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Typical and atypical antipsychotic medications differentially affect two nondeclarative memory tasks in schizophrenic patients: a double dissociation

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Abstract

Nondeclarative memory (NDM) has subtypes associated with different brain regions; learning of a probabilistic classification task is impaired by striatal damage and learning of a gambling task is impaired by ventromedial prefrontocortical damage. Typical and atypical antipsychotic medications differentially affect immediate early gene expression in the striatum and frontal cortex in normal rats. This suggested the hypothesis that schizophrenic patients treated with typical antipsychotics will have impaired probabilistic classification learning (PCL) and that similar patients treated with atypical antipsychotics will have impaired learning of the gambling task. Groups of schizophrenia patients treated with typical or atypical antipsychotics did not differ from each other on the Brief Psychiatric Rating Scale (BPRS), Mini Mental State Exam (MMSE) or a number of indexes of the Wisconsin Card Sorting Task (WCST) but performed worse than normal controls on these instruments. In the first study, patients treated with typicals ($n=20$) but not atypicals ($n=20$) or normal controls ($n=32$) were impaired in probabilistic classification. In the second study, those treated with atypicals ($n=18$) but not typicals ($n=18$) or normal controls ($n=18$) were impaired in the gambling task. Results suggest that typical and atypical antipsychotics differentially affect nondeclarative memory mediated by different brain regions.

Keywords: Atypical antipsychotic; Gambling; Learning; Nondeclarative memory; Probabilistic classification; Schizophrenia; Typical antipsychotic; WCST

1. Introduction

Memories can be declarative (DM), consciously recollected facts and events, or nondeclarative (NDM), expressed through performance without conscious

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recall. DM is impaired following damage to medial temporal or diencephalic structures; NDM includes several subtypes that rely on a number of brain structures (Squire and Knowlton, 2000).

Parkinsonians performing a probabilistic classification learning (PCL) task had intact DM but impaired NDM. The task required them to view a pattern and to predict the weather, rain or shine. Patterns were associated probabilistically with outcomes. Controls gradually predicted accurately over trials and performed well on a DM questionnaire. Amnesics also learned the PCL task but performed poorly on the questionnaire. Parkinson's patients failed to learn the PCL task but had intact DM (Knowlton et al., 1996). As Parkinson's patients suffer from a loss of striatal dopamine (DA), results implicated striatal DA in NDM. This conclusion is consistent with the results of a number of studies using a variety of NDM tasks in Parkinson's patients (Allain et al., 1995; Charbonneau et al., 1996; Heindel et al., 1989; Koeing et al., 1999; Saint-Cyr et al., 1988; Swainson et al., 2000).

Learning of a gambling task, that required choosing a card from four decks, was impaired by bilateral damage to the ventromedial prefrontal cortex (vmPFC; Tranel et al., 1999). Each choice resulted in a payoff of play money and sometimes a penalty. Two decks produced low payoffs and occasionally low penalties and were advantageous over trials; the others produced large payoffs but occasionally large penalties and were disadvantageous over trials. Controls began by choosing from the disadvantageous decks but gradually shifted to the advantageous decks. Shifting began before participants could declare awareness of the contingencies, suggesting that the task assess NDM. Participants with vmPFC damage failed to shift to the less risky decks even after repeated testing implicating this structure in NDM (Bechara et al., 1997, 1999, 2000). Note that Knowlton et al. (1996) reported that PCL of frontal patients was not related to frontal damage, suggesting that PCL and the gambling task may assess different types of NDM.

Schizophrenics are treated with antipsychotics, classified as typical or atypical based on several indices including their side-effects profile. Typicals, e.g., chlorpromazine and haloperidol, often produce extrapyramidal side effects (EPS) including parkinsonism, implicating striatal DA receptor blocking action of these agents in EPS liability. In contrast, atypicals, e.g., clozapine and risperidone, are defined by low EPS liability (Arnt and Skarsfeldt, 1998; Remington and Kapur, 2000; Waddington and O'Callaghan, 1997). This suggests that these two classes of antipsychotics influence different brain regions. Animal research supports this view; for example, typical and atypical antipsychotics differentially affect neurotransmitter receptors (Taylor and Creese, 2000). Studies of induction of the immediate early gene c-*fos* in normal animals show that typicals induce c-*fos* in the dorsal striatum and nucleus accumbens but not in the frontal cortex whereas atypicals induce c-*fos* in the frontal cortex and nucleus accumbens but not the striatum (Wan et al., 1995; Weinberger and Lipska, 1995).

These considerations led us to test the following hypotheses. Schizophrenic patients treated with typical antipsychotics but not those treated with atypicals will be impaired on the PCL but not on the gambling task. Schizophrenic patients treated with atypical antipsychotics but not those treated with typicals will be impaired on the gambling task but not on the PCL task. Although the classification of antipsychotic medications as typical or atypical is not perfectly delineated and may depend on dose (Remington and Kapur, 2000), for the purposes of the present study, as typicals we included phenothiazines, flupenthixol, haloperidol and loxapine and as atypicals we included clozapine, risperidone, olanzapine and quetiapine.

2. Materials and methods

2.1. Participants

The probabilistic classification and gambling studies included 72 and 54 participants, respectively, with three groups in each experiment: 20 and 18 schizophrenic patients treated with typicals, 20 and 18 schizophrenic patients treated with atypicals and 32 and 18 controls. All patients had a DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia and were over 18 years old. They were recruited at Providence Continuing Care Centre Mental Health Services (formerly Kingston Psychiatric Hospital) or through out-patient services supervised

by the hospital. Schizophrenic participants were excluded if they had a history of other neurological disorders (e.g., epilepsy), head injury with loss of consciousness, medical illnesses that may affect brain function, severe visual problems (e.g., cataracts) or colour blindness or substance abuse in the past 1 month. They were excluded if they had not been taking their current medication for at least 4 weeks. Duration of illness was not systematically recorded.

Control participants for each study were recruited from the community with the use of a newspaper ad and postings on local bulletin boards. An attempt was made to match controls to schizophrenic participants in each study on age, gender and level of education (Table 1). Control participants were excluded if they answered affirmatively to any of the following: taking psychoactive medications, previous diagnosis of schizophrenia, first-degree relatives with schizophrenia, colour blindness and learning disabilities.

Analysis of variance (ANOVA) comparing the mean ages of the groups for the PCL study revealed no significant effect. The groups differed in education, $F(2,69) = 9.90$, $p < 0.01$, and post hoc tests (Newman–Keuls) showed the medication groups to differ from the controls ($p < 0.05$) but not from each other. ANOVA comparing the mean ages of the groups in the gambling study revealed no significant effect. There was a significant effect of education, $F(2,51) = 4.97$, $p < 0.05$, the typical antipsychotic group being lower than the other two (Table 1).

2.2. Materials

Screening questions were asked and demographic information was collected with the use of two brief questionnaires. The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) was used to assess psychiatric symptoms in schizophrenic patients and the Mini Mental State Examination (MMSE; Folstein et al., 1975) was used to assess general cognitive functioning in all participants. The Wisconsin Card Sorting Test (WCST; Heaton, 1981; Heaton et al., 1993), assessing aspects of cognitive function (Stratta et al., 1997), was employed to allow comparison of card sorting performance of the present samples of schizophrenic patients with others reported in the literature.

The PCL task was developed by Gluck and Bower (1988) and was used by Knowlton et al. (1996). Participants sat before a 17″ computer screen with a metal box (18 × 11 × 6 cm) outfitted with two buttons (2.4 cm diameter) placed in front of it. One button was labeled below with the word "RAIN" and above with a drawing of a cloud, lightening bolt and rain; the other was labeled "SUN" with a drawing of the sun. Initially the screen showed four virtual cards (4.3 × 6.0 cm) in a row above which was written, "In this game you are the weather forecaster. You will learn how to predict rain or shine using a deck of four cards." On each trial, one, two or three of the cards appeared on the screen; cards depicted either 7 squares, 10 triangles, 9 circles or 13

Table 1
Participant characteristics

	Controls	Typicals	Atypicals
Probabilistic classification task			
Number of participants	32	20	20
Mean (± S.E.M.) age (year)	42.2 (± 2.9)	40.2 (± 1.9)	38.1 (± 2.9)
Gender	18F, 14M	7F, 13M	8F, 12M
Handedness	3L, 29R	2L, 18R	0L, 20R
Mean (± S.E.M.) education (year)	15.2 (± 0.4)	12.1 (± 0.6)*	13.4 (± 0.5)*
Gambling task			
Number of participants	18	18	18
Mean (± S.E.M.) age (year)	45.2 (± 2.8)	45.6 (± 1.4)	42.1 (± 2.3)
Gender	6F, 12M	6F, 12M	6F, 12M
Handedness	1L, 17R	1L, 17R	2L, 16R
Mean (± S.E.M.) education (year)	13.9 (± 0.5)	11.8 (± 0.7)†	13.7 (± 0.5)

* Different from Controls ($p < 0.05$) by Newman–Keuls test following significant ANOVA.
† Different from Controls ($p < 0.05$) and Atypicals ($p < 0.05$) by Newman–Keuls test following significant ANOVA.

diamonds. Participants were not informed that the cards were probabilistically associated with the outcomes. The probabilities for one of the outcomes were 75%, 57%, 43% and 25% and different cards were associated with each probability for each participant. Following a correct response, the card(s) remained on the screen, a high frequency tone (0.5 s) was presented, and a "happy face" icon, the word "correct", and an icon showing the appropriate weather appeared on the screen; incorrect responses were followed by a low frequency tone (0.5 s), and a "nonsmiling face" icon, the word "wrong" and an icon showing the correct weather appeared on the screen. After 5 s, the next trial began. A 20-s break followed each set of 25 trials.

The gambling task was like the one described by Bechara et al. (1997). Four decks of 40 cards, 20 with red faces and 20 with black faces arranged in a predetermined order in each deck, were placed on a table top. The participant was given $2000 in play money and seated at the table. The participant was instructed to select a card from the top of any of the decks. Each selection was followed by a payoff of $50 or $100 and on some occasions a penalty of $25 to $1250. For two of the decks, the payoff was always $50 and for the other two it was always $100. However, for one of the former two decks penalties never exceeded $50 and for the other they were $250 but were infrequent. For one of the latter two decks penalties ranged from $150 to $350 and for the other, although infrequent, penalties were $1250. Cards with a black face always signaled a payoff with no penalty. Cards with a red face were also always followed with a payoff but sometimes also with a penalty. In the long run, the $50-payoff decks were advantageous. Trials were self-paced.

Declarative memory questionnaires followed the PCL and gambling tasks. The former consisted of five items from those used by Knowlton et al. (1996), for example, "What was the maximum number of cards that could be presented at one time?" followed by multiple choices of two, three, four or five. The latter consisted of 10 items patterned after those in the DM questionnaire for the PCL task. Two examples are: "How many decks were there to choose from?" followed by multiple choices of two, three, four or five and "How much money did you start with?" followed by multiple choices of $200, $1000, $1500 or $2000.

2.3. Procedure

The investigator greeted the participants individually at the arranged time, briefed them about the study and asked them to complete the consent form. Participants were then asked to complete the screening and demographics questionnaires. All participants then were administered the MMSE and schizophrenic participants were then given the BPRS. For the PCL experiment, 150 trials of the rain or shine task followed and for the gambling experiment, 100 trials of the gambling task followed. Each of these tasks was followed by the appropriate DM questionnaire. The final instrument was the WCST. Each of the studies required about 1 h per participant. Participants were paid $10 whether or not they completed the study.

2.4. Analyses

Group means were compared using ANOVA followed by post hoc comparisons where appropriate.

3. Results

For the PCL task, the dependent variable was mean number of correct responses on the first 100 trials, analyzed in blocks of 20 trials (Fig. 1A). Performance of the control group improved to near asymptote from the first to the second block and that of the schizophrenic group treated with atypical antipsychotic medications similarly showed the greatest improvement from the first to the second block. The schizophrenic group treated with typical antipsychotic medications showed little evidence of learning. A two-variable mixed design ANOVA revealed significant main effects of group, $F(2,69) = 3.56$, $p < 0.04$, and trial block, $F(4,276) = 5.90$, $p < 0.001$, but a non-significant interaction, $F(8,276) = 1.51$, $p > 0.10$. Pairwise comparisons (Newman–Keuls) of groups revealed that the control and atypical groups did not differ from each other but both differed from the typical group ($p < 0.05$). Although the interaction was not significant, planned one-way ANOVA of the block effect for each group revealed significant effects for the control, $F(4,124) = 3.67$, $p < 0.01$, and atypical groups, $F(4,76) = 3.84$, $p < 0.01$, but not the

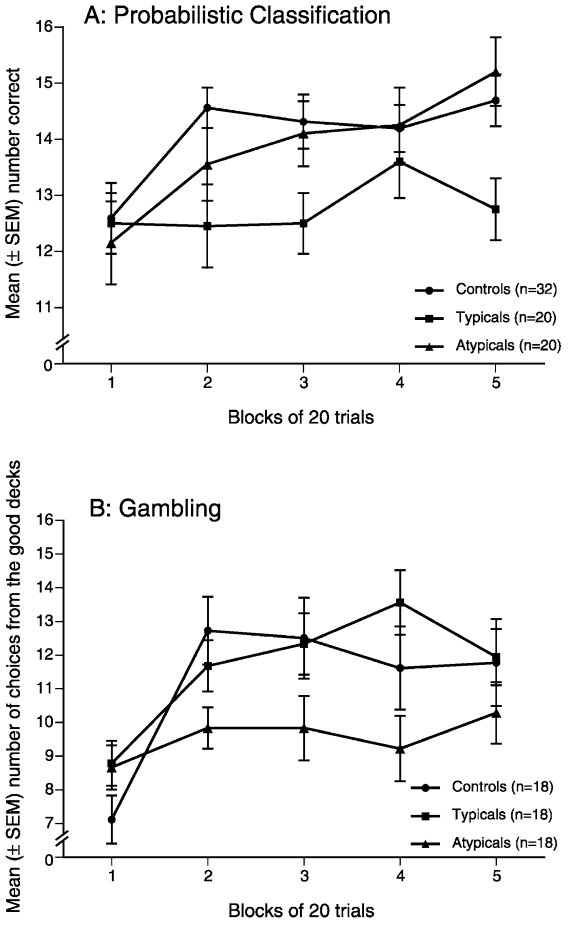

Fig. 1. Mean (± S.E.M.) number correct on the probabilistic classification task (A) and mean (± S.E.M.) number of choices from the good decks in the gambling task (B) for control participants and schizophrenic patients treated with typical or atypical antipsychotic medications. ANOVA revealed a main effect of groups in the probabilistic classification task, the Control and Atypicals not differing significantly from each other and both differing from the Typicals. Planned one-way analysis of the effects of blocks of trials for each group revealed a significant improvement in the Control and Atypicals but not in the Typicals group. For the gambling task ANOVA revealed an interaction and tests of simple main effects of blocks for each group revealed an improvement over trials for the Control and Typicals groups but not for the Atypicals group.

typical group, $F(4,76) = 1.24$, $p > 0.10$. These analyses confirm that the control group and the schizophrenic group treated with atypical antipsychotic medications learned the PCL task whereas the schizophrenic group treated with typical antipsychotic medications failed to learn the PCL task.

For the gambling task, the dependent variable was the mean number of choices from the good (advantageous) decks over 100 trials in blocks of 20 trials (Fig. 1B). The control group improved to near asymptote from the first to the second block. The group of schizophrenic patients treated with typical antipsychotic medications similarly showed the greatest improvement from the first to the second block. The schizophrenic group treated with atypical antipsychotic medications showed little evidence of learning. A two-variable mixed design ANOVA revealed a nonsignificant main effect of group, $F(2,51) = 3.02$, $0.05 < p < 0.06$, a significant effect of trial block, $F(4,204) = 10.87$, $p < 0.0001$, and a significant interaction, $F(8,204) = 2.14$, $p < 0.04$. Tests of simple effects of block for each group showed the block effect to be significant for the control, $F(4,204) = 8.96$, $p < 0.001$, and typical groups, $F(4,204) = 5.53$, $p < 0.001$, but not for the atypical medication group, $F(4,204) = 0.67$, $p > 0.10$. These analyses confirm that the control group and the schizophrenic group treated with typical antipsychotic medications learned the gambling task whereas the schizophrenic group treated with atypical antipsychotic medications failed to learn the gambling task.

The DM questionnaire that followed the PCL task had five items. Both schizophrenic groups scored lower than controls on this instrument (Table 2); ANOVA revealed a significant group effect, $F(2,69) = 6.28$, $p < 0.04$, and Newman–Keuls pairwise comparisons showed that both the typical and atypical groups scored lower than the controls ($p < 0.01$). For the gambling study, the DM questionnaire had 10 items. Once again, the two schizophrenic groups scored lower than the controls (Table 3). ANOVA revealed a significant group effect, $F(2,51) = 4.09$, $p < 0.03$, and post hocs showed the control to differ from the schizophrenic group taking typical antipsychotics ($p < 0.01$). The schizophrenic group taking atypical antipsychotics performed intermediate to the other groups and did not differ significantly from either. In neither study did individual item analyses reveal any significant differences between the two medication groups. Thus, in both studies, DM was impaired to a similar extent in both medication groups.

MMSE performance of the two schizophrenic groups in the PCL study was lower than that of the controls (Table 2) and, similarly, the two schizophrenic

Table 2
Mean (±S.E.M.) probabilistic classification, Brief Psychiatric Rating Scale, declarative memory, Mini Mental State Exam, and Wisconsin Card Sorting Task (WCST) performance of schizophrenic patients taking typical vs. antipsychotic antipsychotic medications

	Control	Typicals	Atypicals
Number of participants	32	20	20
Prob class total correct	70.3 ± 0.5	63.8[a] ± 0.6	69.3 ± 0.7
Brief Psychiatric Rating Scale		32.7[b] ± 2.0	36.1[c] ± 2.9
Declarative memory	4.5 ± 0.1	3.8[d] ± 0.2	3.7[d] ± 0.2
Mini Mental State Exam	28.9 ± 0.2	27.6[d] ± 0.5	27.4[d] ± 0.4
WCST categories completed	5.3 ± 0.3	3.1[d] ± 0.5	3.1[d] ± 0.5
WCST total correct	76.6 ± 1.9	62.2[d] ± 3.6	66.1[d] ± 4.6
WCST % perseverative response	11.6 ± 1.0	29.4[d] ± 4.6	33.3[d] ± 6.8
WCST total errors	27.6 ± 2.8	57.9[d] ± 5.8	53.6[d] ± 6.3
WCST % perseverative errors	9.9 ± 0.9	23.8[d] ± 3.3	26.9[d] ± 5.0
WCST % non-perseverative errors	14.8 ± 1.4	22.3 ± 3.7	16.0 ± 2.3

[a] Different from Control and Atypicals.
[b] Based on 15 participants.
[c] Based on 19 participants.
[d] Dfferent from Control.

groups in the gambling study were lower than their control group (Table 3). ANOVA revealed a significant group effect in the former study, $F(2,69) = 5.33$, $p < 0.01$, and post hoc tests showed the two schizophrenic groups to differ significantly from the controls ($p < 0.05$). The corresponding ANOVA for the gambling study yielded a nonsignificant main effect, $F(2,51) = 1.36$, $p > 0.10$. Thus, in both studies the two medication groups did not differ significantly from each other on the MMSE and in the PCL study the two medication groups differed from the controls.

Mean BPRS scores for the schizophrenic groups from both studies ranged from 31 to 36 (Tables 2 and 3). Note that BPRS scores were not available for five participants in the typical and for one participant in the atypical antipsychotic medication groups from the PCL study. The group treated with typicals did not differ from the group treated with atypicals in either the PCL, $t(32) = 1.04$, $p > 0.10$, or the gambling study, $t(34) < 1.0$, $p > 0.10$. Thus, the level of psychiatric symptoms did not differ significantly in the medication groups in either study.

Several measures from the WCST were analyzed (Heaton, 1981). Results from ANOVA comparing groups for each study are shown in Table 4 and results of pairwise comparisons are indicated in Tables 2 and 3. In both studies, the number of categories completed and the total number of correct responses was lower for both of the schizophrenic groups compared to the relevant control group and the schizophrenic groups did not differ from each other. Thus, regardless of whether schizophrenic participants in either study

Table 3
Mean (±S.E.M.) gambling task, Brief Psychiatric Rating Scale, declarative memory, Mini Mental State Exam, and Wisconsin Card Sorting Task (WCST) performance of schizophrenic patients taking typical vs. antipsychotic antipsychotic medications

	Control	Typicals	Atypicals
Number of participants	18	18	18
Gambling task total correct	55.7±3.5	58.3±2.8	47.8[a]±3.1
Brief Psychiatric Rating Scale		30.8±3.1	34.2±2.4
Declarative memory	8.0±0.2	6.7[b]±0.4	7.3±0.3
Mini Mental State Exam	28.9±0.3	28.3±0.4	28.1±0.4
WCST categories completed	4.7±0.6	2.5[b]±0.6	3.2[b]±0.6
WCST total correct	72.1±2.0	58.2±5.2	66.0±4.6
WCST % perseverative response	13.2±1.5	45.7[b]±8.7	23.6[c]±4.3
WCST total errors	32.1±4.7	62.9[b]±7.1	52.8[b]±6.8
WCST % perseverative errors	12.5±1.4	36.7[b]±6.1	20.8[c]±3.3
WCST % non-perseverative errors	16.1±2.6	14.2±2.3	21.7±3.4

[a] Different from Control and Typicals.
[b] Different from Control.
[c] Different from Typicals.

Table 4
F-test results for Wisconsin Card Sorting Task (WCST) for groups in the probabilistic classification and gambling studies

	df	F	p<
Probabilistic classification			
WCST categories completed	2, 69	9.12	0.001
WCST total correct	2, 69	5.32	0.01
WCST % perseverative response	2, 69	7.95	0.001
WCST total errors	2, 69	11.71	0.0001
WCST % perseverative errors	2, 69	8.99	0.001
WCST % non-perseverative errors	2, 69	2.86	$0.05 < p < 0.07$
Gambling			
WCST categories completed	2, 47	4.90	0.02
WCST total correct	2, 47	3.09	$0.05 < p < 0.06$
WCST % perseverative response	2, 47	9.63	0.001
WCST total errors	2, 47	7.75	0.001
WCST % perseverative errors	2, 47	10.66	0.0001
WCST % non-perseverative errors	2, 47	2.24	ns

df: Degrees of freedom; ns: not significant.

Table 5
Mean total correct on the probabilistic classification task for schizophrenic patients taking individual typical or atypical antipsychotic medications

	N	Total correct
Typical antipsychotic		
Control	32	70.3
Typicals combined	20	63.8[a]
Chlorpromazine	1	70.0
Fluphenazine	3	69.0
Perphenazine	7	65.1
Flupenthixol	4	55.8
Haloperidol	3	57.7
Loxapine	2	73.5
Atypical antipsychotic		
Control	32	70.3
Atypicals combined	20	69.3
Clozapine	1	60.0
Risperidone	7	68.3
Olanzapine	11	70.6
Quetiapine	1	59.0

[a] Different from Control.

were treated with typical or atypical antipsychotics, they were impaired in shifting from category to category in the WCST.

The percent perseverative responses, total errors and percent perseverative errors in the WCST were higher in both medication groups compared to their respective control group in each study. With two exceptions, the medication groups did not differ significantly from each other but both differed from the control. The exceptions were in the gambling study; for percent perseverative responses and for percent perseverative errors, the typical antipsychotic medication group scored higher than the control and the atypical groups which did not themselves differ significantly (Tables 2, 3 and 4).

The final index from the WCST, percent nonperseverative errors yielded no significant effects. In summary for the WCST task, the two medication groups generally did worse than the controls and generally did not differ from each other.

To address the possibility that the samples differed, typical and atypical medication groups from each sample were compared (*t*-tests) on age, education, BPRS scores, MMSE scores and WCST categories completed. These tests yielded only one significant difference; i.e., the ages of the typical groups were different (PCL group 40.2 years; gambling group 45.6 years, $t(36) = 2.25$, $p < 0.05$). These results suggest that the samples used in the two tasks were not different from each other.

Participants in the typical and atypical medication groups from both studies took a variety of medications. As can be seen in Table 5 for the PCL study, typical medications included chlorpromazine, fluphenazine, perphenazine, flupenthixol, haloperidol and loxapine. Atypicals included clozapine, risperidone, olanzapine and quetiapine. The number of participants taking some medications was low (only one in some cases) making statistical analyses of these results impossible. Of the typicals, those treated with chlorpromazine, fluphenazine or loxapine seemed to be least affected but the numbers in these cases were very small. Of the atypicals, clozapine and quetiapine were associated with poorer performance but there was only one case in each dose category. For the gambling task (Table 6), typicals included fluphenazine, perphenazine, flupenthixol, haloperidol, and loxapine; atypicals included clozapine, risperidone and olanzapine. The typical antipsychotic medication fluphenazine seemed to be associated with poorer performance of the gambling task but this subgroup numbered only three. Of the atypicals, the subgroup of four receiving risperidone seemed to score higher than those receiving clozapine or olanzapine. It is perhaps worth noting

Table 6
Mean total correct on the gambling task for schizophrenic patients taking individual typical or atypical antipsychotic medications

	N	Total correct
Typical antipsychotic		
Control	18	55.7
Typicals combined	18	58.3
Fluphenazine	3	52.3
Perphenazine	2	63.5
Flupenthixol	4	54.5
Haloperidol	5	59.5
Loxapine	2	67.0
Mixed (two typicals)	2	47.5
Atypical antipsychotic		
Control	18	55.7
Atypicals combined	18	47.8[a]
Clozapine	7	47.3
Risperidone	4	55.7
Olanzapine	7	43.9

[a] Different from Control.

that risperidone was not, however, acting like a typical antipsychotic; in the PCL task the subgroup of seven who were taking risperidone was not impaired. Although the numbers are small and caution is necessary, the three participants from each study who were treated with fluphenazine present an interesting profile. Thus, in the PCL task where typicals on average impaired learning, fluphenazine appeared to be less disruptive; in the gambling task where typicals did not on average affect learning, fluphenazine appeared to impair performance.

We have only incomplete information concerning the use of anticholinergics in the PCL experiment. This information was available for 17 participants in the typical group and 13 in the atypical group; three and four participants received anticholinergics, respectively. For the gambling task experiment, 11 of the 18 participants in the typical group and 4 of the 18 participants in the atypical group were receiving anticholinergics.

4. Discussion

Controls performing the PCL task learned over the first two trial blocks in agreement with the control data of Knowlton et al. (1996). Similarly, schizophrenics treated with atypical antipsychotics learned. Schizophrenic participants treated with typicals, alternatively, failed to learn. This failure is comparable to that of the Parkinson patients of Knowlton et al. (1996). Controls performing the gambling task learned over the first two trial blocks, shifting their choices to the advantageous decks, like the controls of Bechara et al. (1997, 1999, 2000). Schizophrenic participants treated with typicals similarly learned. In contrast, schizophrenics treated with atypicals failed to learn. The poor performance of this group is similar to the poor performance of participants with damage to the vmPFC on the gambling task (Bechara et al., 1997, 1999, 2000). Results reveal a double dissociation of antipsychotic medication class and NDM task type.

There is one report each in the literature of performance on the gambling task and on the PCL task in schizophrenic patients. Wilder et al. (1998) tested 12 schizophrenics treated with typicals ($n=4$), atypicals ($n=7$) or no medication ($n=1$) and found no significant difference from controls. There was a nonsignificant trend towards fewer choices from the advantageous decks in the schizophrenic group. Perhaps this trend reflects poorer performance of the subgroup treated with atypicals but it is not possible to tell from the paper because participants were not separated into subgroups based on the class of antipsychotic that they received. Kéri et al. (2000) reported that schizophrenic patients were not impaired in PCL using the rain or shine task. They did not report the medication status of their participants.

In the present studies, schizophrenic participants were recruited and then assigned to medication group according to the medication they were taking. Thus, participant assignment to group was not randomized. If there was a prescribing bias among psychiatrists in the Kingston area, for example, to always treat first with typicals and then to shift to atypicals if the outcome was poor (as was the case in the early 1990s), it might have been possible that atypical medication groups were more symptomatic than typical groups. Although this might appear to explain the poor performance of the atypical group on the gambling task, it does not explain the intact performance of the atypical group on the PCL task. The suggestion that the level of functioning of the two groups within each study may have been different is further weakened by the failure to observe significant differences between groups in BPRS scores. The finding of a double dissociation of medication class and task type makes unlikely the possibility that the present results can be attributed to nonrandom assignment of participants to groups.

One weakness of the present study with respect to the conclusion that a double dissociation of medication class and task type was found is that the samples used for each task were different. Comparison of typical and atypical medication groups from each sample on age, education, BPRS scores, MMSE scores and WCST categories completed yielded only a significant difference in age for the typical groups. It is noteworthy that it was the younger group that showed an impairment in the PCL task. These results suggest that the samples used in the two tasks were not different from each other. However, instruments other than the BPRS would provide further details of symptom subtypes and intelligence quotient assessments would provide a stronger basis than education

for comparing group intelligence; even with the results of these types of tests, the possibility that the two groups differed on important variables could not be ruled out but it could be lessened. In future studies, it will be important to compare PCL and gambling performance of the same participants (we are currently conducting such an experiment).

It is unlikely that differential performance of medication groups can be attributed to impaired cognition. Although both groups of patients in the PCL study had lower education and MMSE scores relative to controls, only the group treated with typicals differed from controls on the task itself. Furthermore, in the gambling study, the mean years of education of the typical antipsychotic medication group was significantly lower than that of the other groups, yet this group learned the task as well as controls; the group treated with atypicals, that had an education level similar to that of the controls, failed to learn the gambling task. Clearly, deficits in learning of the two tasks cannot be attributed to group differences in number of years of education or MMSE scores.

Cognitive abilities are impaired by anticholinergic drugs (Drachman, 1978; Beatty et al., 1986). Anticholinergics are often given along with antipsychotic medications and some participants in both of the present studies in both antipsychotic medication groups were receiving anticholinergics. The group with the highest proportion of participants receiving anticholinergics was the typical antipsychotic medication group from the gambling study. However, this group did not show an impairment on the gambling task nor did it differ from the atypical group on the declarative memory questionnaire or the MMSE. Thus, it seems unlikely that the present results can be understood with respect to possible effects of anticholinergic medications.

Heaton (1981) described a number of indexes of the WCST. The scores on those indexes of the control and schizophrenic groups tested here were in good agreement with scores observed by others in controls and schizophrenics (Dieci et al., 1997; Everett et al., 2001; Haut et al., 1996; Stratta et al., 1997). In the PCL study, schizophrenic participants in both medication groups performed worse than controls on indexes of the WCST and did not differ significantly from each other. This was generally the case for the gambling study too but on two indexes, percent perseverative responses and percent perseverative errors, schizophrenic participants treated with atypicals were significantly less impaired than the group treated with typicals and did not differ significantly from controls. However, it was the group treated with atypicals that was impaired in the gambling task. Thus, impairments on indexes of the WCST, although seen in schizophrenic patients, were not specifically associated with impairments on the PCL or gambling tasks.

It has been suggested that deficits in the WCST reflect hypofunctioning of the dorsolateral prefrontal cortex. For example, decreased activation of this area was observed in imaging studies of schizophrenic patients performing below standard on the WCST (Weinberger et al., 1986). However, results of studies showing that impaired performance on the WCST is highly correlated with scores on intelligence tests suggests that the deficit in WCST performance seen in schizophrenics is not selective but rather is part of a more generalized neuropsychological impairment (Dieci et al., 1997). The recent study of Mohamed et al. (1999) showing reduced general intelligence in schizophrenic patients supports this suggestion. From this point of view, the observation of impaired WCST performance in participants evincing intact performance of the gambling task, shown to depend in part on the integrity of the prefrontal cortex, is not contradictory.

On a number of measures including the BPRS and various subscales of the WCST, the schizophrenic groups treated with typical or atypical antipsychotics in the present studies were not different from one another and, furthermore, they were similar to other samples of schizophrenic patients in the literature. This makes it unlikely that the observed deficits in PCL and gambling task performance of schizophrenic groups treated, respectively, with typicals and atypicals can be attributed to the disease. Deficits appear to have been produced by the class of antipsychotic medication with which schizophrenic patients were treated. In future studies, the effects of schizophrenia and antipsychotic medications on NDM task performance could be dissociated by including a nonmedicated schizophrenic control group in a study similar to the present one or by evaluating the effects of typical and atypical antipsychotics administered to normals on NDM task performance.

It is interesting to note the convergence among previous reports of relationships between localized

brain damage and deficits on PCL and gambling tasks, c-*fos* observations in normal animals, and behavioural findings of the present study. Thus, Parkinson patients, known to suffer from a loss of DA innervation of the striatum, are impaired in PCL (Knowlton et al., 1996). Typical antipsychotic medications somewhat selectively increase c-*fos* levels in the striatum in normal animals (Weinberger and Lipska, 1995) and schizophrenic patients treated with these drugs are impaired in PCL (present study). Similar schizophrenic patients treated with atypicals are not impaired (present study) and people with damage to the frontal cortex do not show an impairment that is related to frontal function (Knowlton et al., 1996). People who have suffered damage to the vmPFC are impaired on the gambling task (Bechara et al., 1997, 1999, 2000). Atypicals somewhat selectively increase c-*fos* levels in the medial PFC of normal rats (Weinberger and Lipska, 1995) and schizophrenic patients treated with these medications are impaired on the gambling task (present study). Similar schizophrenic patients treated with typicals are not impaired (present study). Thus, there appears to be a relationship between the regional specificity of some of the neurochemical effects of different classes of antipsychotics and impairments on tasks known to be sensitive to damage to specific brain regions. At present it is not possible to specify the nature of these putative relationships.

There are a number of cautions with respect to these suggested relationships. Thus, it is not known if typical and atypical antipsychotics differentially affect c-*fos* expression in the brains of nonhuman primates or people nor is it known whether c-*fos* expression is affected by schizophrenia. Neither is it known if changes in c-*fos* expression produce mnemonic deficits like those reported here and that are known to result from regional brain damage. These cautions make it clear that although there are suggested relationships between localized brain damage, NDM task performance, and regional differences in immediate early gene induction in normal rats produced by typical and atypical antipsychotics, published results providing much of the empirical bases for making these connections are still lacking.

In the present study, participants were assigned to groups based on the class of antipsychotic they were taking. Antipsychotic medications are classified as typical or atypical based on a number of indices including EPS liability. In the present study, medications were classified as typical or atypical according to the general use in the literature (Arnt and Skarsfeldt, 1998; Remington and Kapur, 2000; Waddington and O'Callaghan, 1997). Insufficient numbers of individuals taking specific medications were tested to allow for any systematic analysis of their effects. Although caution is required and no conclusions can be drawn at present, the data presented in Tables 5 and 6 showing that fluphenazine had a profile suggestive of an atypical rather than a typical and that risperidone appeared to produce little impairment on either task suggest that further evaluations of larger numbers of individuals treated with specific medications would be useful. We are presently carrying out such an investigation.

Both the PCL and gambling tasks require NDM. The specific differences between tasks that may be responsible for their differential sensitivity to striatal and ventromedial prefrontal cortical damage are not known. One difference that may be relevant is that the gambling task provides information about cumulative success or failure with the use of play money. The PCL task provides feedback on each trial but there is no cumulative feedback concerning the total number correct. Perhaps cumulative information about ongoing success invokes executive functions normally mediated by the prefrontal cortex. Manipulation of this feature of the tasks might lead to a change in their sensitivity to damage to particular brain regions.

At present, the mechanisms of the therapeutic action of atypical antipsychotics remain the topic of lively debate and intense investigation (Meltzer and McGurk, 1999; Remington and Kapur, 2000). The findings reported here showing impaired gambling task performance of schizophrenic patients treated with these medications may provide another clue to those mechanisms and to understanding the side-effects profile of atypicals. Further studies are needed to better understand the relationship between the therapeutic and iatrogenic deficit-inducing actions of antipsychotic medications.

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