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Do neuroleptics impair learning in schizophrenic patients?

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Dopamine (DA) has been shown to be involved in reward-related (incentive) learning but not stimulus-stimulus (s-s) associative learning. Schizophrenic individuals receive neuroleptics (DA receptor blockers) for therapy and therefore may have impaired incentive learning. To test this hypothesis, in experiment 1, schizophrenic outpatients receiving haloperidol or flupenthixol and matched controls were tested on tasks involving incentive or s-s learning. Patients were also given the Brief Psychiatric Rating Scale (BPRS). Results showed the patients to be significantly impaired in every task. However, only impairments of s-s learning were correlated with psychiatric state. Thus, deficits on the tasks involving incentive learning were interpreted as resulting from neuroleptic drugs rather than psychiatric state. Experiment 2 tested 26 schizophrenic inpatients receiving a variety of neuroleptics (converted to chloropromazine equivalency (CPZEQ)) on the same tasks. A blood sample was collected from the patients and from age-matched controls and prolactin levels were found to be significantly higher in the patients. Multiple regression analysis was used on patient data to determine whether prolactin level or CPZEQ were related to performance. It was found that incentive learning but not s-s associative learning was significantly predicted by one of these two indexes of neuroleptic drug dose. The results of these experiments provide some support for the hypothesis that neuroleptics might impair incentive but not s-s associative learning in schizophrenics. The observation that neuroleptics affect human incentive learning might lead to more efficient use of behavior modification programs in the treatment of schizophrenia.

Key words: Learning; Neuroleptics; Schizophrenic patient; Motor behavior; Prolactin

INTRODUCTION

Although there have been numerous studies examining the effects of neuroleptics in a number of test paradigms (e.g., Gibbs, Wilkens and Lauterbach, 1956), there have been very few tests of the effects of neuroleptics in specific tests of learning in human subjects. In a preliminary study, Fischman et al. (1976) found that chloropromazine (CPZ) impaired avoidance learning in humans. In a further study CPZ was found to similarly impair money loss avoidance learning suggesting that this task may be useful for studying the effects of neuroleptics on incentive learning in an avoidance paradigm (Fischman and Schuster, 1979). To our knowledge, there have been no studies of the effects of neuroleptic drugs on either motor learning and performance or associative learning in human subjects. As a consequence of the paucity of human studies most of what is known about the effects of neuroleptics on learning is based on research with animals.

Animal studies of the neurotransmitter dopamine (DA) show that it is involved in reward-related (incentive) learning (Fibiger, 1978; Wise, 1981; Beninger, 1983, 1988a). Examples of incentive learning include the acquisition of appetitive oper-

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ant responses that has been reported to be impaired when DA receptors were blocked by a neuroleptic (e.g., Wise and Schwartz, 1981). In addition, it has been shown that incentive learning in avoidance paradigms was impaired by neuroleptics. Thus, animals treated with pimozide, a DA receptor blocker, failed to acquire an aversively motivated shuttle response (e.g., Beninger et al., 1980, 1983). They were able to make the response during shock, or following drug-free pretraining however, which argued against an explanation based on simple motor impairments. DA is clearly involved in motor performance (Beninger, 1983; Mekarski, 1989), however, motor learning has not been well studied. Other studies have shown that another form of learning, stimulus-stimulus (s-s) associative learning may be unaffected by neuroleptics (Ahlenius et al., 1977; Beninger et al., 1980).

One subgroup of humans who receive treatments with DA blockers are schizophrenic patients. Based on the results of animal studies and the work of Fischman et al. (1976) with humans, it is important to ask, therefore, whether neuroleptics impair incentive, motor or s-s learning in schizophrenic patients. A major difficulty in answering this question concerns the disease process itself. If learning impairments are found in neuroleptic-treated schizophrenic patients, are these impairments attributable to DA receptor blockade or to psychopathology? The present experiments were carried out in an effort to distinguish between these two possibilities.

The approach was based on a consideration of the following: (1) there are at least two possible contributions to learning deficits in schizophrenic patients, viz., neuroleptic drug (DA receptor blockade) and psychopathology; (2) it is possible to assess at least two types of learning, viz., incentive and s-s associative, with deficits in the former being associated with DA receptor blockade; (3) it may be possible to show that indexes of schizophrenic psychopathology are correlated with deficits in s-s associative learning but not incentive learning; (4) it may be possible to show that indexes of DA receptor blockade are correlated with deficits in incentive learning but not s-s associative learning. Experiments 1 and 2 addressed the possibilities suggested in points 3 and 4, respectively.

In experiment 1 it was predicted that the neuroleptic treated group would evidence avoidance learning impairments as well as motor learning and performance deficits relative to controls but that these impairments might show no correlation with BPRS scores. s-s associative learning may not be affected by DA receptor blockade; however, this measure could be significantly correlated with BPRS scores as it has been shown that schizophrenic patients may have difficulty with paired associates learning (Cutting, 1979).

In experiment 2 it was predicted that avoidance learning would show an inverse relation with chloropromazine equivalency of neuroleptic drug (CPZEQ) and prolactin level. Motor learning and performance would also show an inverse relation with these indexes of DA receptor blockade, but no correlation would be found with paired associates learning. However, this latter measure of s-s learning may show a negative relationship with BPRS scores.

METHOD

In experiment 1, the performance of a sample of schizophrenic outpatients receiving DA receptor blockers was tested in tasks of s-s associative learning and incentive learning and psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS).

The schizophrenic outpatients also were compared to nonmedicated nonschizophrenic controls. Although, from a methodological point of view, it would be desirable to compare schizophrenic patient subgroups receiving or not receiving DA blockers there are good reasons for avoiding this strategy. Davis et al. (1983) described long-term follow-up studies of schizophrenic patients who either received or did not receive drugs during first admission to hospital. Those in the no-drug condition evidenced a significantly poorer response to later drug treatment in a 5 year follow-up. They concluded, 'to be denied drugs during serious acute episodes may do harm which persists over a 3 to 5 year period' (p. 47).

A paired associates task was used to assess s-s learning. Incentive learning was assessed using an avoidance task similar to that employed by Fischman and Schuster (1979). As DA is also well

known to be involved in motor behavior (Beninger, 1983; Fowler et al., 1984) tasks assessing motor learning (rotary pursuit) and performance (button pressing and simple reaction time) were included.

Experiment 2 was undertaken to estimate the relative level of DA receptor blockade in chronic schizophrenic inpatients using indirect physiological measures and to look at correlations with performance on the tasks used in experiment 1. DA receptor blockade was assessed by measuring blood prolactin levels (Seeman, 1981; Meltzer et al., 1983). As a further index of this parameter, CPZEQ were computed, since these have been reported to be highly correlated with DA receptor blockade (Seeman, 1981). It was expected that CPZEQ and prolactin would be highly correlated.

Subjects

Experiment 1. 20 male patients with DSM III (American Psychiatric Association, 1980) diagnosis of schizophrenia were recruited from an outpatient clinic at a regional psychiatric hospital. Patients with a history of neurological impairment were excluded. 14 male subjects were also recruited from Canada employment services (see Table 1). The controls were also given the Brief Psychiatric Rating Scale and no significant effects were found.

Experiment 2. 26 inpatients (none of whom participated in experiment 1) with a DSM III diagnosis of schizophrenia were recruited from the rehabilitation unit of the same hospital. Patients with a history of neurological impairment were excluded. All patients had been on a particular neuroleptic drug regimen for at least 4 weeks. Two patients who were drug free for 4 weeks (for reasons unrelated to this study) were also included. These patients received no drugs at the time of testing and were included as they were at the low extreme in the continuum of drug dose (i.e. zero dose of drug). Patients willing to participate in the study were recruited over an 8-month period and no other medications were being taken, excepting a very low dose of an anticholinergic (1–4 mg/day) by nine patients. Statistical analysis did not show any significant effect of anticholinergics on task performance. 11 individuals from the hospital staff not taking any psychoactive medications gave a blood sample but did not participate further in the study.

TABLE 1

Subject characteristics (Mean (±SEM))

Experiment 1

	Control	*Schizophrenic patients*	
Sample size	14	12	8
Medications	None	Depot Flupenthixol	Depot Haloperidol
Dose (mg/kg/day)		0.047 (0.013)	0.092 (0.017)
Age	30.00 (1.64)	34.33 (2.03)	28.13 (2.44)
Education (years)	11.79 (0.43)	10.83 (0.53)	12.00 (1.39)
QTI score	42.71 (1.17)	40.17 (1.12)	38.89 (1.39)

Experiment 2

	Control	*Schizophrenic patients*
Sample size	11 (5 males) (6 females)	26 (20 males) (6 females)
CPZEQ (mg/kg/day)	N/A	11.95 (2.25)
Age	33.36 (2.81)	32.15 (2.66)
Education	N/A	11.04 (0.41)
QTI score	N/A	39.35 (0.95)

Apparatus and test materials

Drugs. In experiment 1, 12 patients were taking depot flupenthixol (FLU) with the dose ranging from 0.7 to 10.7 mg/day. Eight subjects were taking depot haloperidol (HAL) with the dose ranging from 1.4 to 12 mg/day. These two neuroleptics were of interest since both drugs have a high specificity for DA receptors (Cross and Owen, 1980) albeit with somewhat different profiles of action at DA receptor subtypes, FLU having a higher affinity than HAL for D1 receptors (Kebabian and Calne, 1979; Seeman, 1981). In experiment 2 the number of patients taking each type of neuroleptic was: eight chloropromazine (CPZ), six HAL, seven FLU, two fluphenazine, three thioridazine, one trifluoperazine, two were drug free. Three patients were taking two different neuroleptics. The drug regimen was highly variable among patients.

Computer and software. An Apple II^+ microcomputer was used to collect the data for each of the tasks. A cathode ray tube (CRT) with a screen 21×28 cm was used to present information. Each task was monitored by a program written in BASIC. Timing was done using assembly code subroutines. Letters presented on the screen were 8 mm high.

Quick Test of Intelligence (QTI). Two cards (15×20 cm) with one picture in each quadrant were used. The pictures showed simple situations usually with several characters or objects. Two words from word set 1 and all 50 words of set 2 were used (see Ammons and Ammons, 1962; Feldman, 1968). Each word related to one of the four pictures on a card and the order of words in a set was graded in difficulty.

Rotary Pursuit device. This device is similar to that described by Ammons (1955). The turntable had a 25 cm diameter flat gray platter insulated against electric current except for a shiny silver circular region with a diameter of 2 cm, the center being 4 cm from the edge of the turntable. A variable speed control allowed adjustment of rotor rotation rate. A stylus with a 10 cm insulated handle and 10 cm metal tip when touched to the conductive area of the turntable closed a circuit which was monitored by the computer. The turntable was driven by an electric motor housed in a wooden box ($21 \times 37 \times 37$ cm).

Paired Associate Words. 50 word pairs for the PA task were randomly selected from the easier half of the Underwood (1982) word pool which contains 300 words.

Button Box. An aluminum box measuring $23 \times 35 \times 5$ cm had two red buttons, 2.5 cm diameter and 24 cm apart, connected to microswitches. A 1.69 W light with a red plastic cap was centered between the two buttons. This device was used for the reaction time (RT), button press (BP) and operant avoidance (OP) tasks.

Brief Psychiatric Rating Scale. The BPRS consists of 18 items on which symptoms are rated for severity from 0 (not present) to 6 (extremely severe). The total scale and thought disorder subscale were used (Overall, 1982).

Procedure

All subjects performed the battery of tests, given in a constant order to eliminate variance which might be contributed by using different task orders (see Table 2). The rotary pursuit task was the most demanding and was the first task following psychological assessment. The operant avoidance task, on which money could be earned, was given last.

Psychological assessment. All drug subjects were initially assessed in a 20 min informal interview for degree of psychopathology using the BPRS, the time period recommended by Overall (1982). This was followed by the QTI (see Ammons and Ammons (1962) for administration details). Total BPRS scores (BPRSTOT), the score on the thought disorder subscale (THDIS) and QTI scores were calculated.

TABLE 2

Procedural protocol for experiments 1 and 2

Procedures	*Time (min)*
(1) Brief description of study, subject read and signed consent form	5
(2) Quick Test of Intelligence (QTI)	5
(3) Rotary Pursuit (RP) Learning	20
(4) Paired Associate (PA) Learning	15
(5) Break	10
(6) Reaction Time (RT) and Button Press (BP)	5
(7) Operant Avoidance (OP) Learning	30
	Total 90

Rotary Pursuit task. The object was to keep the metal tip of the stylus in continuous contact with the conductive circle (the target) on the rotating platter. The percent time on target was monitored by computer. The subject stood in front of the apparatus, with the platter at a height of 150 cm from the floor. To track the target the subject had to use a smooth circular motion of the hand and arm with the metal tip lightly making contact with the platter.

Twenty 30 s trials were given with a 15 s rest between trials (i.e., a spaced practice method (Reynolds and Adams, 1953)). The beginning of each trial was signalled 3 s in advance. At the end of each trial the CRT displayed to the subject the total time of contact with the target for that trial. A rotation speed of 50 rpm was used. This had been found to produce a reasonable learning curve in normal subjects (Cutmore, 1987).

Paired Associate task. The subject sat approximately 50 cm from the CRT and received alternate study and recall trials. On a study trial a list of word pairs (stimulus-response) was presented in random order. The subject was instructed to remember which words were paired together as they were required to give the appropriate response word when the stimulus words were later presented alone in random order in recall trials. Ten word pairs were used (Cutmore, 1987).

Pairs were presented for 2 s on the CRT with a 2 s inter-pair interval. During recall trials a maximum of 10 s was allowed for a response. The subject gave a verbal response which was entered by the experimenter at the keyboard. The computer scored each response as it was given. Alternate study and recall trials continued until two successive perfect recalls were reached or five recall trials were completed.

The number of correct responses was recorded for each trial. If a subject reached the criterion in fewer than five trials they were assigned a score of 10 for any remaining trials. The number of times a subject responded with one of the other response words was also recorded (called response intrusion errors). A 10 min break followed this task.

Reaction Time task. Procedural considerations for this task were guided by Treichner (1954). Each subject was seated in front of the button box with one button proximal and the other distal. The right hand was required for responding. The subject depressed the proximal button and waited until the light came on. When this signal was presented the subject was to respond as quickly as possible to press the distal button with the same hand.

This task was implemented to give an index of attentional functioning. Thus, no warning stimulus was given prior to the light signal. Signals were presented on a variable interval 8 s schedule with values ranging from 6 to 10 s. A total of 15 trials was given.

The computer assessed two aspects of the reaction time: (1) the time for the subject to release the proximal button (a measure of vigilance for the signal, termed attentional reaction time), and (2) the time taken to move the right hand from the proximal to the distal button (termed motor reaction time).

Button Press task. The subject was seated in front of the button box and told to press as rapidly as possible on the proximal button of the button box. The interval lasted 30 s and subjects were urged not to pace themselves but to press as fast as possible for the entire time interval. Unknown to the subject, the interval was divided into three 10 s subintervals (time bins). The dependent measure was the number of responses in each 10 s time interval.

Operant Avoidance task. The subject was asked to respond on the proximal button in a trial and error fashion to discover the two reward contingencies. An avoidance paradigm was used in which a 10 dollar stake was given at the beginning of the task which the subject was to 'protect' by solving the reward contingencies (Fischman and Schuster, 1979) or, if failure occurred on a trial, producing an escape response by pressing the distal button once. One contingency was differential reinforcement for low rate of responding (DRL) on which the subject had to produce ten inter-response intervals of at least 1 s duration each (a DRL 1 s schedule). The other contingency was differential reinforcement for high rates of responding (DRH) and 20 intervals of at most 0.25 s had to be produced (a DRH 0.25 s schedule). Trials were a maximum of 30 s in duration and the two schedules were interleaved as follows, DRL, DRL, DRH, DRH, DRL... (i.e., alternating in pairs). The screen displayed a message on each trial, either 'RESPONSE PATTERN 1' or 'RESPONSE PATTERN 2'.

This served as a discriminative stimulus for a change in the contingency of reward.

Visual feedback on rate of responding was presented in the form of Xs spread out along the bottom of the screen. Responding quickly placed the Xs close together, responding slowly spread them out. A star scanned across the screen once every 5 s and wherever the star happened to be an X could be placed there when the proximal button was pressed.

A penalty of 15 cents was deducted for an incorrect avoidance (failure to produce the DRL or DRH as appropriate). In addition, 2 cents/s were deducted until the 'escape' response was made. A total of 60 trials were given (30 for each schedule). A 2 min rest was given after each block of 20 trials. The number of trials correct and escape latencies were recorded.

Both experiments used the above procedures. In addition, in experiment 2 a 10 ml blood sample was collected between 7:30 and 9:30 a.m. for all patients and the control subjects. Samples were spun in a centrifuge, the serum separated and frozen. All samples were later analysed in batch for prolactin levels using radio-immunoassay (Sinha et al., 1973). Prolactin level was used as a predictor variable along with CPZ clinical equivalency (CPZEQ) of drug, age, QTI score, BPRSTOT score and THDIS subscale score. These variables were used in a multiple regression design to predict performance on each task.

RESULTS

Experiment 1

The 'group' variable was used to denote the three groups: control, HAL and FLU. 'Cont-drug' refers to a planned comparison of the control group versus the drug groups combined. The other planned (orthogonal) comparison, 'hal-flu', was between the two drug groups. Whenever repeated measures were included in the analysis of variance (ANOVA), the Greenhouse and Geisser (Keppel, 1982) adjusted degrees of freedom were used to reduce positive bias in F ratios resulting from violation in homogeneity of variance assumptions. The probability values (Ps) based on these adjusted degrees of freedom were provided by the BMDP 4V statistical software package.

A one-way ANOVA of groups was computed for each of the subject descriptors (age, education and QTI scores; see Table 1) and no significant differences were found. Inter-task correlations were performed and the only significant effect was the correlation of -0.65 ($P<0.01$) between mean reaction time and mean number of button presses, suggesting that the tasks are, for the most part, independent.

Rotary Pursuit. A two-factor ANOVA was conducted on group and trial blocks. The block factor consisted of four levels each formed by averaging five trials. The apparatus failed for one control subject so there are only 13 subjects included for this group.

Fig. 1 (RP) shows the control group to have had higher mean percent time on target and the main effect of group was significant (F (2,30) = 3.37, $P<0.05$). The cont-drug comparison was significant with the control group having a higher mean time on target than the combined drug groups (F (1,30) = 6.72, $P<0.01$). The main effect of block (practice) was also significant (F (2.31, 69.16) = 128.81, $P<0.001$) with time on target increasing over this factor. Linear, quadratic and cubic trends for block were all statistically significant.

The block x cont-drug interaction, although in the expected pattern, with a slower acquisition rate for the drug subjects than controls, did not reach statistical significance (F (2.31, 69.16) = 2.59, $P<0.07$). No effects involving the hal-flu comparison were significant.

Paired Associate task. Since QTI score gave a measure of intelligence that was expected to correlate with PA learning, it was used as a covariate in these analyses.

A two-way ANOVA was conducted on the group and trial factors. Both main effects were significant as was the covariate (Fig. 1, PA). Of greater interest was the significant trial by cont-drug interaction (F (2.53, 78.35) = 3.75, $P<0.05$). The figure shows the control group to have had a higher acquisition rate than either drug group and interaction contrast analysis showed a significant interaction between the quadratic component of trial and cont-drug (F (1,31) = 19.58, $P<0.001$). The quadratic function was apparent for the control group as these subjects reached an asymptote of performance; it was notably absent for the drug group.

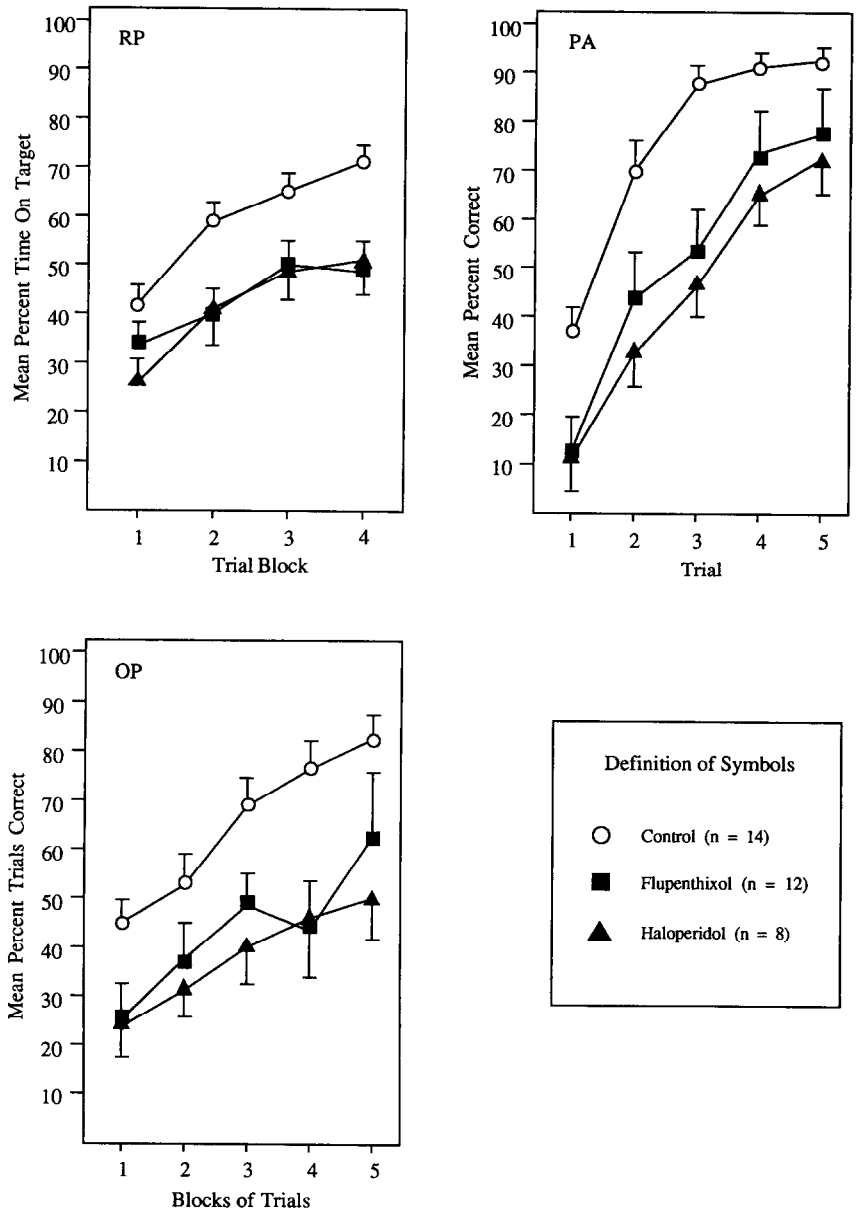

Fig. 1. Means and standard errors for learning tasks in experiment 1. The rotary pursuit (RP) task showed controls to have a higher overall time on target than drug groups combined ($P<0.01$), the interaction of control and combined drug groups with trial blocks approached significance ($P<0.07$). The paired associates (PA) task showed controls to have both higher overall scores ($P<0.01$) and faster overall learning ($P<0.05$) than the combined drug groups. The operant (OP) task showed controls to produce a higher number of correct avoidances than the combined drug groups.

The drug group was found to produce a greater mean ($\pm$ SEM) number of response intrusion errors (4.2 ± 0.81) than the control group (1.5 ± 0.48). This difference was statistically significant (t (32) $=2.57$, $P<0.05$).

Operant Avoidance task. A three factor ANOVA was conducted on the variables group, block and schedule. Each level of block consisted of six trials averaged together. The schedules were DRL and DRH. The dependent measure, number

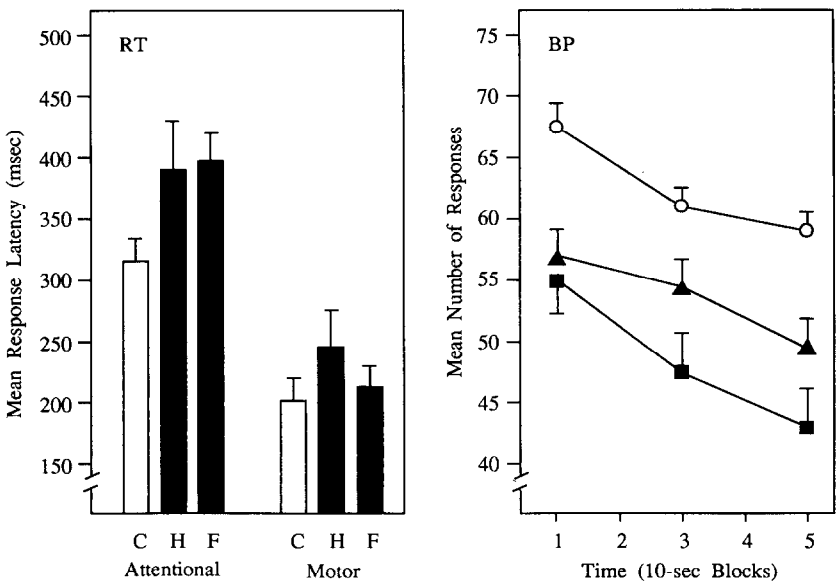

Fig. 2. Means and standard errors for motor tasks in experiment 1. Symbols are defined as in Fig. 1. Reaction time (RT) was faster for controls than combined drug groups ($P<0.01$). The interaction between the two drug groups and RT components was also significant ($P<0.05$). The button press (BP) task revealed controls to have a faster response rate than combined drug groups ($P<0.001$), the interaction between the two drug groups and time block was also significant ($P<0.05$).

of trials correct, was expressed as a percent of perfect performance for analysis. The group and block variables failed to interact significantly with schedule. Therefore, data was collapsed over this variable in Fig. 1 (OP). Results showed the control group to have had a higher mean number of trials correct than the drug groups. The main effect of group was significant (F (2,31) = 3.66, $P<0.05$) which was accounted for by the significant effect of cont-drug (F (1,31) = 7.19, $P<0.01$). The main effect of block was also significant (F (2.38, 73.89) = 17.00, $P<0.001$). This was found to be accounted for by the significant linear trend (F (1,33) = 30.65, $P<0.001$). No effects involving hal-flu were significant, neither was any interaction significant. Analysis of escape latencies failed to reveal any significant group differences; the mean ($\pm$ SEM) escape latencies (in ms) for the HAL, FLU and control groups were 1353 ($\pm$ 77), 1817 ($\pm$ 123) and 1363 ($\pm$ 108) respectively.

Reaction Time task. A two-way ANOVA was conducted on the log transformed scores for the factors, group and component (attentional and motor RTs). Fig. 2 (RT) shows the mean response latency for each RT component. The main effect of group was significant (F (2,31) = 3.85, $P<0.05$). This was accounted for by the significant cont-drug effect, with control subjects showing faster mean RT (components combined) (F (1,31) = 6.86, $P<0.01$). The motor response was executed faster than the attentional response as shown by the main effect of component (F (1,31) = 244.99, $P<0.001$).

The figure shows the drug groups to have had slower attentional RTs than the control group, with only the FLU group having a motor RT very similar to controls. This pattern of results was isolated by the significant interaction contrast of hal-flu and component. The HAL group showed a smaller difference between the attentional and motor RTs than the FLU group (F (1,31) = 5.23, $P<0.05$).

Button Press task. A two-way ANOVA was conducted on group and time bin. Fig. 2 (BP) shows the control subjects to have had a higher mean response rate than either drug group. The main effect of group was significant (F (2,31) = 10.56, $P<0.001$) and the cont-drug effect accounted for this difference (F (1,31) = 18.68, $P<0.001$). The main effect of time block was also significant (F (1.35, 41.95) = 35.83, $P<0.001$) with all groups showing a tendency to reduced response

rates over time. A significant two-way interaction was found between block and hal-flu (F (2,30 = 3.30, $P < 0.05$). Further analysis showed the HAL group to have had a greater quadratic component over time blocks than the FLU group (F (3.06, 47.43) = 3.05, $P < 0.01$) suggesting that the rate of decline was greater for the HAL group.

BPRS. Only drug subjects were rated on this scale. The mean (± SEM) for the THDIS subscale score was 2.71 (± 0.67) and for the BPRSTOT, 11.62 (± 1.47).

BPRSTOT and THDIS scores were used in a correlation analysis with summary indexes of performance on the experimental tasks to determine whether psychopathology was associated with task performance. The summary indexes were as follows. For the RP task, the difference between the means of the first two and last two trials were calculated to give an index of change from baseline (learning). Performance on the last two trials was used as an index of terminal performance. For the PA task, total percent correct and total number of response intrusion errors were tallied over the five trials. Mean attentional reaction times were computed for the RT task. For the BP task, the total number of responses in 30 s was used. For the OP task total trials correct was used.

The intercorrelation matrix is shown in Table 3. The only significant correlation was a positive one between number of response intrusion errors of the PA task and the THDIS score of the BPRS (r (19) = 0.45, $P < 0.01$) (one tailed test).

Experiment 2

A step-wise multiple regression was the primary analytic method used (Hull and Nie, 1981). It should be noted that the order of 'importance' of predictor variables as to which best accounts for variance in the predicted variable cannot be reliably determined from a single study. Thus, in a cross validation, although the same predictors would be expected to be resolved (since each is significant at $\alpha < 0.05$) their order in the equation may not be the same.

Table 4 provides a summary of the findings. For each task, those predictors which accounted for statistically significant variance were isolated and used to form a regression equation. This entailed examining the stepwise regression analysis and using those variables that (1) showed a significant R^2 change (RSQCH) or (2) together with other variables (as a multiple R) accounted for a significant proportion of variance in the task measure. It should be noted that predictor variables that are correlated moderately may enter the regression equation in a mutually exclusive fashion even though both predictors may correlate well with the dependent variable (Kerlinger and Pedhauzer, 1973). As is shown below, this may have been the case with the CPZEQ and PROL variables. In no case did both of these predictors enter the same regression equation. The dependent variables for task performance were the same as described for the correlational analysis of experiment 1.

TABLE 3

Summary of correlations between task measures and psychiatric state measures for experiment 1
Only the paired associate task shows a significant correlation

Task	*Measure*	*BPRS total score*		*Thought disorder*	
		r	P	r	P
RP	Change from baseline	0.05	n.s.	−0.11	n.s.
	Terminal performance	−0.18	n.s.	−0.38	n.s.
OP	Total trials correct	0.05	n.s.	−0.02	n.s.
RT	Attentional latency	0.13	n.s.	−0.08	n.s.
BP	Total responses	0.18	n.s.	0.12	n.s.
PA	Total percent correct	0.06	n.s.	0.01	n.s.
	Response intrusions	0.28	n.s.	0.45	<0.01

Abbreviations:
Tasks: BP = Button Press, OP = Operant, PA = Paired Associates, RP = Rotary Pursuit, RT = Reaction Time.

TABLE 4

Summary of experiment 2 results showing that for each task measure a significant relationship existed with one of the drug related predictors except for the paired associate task

Task	*Measure*	*Standardized equation*[a]	*MULT* R	P
RP	Change from baseline	−0.57 (AGE) − 0.36 (CPZEQ)	0.64	<0.01
	Terminal performance	−0.47 (AGE) − 0.34 (CPZEQ)	0.54	<0.05
OP	Total trials correct	0.40 (QTI) − 0.39 (PROL)	0.53	<0.05
RT	Attentional latency	0.69 (CPZEQ) − 0.42 (QTI)	0.74	<0.001
BP	Total responses	0.50 (QTI) − 0.35 (PROL)	0.61	<0.01
PA	Total percent correct	No relationship found		
	Response intrusions	No relationship found		

Abbreviations:
Tasks: BP = Button Press, OP = Operant, PA = Paired Associates, RP = Rotary Pursuit, RT = Reaction Time; predictors: CPZEQ = chloropromazine clinical equivalency, PROL = serum prolactin, QTI = Quick Test of Intelligence.
[a]Right half of equation shown.

Prolactin level. Amersham Corporation (1985) reported data on normal individuals for the radioimmunoassay kit used to determine prolactin level. The 95% confidence interval for this measure (males and females combined) was 0.2 to 20.8 μg/l.

The mean (± SEM) prolactin level (PROL) for the patient group was 30.65 (± 8.22) μg/l and for the control group, 11.91 (± 3.37) μg/l. The difference was statistically significant (t (31.8) = 2.11, $P < 0.05$). PROL also correlated significantly with CPZEQ (r (24) = 0.72, $P < 0.001$).

Rotary Pursuit task. Age and CPZEQ were found to be significant predictors of the amount of change in percent time on target from the first two to the last two trials (R (2,23) = 0.64, $P < 0.01$). Age was a significant negative predictor (RSQCH (23) = 0.28, $P < 0.01$), as was CPZEQ (RSQCH (23) = 0.13, $P < 0.05$). Thus, the higher the dose of CPZEQ the smaller the improvement in performance with practice.

Age and CPZEQ also showed a significant regression on terminal performance level (R (2,23) = 0.54, $P < 0.05$). Age was a significant negative predictor (RSQCH (23) = 0.18, $P < 0.05$). CPZEQ, although showing an effect in the expected direction, did not quite remove significant additional variance after age (RSQCH (23) = 0.11, $P < 0.06$).

Paired Associates. Neither of the two task measures (total percent correct or total response intrusion errors) could be predicted reliably.

Operant Avoidance task. QTI was entered first into the equation followed by PROL to account for a significant proportion of variance in total trials correct (R (2,23) = 0.53, $P < 0.05$). PROL added significant predictive power to the equation (RSQCH (23) = 0.25, $P < 0.05$); higher PROL levels were related to a lower number of correct avoidance responses. No effects on escape latency were noted.

Reaction Time. Attentional RT scores were transformed with base ten logarithm to normalize the distribution. CPZEQ and QTI score showed a high multiple R with this variable (R (2,23) = 0.74, $P < 0.001$). CPZEQ was a significant negative predictor of performance on this measure (RSQCH (23) = 0.37, $P < 0.001$) with higher doses being related to a slower reaction time. QTI also added significantly to the prediction, showing a positive relationship (RSQCH (23) = 0.18, $P < 0.05$).

Button Press task. QTI score and PROL showed a significant regression on total responses (R (2,23) = 0.61, $P < 0.01$). QTI was a significant positive predictor (RSQCH (23) = 0.22, $P < 0.05$) and PROL was a significant negative predictor (RSQCH (23) = 0.15, $P < 0.05$) with higher PROL being related to production of fewer responses.

DISCUSSION

The main goal of the present research was to attempt to dissociate effects of neuroleptics on learning of schizophrenic patients from effects of the disease process itself. To achieve this end the correlations between indexes of psychopathology (BPRS) or indexes of DA receptor blockade (prolactin or CPZEQ) and performance on various learning tasks were assessed. As neuroleptic drugs also influence motor performance, tests of this ability were included. In the following paragraphs, the biochemical, motor behavior and learning results will be considered in turn.

Prolactin. Although no attempt was made to control for time after last drug injection and thus increased variance would be expected in PROL levels, the patient group nevertheless was found to have a mean prolactin level nearly three times the level of the control group. As expected, prolactin level correlated highly with CPZ therapeutic equivalency of the neuroleptic being taken, a result consistent with previous research (Meltzer et al. 1983).

Motor performance. Several measures on the tasks showed evidence of basic motor impairments as a function of neuroleptic drugs. The best evidence for this came from the BP task. Total number of responses was found to be less in drugged subjects in experiment 1 and this was noted to be inversely related to PROL level in experiment 2. Given that HAL and FLU are fairly specific DA receptor blockers and increased PROL level has been shown to be associated with DA receptor blockade (Meltzer et al., 1983) the motor impairments found here may have been due to DA receptor blockade.

In experiment 1 the drugged subjects were poorer in their ability to track the revolving target in the rotary pursuit task. This difference was apparent even on early trials (Fig. 1, RP). Thus, basic coordinated motor control may have been impaired as a consequence of neuroleptics and may have limited peak performance even after many learning trials; experiment 2 showed this aspect of performance to be related to CPZEQ of drug.

There were a couple of minor differences shown between HAL and FLU in experiment 1 which suggested that HAL may have produced a greater motor impairment. These drugs have differing receptor affinities at D1 and D2 receptors (Creese et al., 1983) which might account for this difference. On the other hand, little is known regarding the relative potencies of the depot forms of these drugs. It may be that the HAL group simply received a more potent dose of neuroleptic. Further research is needed to resolve these issues.

Motor learning. To our knowledge there has been no research on the effects of DA antagonists on rate of motor skill learning in humans. Experiment 2 gave some preliminary indication that the rate of skill learning may have been impaired on the RP task in proportion to CPZEQ dose of neuroleptic drug, a finding of interest given that CPZEQ has been shown to be highly correlated with affinity for DA receptors (Seeman, 1981; Creese et al., 1983). The interaction of drug versus no drug and RP learning in experiment 1, although not significant ($P<0.07$) gave some additional support. Research with Parkinson patients has shown these individuals to have a variety of motor deficits (Bernheimer et al., 1973; Beninger, 1983; Sanes and Evarts, 1985); however, acquisition parameters for motor behavior in these individuals are lacking. It might be expected, from the results presented here, that motor learning may be impaired in Parkinson's patients.

Incentive and s-s associative learning. The combined results of the two experiments provided some preliminary evidence that DA receptor blockade may lead to impairments of incentive learning but not s-s associative learning in schizophrenic patients. Experiment 1 showed neuroleptic-treated schizophrenic patients to make fewer correct avoidance responses in an operant task in comparison to control subjects. This finding is in good agreement with previous reports that neuroleptics impaired avoidance learning in humans (Fischman and Schuster, 1979) and animals (Beninger et al., 1980, 1983). These findings were reinforced by experiment 2 results which showed a significant negative relationship between an index of DA receptor blockade (prolactin level) and operant learning. Appropriate stimulation of DA receptors may therefore be necessary for optimal learning of operant tasks in humans.

The PA task was found to be learned less well by medicated schizophrenic patients in experiment 1 but performance was not related to either prolactin

level or CPZEQ in experiment 2. Possibly, thought disorder in the schizophrenic patients led to the impairment in ability to learn associations between pairs of words. This hypothesis was supported in experiment 1 where the thought disorder subscale score of the BPRS was positively correlated with number of response intrusion errors. Given that intruding responses may have made learning more difficult, this could explain why schizophrenic subjects learned this task less well. The basis of the deficit could involve attentional (Oltmanns, 1978) or response selection (Marshall, 1973) mechanisms.

Whatever the mechanism, the combined data from experiments 1 and 2 showed, on the one hand, that level of schizophrenic psychopathology (assessed with the BPRS) was correlated with level of performance on the paired associates task but not motor learning or operant learning tasks. On the other hand, indexes of DA receptor blockade (either prolactin levels or CPZEQ) reliably predicted impaired motor and operant learning but not impaired paired associates learning. Thus, although subjects included in the present experiments had *both* schizophrenia and DA receptor blockade, the approaches used allowed a dissociation of the effects of these two variables on performance of several tasks. Results supported the hypothesis that neuroleptic therapy may have led to impaired incentive learning of schizophrenic patients.

Relationship to other interpretations of schizophrenia. McGhie (1977) has presented a theory of schizophrenia which characterizes the disorder in terms of an inability to attend selectively to the environment. A 'defective filter' for incoming stimuli is suggested to be the basis for this difficulty with attentional control. Other researchers have proposed a DA based theory of schizophrenia and, in particular, have asserted that DA may mediate some aspects of attentional functioning (Joseph et al., 1979). As incentive learning involves the acquisition by environmental stimuli in the ability to elicit responses, i.e., control attention (cf. Beninger, 1988b), these interpretations may be closely related to the incentive learning interpretation. Perhaps DA function must be in an optimal range for normal attentional and incentive learning processes; from this point of view, too great a reduction by treatment with a neuroleptic or enhanced DA function in nonmedicated schizophrenic patients may lead to apparent attentional deficits.

From a different perspective, Wise et al. (1978) have advanced an interpretation of DA as mediating the hedonic valence of reward stimuli. This theory has described the effects of neuroleptics as producing 'anhedonia', or the removal of the rewarding quality from a stimulus (but see Beninger and Hahn, 1983). In the present experiments operant (incentive) learning was impaired in schizophrenic patients and this was attributed to neuroleptic drugs. In Wise's terminology, the hedonic valence of the reward stimulus (monetary gain) may have been reduced and this could have resulted in a reduction in learning rate. If 'hedonic valence' and 'ability to elicit responses' are similar phenomena, then the theoretical position of Wise et al. and the incentive learning position discussed here are in general agreement.

Implications for therapy. It may be a little premature to consider practical implications of the present findings for therapy. However, it is well known that neuroleptic-medicated schizophrenic patients performed poorly when incentive learning techniques have been employed in treatment (Liberman et al., 1973; Davis et al., 1976). These techniques involve making reward contingent on emitting (or omitting) target behaviors. Despite encouraging results in the modification of some behaviors (e.g., Wincze et al., 1972; Paul and Lentz, 1977), major problems have been noted in both the learning of new target behaviors and their maintenance in medicated schizophrenic patients (see Curran et al., 1982 for review). A potentially useful approach might be to seek the minimum necessary dose of neuroleptic for successful therapeutic effects. Possibly such a dose would bring dopaminergic neurotransmission into the range where it can still function in incentive learning associated with day-to-day activities without either over functioning to produce schizophrenic symptoms or under functioning to produce impaired learning (Miller, 1987; Beninger, 1988b).

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