial blocks. Overall, there was a significant main effect of block with both groups improving in accuracy across blocks ($F(7, 175)=6.60$, $P<0.001$). There was no significant main effect of group ($F(1, 25)=0.058$, $P>0.05$) or an interaction between block and group ($F(7, 175)=0.759$, $P>0.05$). When broken down into two separate sessions, for session one, there were no significant main effects of group or block or an interaction between block and group ($Fs<1.43$, $Ps>0.05$). For session two, however, there was a main effect of block with both groups increasing in accuracy across blocks ($F(3, 75)=3.21$, $P=0.014$). In addition, within-subjects t-tests revealed that there was an improvement in accuracy for the controls and ROS group between sessions one and two [$t(18)=3.02$, $P=0.007$ and $t(7)=3.25$, $P=0.014$ respectively]. These results indicate that performance continued to improve with extended training in both groups in the

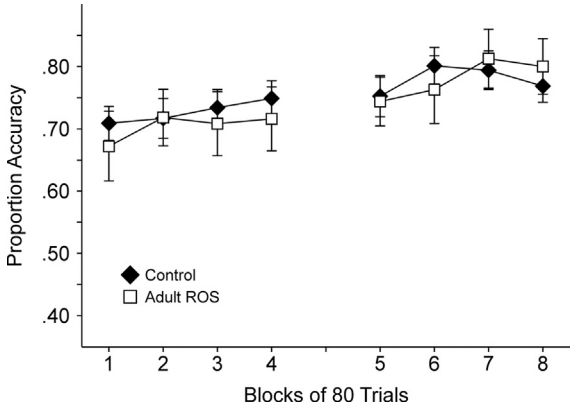

Fig. 3. WPT accuracy of the controls and adult ROS during Day 2. Only single task trials are depicted. Error bars represent the standard error of the mean.

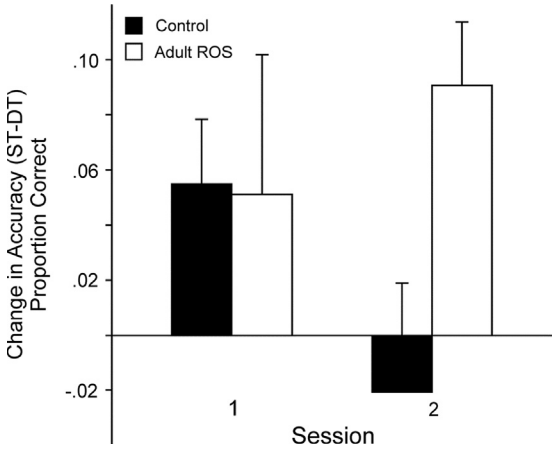

Fig. 4. Performance of the controls and adult ROS group on the WPT during the dual task effect for accuracy on the second day during sessions one and two. Note that a positive number indicates worse performance on the task during dual-task trials.

single task condition and had not yet reached a consistent asymptote.

Reaction time in the single task condition was also analyzed overall for Day 2 as well as separately for session one and two on the second day. Overall, there was a main effect of block with both groups responding faster on the second block ($F(7, 175)=2.384$, $P=0.033$). Within each session, there were no significant effects or interactions between block and/or group ($Fs < 1.35$, $Ps > 0.05$).

3.3. Assessment for automaticity

The effect of the secondary task was assessed by computing the difference 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 (Fig. 4). This yielded a measure of the cost of dual task performance, with greater numbers indicating greater cost. We examined dual task cost at two time points during the second day of training (after 80 and 640 trials) for a block of 80 trials each during early and late training during this time period to examine the development of automaticity in the two groups both early and late in training. A two (group) × two (session) multivariate ANOVA revealed a significant main effect of group ($F(1, 25)=3.304$, $P=0.041$), and a significant interaction between group and session ($F(1, 25)=3.953$, $P=0.029$). There was no main effect of session ($F(1, 25)=0.390$, $P > 0.05$).

To further explore the group x session interaction, we conducted between-subjects *t*-tests during the two time points. This revealed a significant difference between the groups during the second session, with the ROS group being more adversely affected by the dual task than controls ($t(25)=-3.387$, $P < 0.001$). There was no group difference for the first session ($t(25)=0.078$, $P > 0.05$). Within-subjects t-tests revealed that there was a significant reduction in the effect of the dual task in the healthy controls between sessions one and two, with performance in the controls becoming more automatic in the second session ($t(18)=3.049$, $P=0.004$). There was no significant difference in the magnitude of the dual task effect across sessions for the ROS group ($t(7)=-0.578$, $P > 0.05$). In other words, the control subjects showed no dual task cost by the second probe test, while the ROS subjects continued to show a cost of performing a concurrent task.

On the declarative knowledge assessment, there was no significant difference between the controls and relatives in terms of their estimates of the cue–outcome association probabilities ($t(20)=-1.496$, $P > 0.05$).

4. Discussion

Consistent with previous literature showing no overall deficits in WPT performance in adult ROS (Weickert et al., 2010), the ROS patients did not differ from healthy controls in accuracy or reaction time on the WPT either during early or late training on the single-task trials,. Though the ROS group did not perform significantly above chance during much of the early learning phase, during the extended training they performed above chance and at the level of the healthy control group.

However, a difference between the groups emerged in the test of automaticity in the dual-task blocks on the second day of training. In the first dual-task block, after 80 trials of training on Day 2 (after 130 total trials), both groups showed reduced accuracy, suggesting that performance was not yet automatic in either group. By the second dual-task block, control subjects showed no decrement in accuracy compared to surrounding single task blocks (after 640 trials of training). This finding is consistent with previous work comparing patients with schizophrenia and controls showing development of automaticity in the WPT by 600 trials in controls (Foerde et al., 2008), and work with other tasks showing the development of automaticity in just over 500 trials in controls (Granholm et al., 1996).

In contrast to the control group, the ROS group continued to show a cost of performing a concurrent task. While these findings are necessarily preliminary because of the small sample size, it is important to note that the effect size for the dual task cost between groups was quite large ($\eta_p^2=0.137$).

One possible interpretation of the results is that the deficit in automaticity in the ROS group is a consequence of generally reduced cognitive function in this group reflected in their poorer performance on the Vocabulary and Block Design subtests of the WASI. To explore this idea, we computed correlation coefficients between scores on our measures of verbal (Vocabulary subtest) and performance (Block Designs subtest) IQ and dual task cost at the second time point. For controls, there was no relationship between Vocabulary and dual task cost. There was however an inverse relationship between Block Design performance and automaticity, with reduced cost of the secondary task associated with *lower* Block Design performance ($r(19)=0.54$, $P < 0.05$) For the ROS group, there was no significant relationship between Block Design performance and dual task cost. There was a strong trend for a relationship between Vocabulary performance and automaticity in the ROS group, with reduced cost of the secondary task associated with higher Vocabulary scores in the ROS group ($r(5)=0.87$, $P=0.051$) While these results may suggest that lower

Vocabulary scores (verbal IQ) contributed to the deficits in the development of automaticity in ROS, it is also possible that both reduced verbal IQ and impaired automatization reflect liability to schizophrenia. Indeed the findings in controls of an inverse relationship between automaticity and Block Design performance suggest that impaired automatization is not simply a consequence of general intellectual impairment.

Moreover, in a prior study (Foerde et al., 2008), we found that patients with schizophrenia showed deficits on a cognitive skill learning task similar to the one used in the present study but not on a motor skill learning task (serial reaction time). In one set of analyses the tasks were matched in their psychometric properties, thereby demonstrating that the deficits in skill learning were not merely a reflection of a generalized cognitive deficit. Of course, this result needs to be replicated in ROS patients.

The addition of a secondary task decreases declarative memory retrieval by occupying working memory, and results in deficits in tasks relying on controlled processing (Foerde et al., 2007; Logan, 1978; Craik et al., 1996). Data provided by computational modeling and studies of neuropsychological patients provide support for the idea that learning on the WPT can be supported by different memory systems (Foerde et al., 2006; Knowlton et al., 1994, 1996; Gluck et al., 2002). By one view, early in training healthy young adults with good declarative memory abilities acquire simple rule-based strategies that rely on the medial temporal lobe, while the basal ganglia support later learning by utilizing stimulus–response associations to learn the task (Shohamy et al., 2008). In situations where declarative memory is compromised (e.g., dual task conditions or aging), performance may be more reliant on the basal ganglia throughout training. It appears that both declarative memorization of cue–outcome associations and implicit learning of stimulus–response associations can support performance on this task. Their contributions vary depending upon stage of practice.

Our results demonstrate that while the two groups reach similar behavioral endpoints, the ROS group did not develop automaticity, while the control group eventually did during Day 2 of training. Patients with schizophrenia have been shown to have diminished processing resources compared to controls, and this leads to deficits in the development of automaticity (Braff, 1985; Holzman, 1987; Nuechterlein, 1991; Granholm et al., 1991). According to one view, tasks become automatic because they no longer demand processing resources (Logan, 1978). According to another view, dual task costs are the result of response selection processes, and the minimization of dual task costs with practice results from more efficient response selection (Pashler et al., 2001). Regardless of how dual task costs are minimized with practice, the present results suggest that first-degree relatives of patients may be similar to patients with schizophrenia in that they also show deficits in this process.

The dual task paradigm permits the detection of more subtle deficits in skill learning than can be identified in single task paradigm. A prior study (Granholm et al., 1991), found that patients with schizophrenia performed normally on the Multiple Frame Search Task with sufficient practice but still showed deficits relative to controls in a dual task condition, suggesting that their performance was not automatic. Another study (Harvey et al., 2006) found that working memory was impaired in patients with schizotypal personality disorder by a secondary task relative to controls. These findings mirror our results with ROS patients.

In our previous study (Wagshal et al., 2012) we found that both adolescent siblings of patients with COS and controls showed no cost of performing a secondary task. However, in that study, the adolescent siblings of patients with childhood onset schizophrenia performed quite poorly even in the single task condition. Thus, it was not surprising that a concurrent task did not produce a further decrement. In the present study, it appears that the ROS group may be using controlled processing as a compensatory strategy to elevate their performance to the level of controls. The fact that there was no significant difference between the relatives and the controls in terms of declarative knowledge of the cue–outcome associations suggests that both groups had this information available to contribute to performance. Further work using neuroimaging methods may be able to test the hypothesis that first degree ROS patients utilize different brain systems for WPT performance than controls.

The results of the current study and previous work (Wagshal et al., 2012; Weickert et al., 2010) support the hypothesis that deficits in the WPT are associated with familial liability for schizophrenia. However, our results suggest that adult ROS individuals may be able to engage in compensatory strategies to achieve normal levels of performance. In a study by Moody et al. (2004), patients with mild Parkinson's disease were shown to perform normally on the WPT, while fMRI data showed that the patients activated prefrontal and MTL regions involved in declarative memory while the control subjects showed striatal activation during learning. It may be that ROS patients will show a similar alteration in the neural circuits active during the WPT. If so, it would support the idea that altered corticostriatal function is part of the genetic liability for schizophrenia.

In patients with schizophrenia, severe impairments have been reported in the WPT and similar tasks (Weickert et al., 2002; Keri et al., 2005; Foerde et al., 2008; Horan et al., 2008; Gimenez et al., 2003; Purdon et al., 2003). As with other neurocognitive functions, first-degree relatives of schizophrenia patients show a more subtle deficit in cognitive skill learning as measured by the WPT than do patients. The current findings are consistent with the hypothesis that cognitive skill learning deficits reflect familial liability to schizophrenia and not the effects of anti-psychotic medications used to treat psychotic symptoms.

Acknowledgments

We would like to thank the relatives of individuals with childhood onset schizophrenia and healthy control subjects who participated in this study. We thank Heidi Kuppinger for help with data collection. This work was supported by the Della Martin Foundation, and a National Institute of Mental Health Grant (MH 72697). The Della Martin Foundation and the NIMH had no further involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

Asarnow, R.F., 1999. Neurocognitive impairments in schizophrenia: a piece of the epigenetic puzzle. European Child and Adolescent Psychiatry 8, 15–18.
Asarnow, R.F., Asarnow, J.R., 1994. Childhood-onset schizophrenia: editors' introduction. Schizophrenia Bulletin 20, 591–597.
Asarnow, R.F., Brown, W., Strandburg, R., 1995. Children with a schizophrenic disorder: neurobehavioral studies. European Archives of Psychiatry and Clinical Neuroscience 245, 70–79.
Asarnow, R.F., Nuechterlein, K.H., Fogelson, D., Subotnik, K.L., Payne, D.A., Russell, A.T., Asarmen, J., Kuppinger, H., Kendler, K.S., 2001. Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. Archives of General Psychiatry 58, 581–588.
Braff, D.L., 1981. Impaired speed of information processing in nonmedicated schizotypal patients. Schizophrenia Bulletin 7, 499–508.
Braff, D.L., 1985. Attention, habituation, and information processing in psychiatric disorders. In: Michels, R., Cavenar, J.O., Brodie, H.K., Cooper, A.M., Guze, S.B. (Eds.), Psychiatry. J.B. Lippincott, Philadelphia, pp. 1–12.
Craik, F.I.M., Govoni, R., Naveh-Benjamin, M., Anderson, N.D., 1996. The effects of divided attention on encoding and retrieval processes in human memory. Journal of Experimental Psychology: General 125, 159–180.

Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., et al., 2009. Contributions of the basal ganglia and functionally related brain structures to motor learning. Behavioural Brain Research 199, 61–75.
Foerde, K., Knowlton, B.J., Poldrack, R.A., 2006. Modulation of competing memory systems by distraction. Proceedings of the National Academy of Sciences 103, 11778–11783.
Foerde, K., Poldrack, R.A., Knowlton, B.J., 2007. Secondary task effects on classification learning. Memory and Cognition 35, 864–874.
Foerde, K., Poldrack, R.A., Knowlton, B.J., Sabb, F.W., Bookheimer, S.Y., Bilder, R.M., Guthrie, D., Granholm, E., Nuechterlein, K.H., Marder, S.R., Asarnow, R.F., 2008. Selective corticostriatal dysfunction in schizophrenia: examination of motor and cognitive skill learning. Neuropsychology 22, 100–109.
Gimenez, M., Junque, C., Perez, M., Vendrell, P., Baeza, I., Salamero, 2003. Basal ganglia N-acetylaspartate correlates with the performance in the procedural task 'Tower of Hanoi' of neuroleptic-naïve schizophrenic patients. Neuroscience Letters 347, 97–100.
Gluck, M.A., Shohamy, D., Myers, C., 2002. How do people solve the "weather prediction" task? Individual variability in strategies for probabilistic category learning. Learning and Memory 9, 408–418.
Granholm, E., Asarnow, R.F., Marder, S.R., 1991. Controlled information processing resources and the development of automatic detection responses in schizophrenia. Journal of Abnormal Psychology 100, 22–30.
Granholm, E., Marder, S.R., Asarnow, R.F., 1996. Dual-task performance operating characteristics, resource limitations, and automatic processing in schizophrenia. Neuropsychology 10, 11–21.
Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophrenia Bulletin 26, 119–136.
Harvey, P.D., Keefe, R.S.E., Mitroupolou, V., Dupre, R., Roitman, S.L., Mohs, R.C., Siever, L.J., 1996. Information-processing markers of vulnerability to schizophrenia: performance of patients with schizotypal and nonschizotypal personality disorders. Psychiatry Research 60, 49–56.
Harvey, P.D., Moriarty, P.J., Serper, M.R., Schnur, E., Lieber, D., 2000. Practice-related improvement in information processing with novel antipsychotic treatment. Schizophrenia Research 46, 139–148.
Holzman, P.S., 1987. Recent studies of psychophysiology in schizophrenia. Schizophrenia Bulletin 13, 49–75.
Horan, W.P., Green, M.F., Knowlton, B.J., Wynn, J.K., Mintz, J., Nuechterlein, K.H., 2008. Impaired implicit learning in schizophrenia. Neuropsycholgy 22, 606–617.
Keri, S., Juhasz, A., Rimanoczy, A., Szekeres, G., Kelemen, O., Cimmer, C., et al., 2005. Habit learning and the genetics of the dopamine D3 receptor: evidence from patients with schizophrenia and healthy controls. Behavioral Neuroscience 119, 687–693.
Knowlton, B.J., Mangels, J.A., Squire, L.R., 1996. A neostriatal habit learning system in humans. Science 273, 1399–1402.
Knowlton, B.J., Squire, L.R., Gluck, M.A., 1994. Probabilistic classification learning in amnesia. Learning and Memory 1, 1–15.
Logan, G.D., 1978. Attention in character classification tasks: evidence for the automaticity of component stages. Journal of Experimental Psychology: General 107, 32–63.
Marsh, R., Alexander, G.M., Packard, M.G., Zhu, H.T., Wingard, J.C., Quackenbush, G., Peterson, B.S., 2004. Habit learning in Tourette syndrome—a translational neuroscience approach to a developmental psychopathology. Archives of General Psychiatry 61, 1259–1268.
Moriarty, P.J., Harvey, P.D., Mitropoulou, V., Granholm, E., Silverman, J.M., Siever, L.J., 2003. Reduced processing resource availability in schizotypal personality disorder: evidence from a dual-task CPT study. Journal of Clinical and Experimental Neuropsychology 25, 335–347.
Nicolson, R., Rapoport, J.L., 1999. Childhood-onset schizophrenia: rare but worth studying. Biological Psychiatry 46, 1418–1428.
Nuechterlein, KH., 1991. Vigilance in schizophrenia and related disorders. In: Steinhauer, S.R., Gruzelier, J.H., Zubin, J. (Eds.), Handbook of Schizophrenia, Neuropsychology, Psychophysiology and Information Processing. Elsevier Science Publishers, Amsterdam, The Netherlands, pp. 397–433.
Pashler, H., Johnston, J.C., Ruthruff, R., 2001. Attention and performance. Annual Review of Psychology 52, 629–651.
Peigneux, P., Maquet, P., Meulemans, T., Destrebecqz, A., Laureys, S., Degueldre, C., Delfiore, G., Aerts, J., Luxen, A., Franck, G., Van der Linden, M., Cleeremans, A., 2000. Striatum forever, despite sequence learning variability: a random effect analysis of PET data. Human Brain Mapping 10, 179–194.
Posner, M.I., Snyder, C.R.R., 1975. Attention and cognitive control. In: Solso, R.L. (Ed.), Information Processing and Cognition: The Loyola Symposium. Erlbaum, Hillsdale, NJ, pp. 55–82.
Purdon, S.E., Woodward, N., Lindborg, S.R., Stip, E., 2003. Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol. Psychopharmacology (Berl) 169, 390–397.
Schroder, J., Tittel, A., Stockert, A., Karr, M., 1996. Memory deficits in subsyndromes of chronic schizophrenia. Schizophrenia Research 21, 19–26.
Serper, M.R., Bergman, R.L., Harvey, P.D., 1990. Medication may be required for the development of automatic information processing in schizophrenia. Psychiatry Research 32, 281–288.
Shohamy, D., Myers, C.E., Kalanithi, J., Gluck, M.A., 2008. Basal ganglia and dopamine contributions to probabilistic category learning. Neuroscience and Biobehavioral Reviews 32, 219–236.
Wagshal, D., Knowlton, B.J., Cohen, J.R., Poldrack, R.A., Bookheimer, S.Y., Bilder, R.M., Fernandez, V.G., Asarnow, R.F., 2012. Deficits in probabilistic classification learning and liability for schizophrenia. Psychiatry Research 200, 167–172.
Weickert, T.W., Goldberg, T.E., Egan, M.F., Apud, J.A., Meeter, M., Myers, C.E, et al., 2010. Relative risk of probabilistic category learning deficits in patients with schizophrenia and their siblings. Biological Psychiatry 67, 948–955.
Weickert, T.W., Terrazas, A., Bigelow, L.B., Malley, J.D., Hyde, T.T., Egan, M.F., et al., 2002. Habit and skill learning in schizophrenia: evidence of normal striatal processing with abnormal cortical input. Learning & Memory 9, 430–442.
Winter, W.E., Broman, M., Rose, A.L., Reber, A.S., 2001. The assessment of cognitive procedural learning in amnesia: why the tower of Hanoi has fallen down. Brain and Cognition 45, 79–96.