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ORIGINAL INVESTIGATION

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Effects of acute administration of *d*-amphetamine and haloperidol on procedural learning in man

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Abstract The effects of an indirect dopamine-agonist, *d*-amphetamine, and a non-selective dopamine receptor antagonist, haloperidol, were investigated in normal male volunteers using a between-subjects double-blind design in a procedural learning task, thought mainly to involve unconscious/automatic learning. The results showed: (1) *d*-amphetamine facilitated response speed, whereas haloperidol inhibited it, in comparison to placebo; (2) the linear increase in procedural learning corresponded with pharmacological manipulation of degree of dopaminergic activity, i.e. subjects given haloperidol showed the least, and subjects given *d*-amphetamine the greatest, procedural learning. The implications of these findings are discussed in relation to investigation of abnormalities of procedural learning processes in schizophrenia.

Key words *d*-Amphetamine · Haloperidol · Procedural learning · Automatic processing · Dopamine · Neuroleptic medication

Introduction

Procedural learning is a kind of rule-based learning in which performance increment occurs as a function of practice on task (e.g. mirror reading) without the need for conscious awareness (Cohen and Squire 1980; Squire and Zola-Morgan 1988); this contrasts with declarative learning, in which performance depends on explicit knowledge of facts (e.g. verbal memory tests) and correlates positively with intelligence (Feldman et al. 1995). On the basis of neuropsychological evidence (e.g. Richardson-Klavehn and Bjork 1988; Delis 1989; Heindel et al. 1989; Shimamura 1989; Harrington et al. 1990; Knopman and Nissen 1991; Knowlton et al. 1996), it has been postulated (e.g. Pascual-Leone et al. 1993) that the central nervous system structures involved in the acquisition and storage of procedural learning differ from those involved in declarative learning. The brain structures postulated to have important roles to play in procedural learning are the basal ganglia (Heindel et al. 1988, 1989; Harrington et al. 1990; Grafton et al. 1992), striatum (Heindel et al. 1988, 1989; Knowlton et al. 1996; also supported by a study on non-human primates by Mishkin and Petri 1984) and cerebellum (Pascual-Leone et al. 1993).

Attempts to investigate procedural learning in psychotic patients have yielded conflicting results. There are reports (Goldberg et al. 1990, 1993; Schmand et al. 1992) which indicate that procedural learning remains intact in this population, but an impairment, particularly in chronic schizophrenics, has also been found (Schwartz et al. 1992). Although Schwartz et al. (1992) reported that degree of procedural learning was unrelated to the dose of antipsychotic medication or duration of illness, this conclusion may be premature. The patients in their study were receiving on average high levels of medication (mean neuroleptic dose in chlorpromazine equivalents about 900 mg), which could have militated against finding a significant relationship between procedural learning and medication dose. This suggestion is further supported by the findings of Granholm et al. (1993), who observed that increased severity of tardive dyskinesia (a condition produced by medication with dopamine-receptor blockers) in schizophrenics was associated with decreased motor

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procedural learning and shortened caudate nucleus T-2 relaxation times in magnetic resonance imaging. Experimental investigation of the effects of drugs which interact with the dopaminergic system, using normal drug-free volunteers, may help to further understanding of the role of dopamine-receptor blockade in procedural learning.

We have therefore examined the effects of acute administration of an indirect dopamine agonist, *d*-amphetamine, and a non-selective dopamine receptor antagonist, haloperidol, on a procedural learning task (Lewicki et al. 1988; Corr et al. 1995) in a healthy population with no past history of schizophrenia. Haloperidol is a common neuroleptic medication for schizophrenic patients (Klieser et al. 1994), whereas *d*-amphetamine elicits symptoms in normal volunteers similar to those seen in paranoid schizophrenics (Lieberman et al. 1987). We predicted on the basis of previous findings (e.g. Granholm et al. 1993) that there would be impaired procedural learning under haloperidol, relative to placebo; assuming this effect, if observed, to be due to reduced dopaminergic transmission, it can also be predicted that *d*-amphetamine would improve procedural learning.

Materials and methods

Subjects

Sixty right-handed (age-range 18–45 years) male subjects were recruited by advertisements and referrals by other healthy subjects. All potential subjects underwent a semi-structured medical screening for thyroid dysfunction, glaucoma, heart disease, hypo- or hypertension, a history of severe mental illness, anorexia, violent or rapid mood changes, regular medical prescription, alcohol dependency and drug abuse (ascertained by urine analysis), before being accepted as subjects. All subjects who participated in the study signed a consent form approved by the Ethical Committee at the Institute of Psychiatry, London. Subjects received £50 each for their participation.

Experimental design

Subjects were randomly assigned in equal numbers (20) to one of three experimental (placebo, *d*-amphetamine and haloperidol) groups. One subject in the haloperidol group could not complete the task due to adverse extrapyramidal side-effects, and the data on one subject in the *d*-amphetamine group were lost due to computer disk error. The final study sample, therefore, consisted of 19 subjects each in the *d*-amphetamine and haloperidol groups and 20 subjects in the placebo group. Table 1 presents subjects' ages and weights.

Drug administration

Placebo (empty capsule), *d*-amphetamine (5 mg) and haloperidol (5 mg) were administered orally in identical appearing capsules. The dose of 5 mg *d*-amphetamine was chosen because this was found to be effective in normal volunteers in a previous study (Gray et al. 1992). The choice to use the dose of 5-mg haloperidol was dictated in part by ethical reasons; this dose has been successfully used in normal volunteers without causing excessive side effects (Dawe et al. 1995). Since a smaller oral dose (4 mg) of haloperidol than that used in the present study produced around 73% dopamine receptor occupancy in normal volunteers (Nordström et al. 1992), the dose of 5 mg haloperidol was deemed sufficient for our purposes.

Table 1 Subjects' mean (SD) age and weight for the placebo and the two drug groups

Group	*n*	Age (years)	Weight (kg)
Placebo	20	26.20 (7.03)	77.76 (11.82)
d-Amphetamine	19	28.63 (5.61)	72.85 (9.65)
Haloperidol	19	28.00 (5.99)	73.26 (10.21)

Table 2 Schedule of drug administration

Time	Placebo group	*d*-Amphetamine group	Haloperidol
0 min	Placebo	Placebo	Haloperidol
90 min	Placebo	*d*-Amphetamine	Placebo

The study was run double-blind. Drug latency period was determined on the basis of previous studies; it was 90 min in the case of *d*-amphetamine as in Gray et al. (1992) and 3 h in the case of haloperidol (Nordström et al. 1992). In order to be able to run the study double-blind, all subjects were given two capsules, one at 0 min and the other 90 min after the first capsule. The placebo group had two placebo capsules, while the *d*-amphetamine and haloperidol groups had one placebo capsule and the other containing 5 mg *d*-amphetamine and 5 mg haloperidol, respectively. The schedule of drug administration was as shown in Table 2.

Subjects who received haloperidol were routinely given a single oral dose of orphenadrine (50 mg) after the completion of the experiment to counteract any possible extrapyramidal reactions to haloperidol by one of the co-authors (P.A.C.); the experimenter (V.K.) had no knowledge of which subjects were administered orphenadrine until after the study had been completed. Medical cover was made available to subjects on a 24-h basis.

All subjects were given the first drug/placebo capsule between 9.30 and 11.00 a.m. to control for the possible differential time of day effects on drug metabolism. Similarly, the study sample was restricted to males only, to reduce another potential source of variance.

Task details

The task used was identical to that described by Corr et al. (1995; see also Lewicki et al. 1988), with the exception that only six segments were used. Each of these six segments consisted of 240 target movements, grouped into 48 blocks of five target movements. A white target stimulus moved between four locations on the computer monitor (black screen), which was divided into four equal quadrants by two intersecting white lines. The target movements were either predictable (i.e. movements of the target were determined following specific rules; see below) or random. For the predictable blocks, the first two target movements (trials 1 and 2) were always random, and the last two target movements were always predictable (trials 4 and 5). The third trial target movements were excluded from the analyses following Corr et al. (1995) (see Perruchet et al. 1990, for the reasons for excluding these trials).

Predictable trials rules

(1) A horizontal target movement was followed by a vertical target movement; (2) a vertical target movement was followed by a diagonal target movement; and (3) a diagonal movement was followed by a horizontal movement. A maximum of 12 different five-trial sequences were governed by these rules; each of these sequences was presented four times, giving a total of 48 blocks.

Random trials rules

The target movements did not follow any specific rule, and violated the above predictable target rules.

All 48 blocks were randomly (randomized for each subject) presented to subjects with the following limitations: that the first trial of any block was not predicted from the last trial of the preceding work; and that the target stimulus never remained in the same quadrant on two successive trials.

An asterisk (*) comprised the target stimulus, which appeared centrally in one of the quadrants. The movement of the target was almost instantaneously initiated by the subject touching the target area (2 cm radius around the target on the screen) with a wand. A musical note accompanied each target movement unique to each of the five trials (the sequence of notes resembled the well-known theme tune of Steven Spielberg's film *Close Encounters of the Third Kind*). The tune was helpful in demarcating the blocks. Subjects were not provided with any information about blocks. It has been shown that the performance of normal subjects on this task does not involve conscious awareness (Stadler 1989; Corr 1994) and is also largely independent of intelligence (Corr 1994).

General procedure

Subjects were told that the study was concerned with the psychological effects of a stimulant drug, *d*-amphetamine, and a neuroleptic drug, haloperidol. They were requested to have a light breakfast on the day of testing and to abstain from alcohol for at least 12 h prior to their appointment.

After measurement of body weight, heart rate and blood pressure, subjects were administered the drug/placebo, following the schedule described in the Drug administration section. After 3 h (starting with the first placebo/drug capsule), subjects participated in two other experiments, taking 35 min in all. This experiment, therefore, was conducted 2 h 05 min and 3 h 35 min after the administration of *d*-amphetamine and haloperidol, respectively, in a quiet room with subjects sitting in a comfortable chair.

Subjects were presented with a computer screen, with the target stimulus already appearing in one of the quadrants. The correct use of the wand and screen was then demonstrated to each subject by the experimenter, before issue of the written instructions (as in Corr et al. 1995).

"As you can see, the screen is divided into quadrants. A target (*) will move between these quadrants and your task is to touch each target as fast as possible with the wand in the manner already described to you. A practice period follows to familiarise you with the task. *Remember that your response should be fast and accurate.* Please press 'GO' to start."

After completion of the short practice session, and once subjects were able to use the wand and touch screen in the appropriate manner, they were told that they could initiate the main part (beginning with the first segment) of the task by touching a "GO" box with the wand, which at that stage appeared in the centre of the screen. A rest period of 30 s followed each segment, with the next segment again being initiated by the subject's touching the message on the screen to "Press GO to continue".

Subjects given haloperidol showed a tendency to need frequent urination; this caused disruption of the experimental session in one subject. Subjects' heart rate and blood pressure were monitored by a nurse every 30 min throughout.

Equipment

The equipment used was as described by Corr et al. (1995). An Atari ST1020 microcomputer was used to control the task and to record the responses. The stimuli were presented to subjects on a Atari SC1224 monitor, with a "Microvitec touchtec 501" touch screen fitted over it. A 12-in long thin perspex tube was used as an "wand". To register a response, the wand had to break a matrix of infrared beams of light which crisscrossed the touch screen and covered the monitor. There was an exact correspondence between the spatial positions of the target stimulus on the touch screen and on the computer monitor screen.

Data reduction and statistical analyses

For each segment the mean RT (ms) for each of the five trials was recorded (RTs to the third trial were recorded, but not included in the analyses; see above). The error scores were also recorded. The preliminary analysis of the data, however, revealed very similar error scores for the three experimental groups during both random and predictable trials. There were very few errors in any condition.

The main dependent variables therefore were RTs to random (means of trials 1 and 2) and predictable (means of trials 4 and 5) trials; the difference between these two trial types represented procedural learning. Initially, a 3 × 2 × 6 [Drug (placebo, *d*-amphetamine and haloperidol) × Trial Type (random and predictable trials) × Segment (six segments)] multivariate analyses of variance (MANOVA) was performed. Drug comprised the between-subjects factor and Trial Type and Segment were taken as within-subjects factors. Following this, a 3 × 2 × 6 [Drug × Trial Type × Segment] MANOVA with prior drug contrasts (*d*-amphetamine versus placebo, haloperidol versus placebo) was performed. The same model was then run with a *d*-amphetamine versus haloperidol drug contrast. Two-way (Trial Type × Segment) separate MANOVAs were conducted to look at the procedural learning in each Drug group. All MANOVAs were performed by SPSS Windows (Version 6.0) MANOVA routines. Analysis of variance on procedural learning scores (differences between RTs on trials 1, 2 and trials 4, 5, respectively) was carried out to examine whether the linear increment in procedural learning scores, from segment 1 to segment 6, corresponded (linearly) with increasing levels of dopaminergic transmission [ordered haloperidol (0)-placebo (1)-*d*-amphetamine (2)].

Since the subjects in the placebo group were somewhat (though non-significantly) younger and heavier (Table 1) than the other two groups, the possible confounding effects of age and weight in procedural learning were examined by correlational analyses (Spearman *rho*), separately in the placebo and each of the drug (*d*-amphetamine and haloperidol) groups.

Results

Response speed

Figure 1 shows mean RTs (ms) under all experimental conditions. As compared to the placebo group, subjects in the *d*-amphetamine group had smaller [$F(1, 55) = 4.65$, $P < 0.05$], and subjects in the haloperidol group had larger [$F(1, 55) = 10.84$, $P < 0.01$]RTs, across both trial types. There was a significant Drug × Segment interaction for the haloperidol versus placebo group

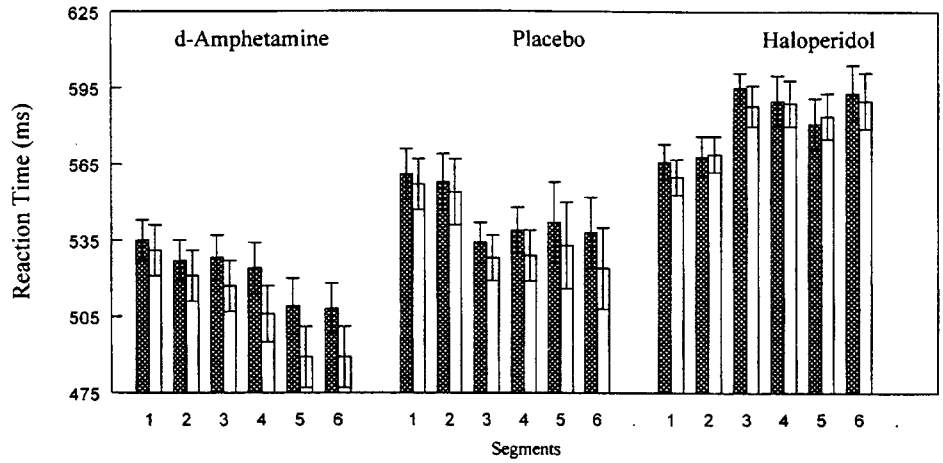

Fig. 1 Mean (error bars display ±1 SEM) reaction times (ms) for the random and predictable trials during the six segments after the administration of placebo, *d*-amphetamine and haloperidol in normal volunteers. ▩ Random trials; □ predictable trials

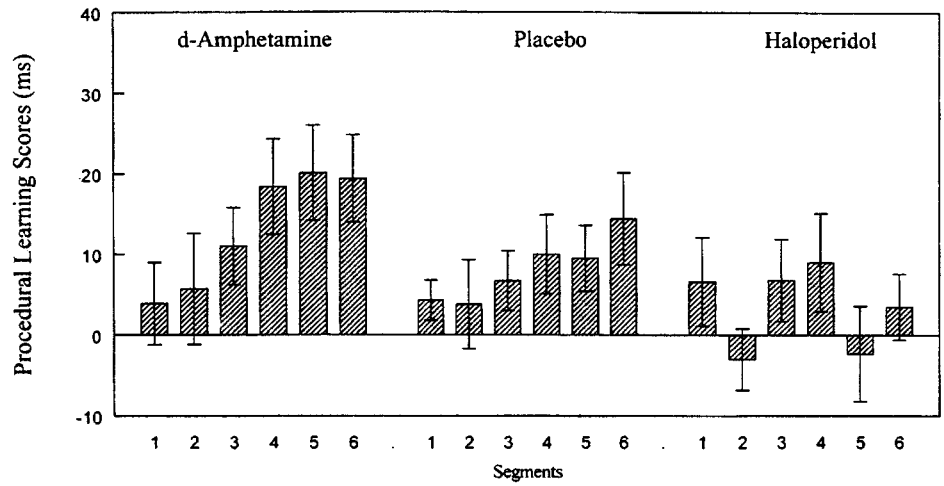

Fig. 2 Mean (error bars display ±1 SEM) procedural learning scores (ms) in subjects after administration of placebo, *d*-amphetamine and haloperidol in normal volunteers

comparison [$F(5, 51) = 6.58$, $P < 0.001$], reflecting a progressive decrease in RTs for the placebo group [main effect of Segment: placebo, $F(5, 15) = 3.34$, $P < 0.05$], but an increase in RTs for the haloperidol group [main effect of Segment: $F(5, 14) = 3.25$, $P < 0.05$]. The *d*-amphetamine group also showed a progressive reduction in RTs over segments [main effect of Segment: $F(5, 14) = 5.31$, $P < 0.01$].

Procedural learning

Figure 2 represents mean procedural learning scores (ms) under all experimental conditions. Procedural learning differed as a function of drug treatment, as indicated by the two-way Drug × Trial Type interaction [$F(2, 55) = 3.46$, $P < 0.04$]. The two drug (*d*-amphetamine and haloperidol) groups, however, did not differ significantly in their mean procedural learning scores from the placebo group ($Ps > 0.05$), but differed significantly from each other [$F(1, 55) = 6.91$, $P < 0.01$]. Procedural learning had occurred in the placebo and *d*-amphetamine groups [main effects of Trial Type: placebo, $F(1, 19) = 10.23$, $P < 0.01$; *d*-amphetamine, $F(1, 18) = 13.23$, < 0.01], but not in the haloperidol group ($F = 1.34$). Although the three-way Drug × Trial Type × Segment interaction was not significant, the linear increase in learning scores from segment 1 to segment 6 itself showed a linear increase across levels of dopaminergic transmission, i.e., across the haloperidol, placebo and *d*-amphetamine groups [Group (Linear) × Segment (Linear), $F(1, 330) = 6.52$, $P = 0.01$] (Fig. 2). The linear regression coefficients for change in procedural learning scores over segments were: haloperidol, −0.003 (SE = 0.005); placebo, 0.008 (SE = 0.005); and *d*-amphetamine, 0.015 (SE = 0.006).

There were no relationships between the subjects' age and weight and procedural learning scores (individual segments and the mean procedural learning) in either the placebo or the drug (*d*-amphetamine and haloperidol) groups.

Discussion

Our chief finding is of an orderly increment in procedural learning, as measured in Lewicki et al.'s (1988)

task, with increasing levels of dopaminergic activity, defined by grouping the three treatment groups in the order haloperidol, placebo, *d*-amphetamine. In addition, haloperidol inhibited overall response speed, whereas *d*-amphetamine facilitated it. Although *d*-amphetamine acts upon several different neurotransmitter systems (Moore 1977), opposite effects of *d*-amphetamine to those of haloperidol suggest that the observed effects may be dopaminergically mediated. Previously, Nissen et al. (1987) found no effects of scopolamine, an anticholinergic agent, on procedural learning using a different experimental paradigm from ours. Corr et al. (1995) observed that procedural learning was better in subjects given caffeine than in subjects given placebo, but only if they scored high on extraversion; the reverse was true for subjects who scored low on this dimension. Our findings indicate that procedural learning may be particularly strongly affected by the level of dopaminergic activity, and suggest that observed impairments in this type of learning in schizophrenic patients (Schwartz et al. 1992; Granholm et al. 1993) may have been due to their use of neuroleptic medication. Further experiments are needed to determine whether there are dose-dependent effects of *d*-amphetamine (and haloperidol) on procedural learning, as found for various other behavioural measures (see Lyons and Robbins 1975; Robbins 1981, for reviews; Cherek et al. 1989, 1990).

The general decrease in reaction time with *d*-amphetamine has previously been found by other researchers (e.g. Halliday et al. 1994). In subjects given haloperidol, a lack of motivation (Belmaker and Wald 1977) may have accounted for their slow response speeds, while the reverse may have been true for subjects given *d*-amphetamine. It is unclear from our results whether these overall changes in response speed, and the changes in procedural learning also induced by *d*-amphetamine and haloperidol, are related phenomena or separate drug effects. In the amphetamine condition, faster response speed might itself have facilitated insight into the complex pattern of stimuli (with the reverse happening in the haloperidol condition), but retrospective post-experimental (double-blind) questioning of subjects did not point to any differences between subjects with relatively fast and slow response speed; subjects could only tell that on some of the trials, the target was moving faster than at other times, but had no insight that they themselves were initiating such target movements by following them at a faster speed. Motivational changes induced by amphetamine and haloperidol, respectively, may have also played a role in creating the observed differences in procedural learning. If so, this would suggest that, although unconscious, this kind of learning may be sensitive to motivation, as well as general arousal. However, it is also possible that our findings reflect pharmacologically induced changes in a dopaminergically mediated process that underlies associative, procedural learning. This more interesting possibility deserves further investigation.

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