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ORIGINAL INVESTIGATION

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The effects of psychotomimetics and psychomotor stimulants on two schedules promoting response switching in the rat

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Abstract *Rationale:* Psychosis and psychotomimetic drugs result in a disorganisation of the structure of thought and behaviour. Normalising these is one of the objects of antipsychotic therapy, and methods for predicting such a therapeutic effect would be of value. *Objective:* The effects of a number of psychotomimetic agents were examined on the way in which rats distributed responding over two response levers using two different procedures, to assay their effects on behavioural organisation. Previously, amphetamine has been found to increase response switching using these schedules. *Methods:* In the first, the random reinforcement procedure, one of the two levers was selected at random as "correct", and responses on this lever were reinforced with food under a random ratio schedule. No signal was given to distinguish the levers. Responding could also result in the food tray being illuminated, but no food pellet was delivered ("no-food" event). Responses on the second lever ("incorrect") had no programmed consequences. After each food delivery or "no-food" event the levers designated as "correct" and "incorrect" were reassigned at random, and the rat had to open the food tray to restart the schedule. In the second procedure, the rats were required to make 21 responses before a switch between the two levers resulted in food delivery [Fixed Ratio (FR) 21-switch]. The responses making up the FR could be distributed freely between the two levers. *Results:* Phencyclidine (PCP), scopolamine, caffeine and ethanol increased switching under the random reinforcement procedure, but (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) and atropine did not. PCP, caffeine, lysergic acid diethylamide (LSD) and atropine increased switching under the FR21-switch procedure, but ethanol did not. The increases in switching produced by PCP, LSD and the anticholinergics were accompanied by marked reductions in response rate, whereas those produced by amphetamine and caffeine were not. The effects of amphetamine, and PCP were strongly dependent on the baseline probability of switching, those of atropine and caffeine moderately so, and those of LSD and ethanol only weakly so. *Conclusions:* Of the agents tested, psychomotor stimulants appear to produce the most selective increases in switching. The procedures described here may be useful for assaying the disorganisation of behaviour produced by other psychotomimetics and may have value in the detection of novel antipsychotic drugs.

Keywords Psychotomimetics · Behaviour sequences · Response switching · Amphetamine · PCP · LSD

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Introduction

Schizophrenia has long been characterised in clinical descriptions as a fragmentation of the cognitive processes leading to bizarre patterns of thought and behaviour. Andreasen (2000) refers to a metaprocess, the misregulation of information processing in the brain, which leads to a set of symptoms that can be categorised in a number of ways. These include the well-recognised psychotic symptoms, negative symptoms and a group of disorganised symptoms: positive formal thought disorder, bizarre/disorganised behaviour and inappropriate affect (for review, see Andreasen et al. 1995). In humans, disorganization of thought and behaviour is most frequently studied experimentally using verbal behaviour and verbal or complex visual stimuli, but, for example, includes disturbance of social behaviour and thus is significantly correlated with quality of life (e.g. Breier and Berg 1999). In their most florid guise, these symptoms do respond to treatment with antipsychotic agents, but in residual form impede re-integration of the patient into society. The organisation of thought or speech cannot be studied in non-human animals, but it is possible to study the organisation of behaviour. In this vein, models of schizophrenia have been proposed based upon impair-

ments in social behaviour (Sams-Dodd 1997, 1999; Mohn et al. 1999; Gainetdinov et al. 2001). However, even in mice and rats, social behaviour is a complex of components which may each be differentially sensitive to the effects of drugs. To study the effects of drugs on the pattern of behaviour without concern for the effects on the individual components, and thus address the same metaprocess identified by Andreasen (2000), Robbins and colleagues advocated using schedules of reinforcement based upon choices between two (or more) similar responses (Robbins and Watson 1981; Robbins and Evenden 1986).

Behavioural organisation in animals has been studied using two different but complementary approaches. The first, exemplified by Moerschbaecher and colleagues (Thompson and Moerschbaecher 1984; Savage et al. 1996; Winsauer and Moerschbaecher 2000), is to train animals to make a series of responses in a set order and examine the effects of drugs on either the performance of well-learned sequences or the acquisition of new sequences. In general, drugs induce more erroneous responses during acquisition, when stimulus control is weak, than during performance when it is relatively strong (Thompson and Moerschbaecher 1979). Robbins and colleagues (see below), including the present authors, have chosen a second approach: to require the animal to self-organise the response sequences, while minimising the negative consequences of inefficient ones. The primary measure of behavioural organisation is the frequency of switching between response alternatives (usually two similar lever press responses) compared to the frequency of repeating the response. In the present study, two procedures were used, the random reinforcement procedure and the fixed ratio-switch procedure, to generate patterns of responding distributed on two response levers. Briefly, in the first rats were required to press two levers to obtain reinforcement distributed equally, at random, but on only one lever at any time. In this procedure, switching is necessary to obtain the reinforcer, but under the schedule parameters used here, it is not explicitly reinforced. Varying schedule parameters, apparatus design or relying on individual differences between subjects (Robbins and Watson 1981; Evenden and Robbins 1983b) have been used to generate differences in the baseline probability of switching. In the second, explicit reinforcement is provided for the first switch made after the completion of 21 responses [fixed ratio (FR) 21], which can be distributed over the two levers without restriction (FR-switch). During training, a pattern develops in which the subjects tend to repeat responses at the beginning of the FR21, but to switch between the two levers with greater frequency as the FR progresses, generating a variety of baseline probabilities of switching in each session for each individual subject (Evenden 1986; Evenden and Doggett 1989).

Robbins and Watson (1981) found that amphetamine reduced the probability of repeating responses (an increase in switching). Evenden and Robbins (1983a, 1983b) showed a degree of pharmacological specificity of this effect, using chlordiazepoxide and α-flupenthixol, but also that the size of the increase was dependent on the baseline probability of switching. Amphetamine has often been used as an animal model of schizophrenia, since it produces psychosis in humans, although the symptoms are not identical with schizophrenia (Rylander 1971), and antipsychotics typically block the effects of amphetamine on behaviour. However, it has long been recognised that other psychotomimetic drugs can also be used to model the acute psychotic symptoms of schizophrenia. The aim of the present study was to take a selection of these drugs and compare them to amphetamine in the random reinforcement and FR-switch procedures to see if there are differences amongst the drugs that could be related to their different mechanisms of action. In addition to amphetamine the drugs used were LSD, which probably exerts its hallucinogenic effect via agonism at 5-HT_{2A} receptors (Glennon 1990), and the selective 5-$HT_{2A/2C}$ agonist DOI. The list was completed by phencyclidine (PCP), an NMDA receptor channel blocker, and the anticholinergics, scopolamine and atropine, which may also mimic acute organic psychosis (Gilman et al. 1980). As a comparison, two drugs frequently self-administered in humans, but which are not psychotomimetics, caffeine and ethanol, were also included.

Materials and methods

Subjects

The subjects were eight Long Evans rats (experiment 1, Harlan) and 16 Lister Hooded rats (experiments 2 and 3, Mollegård) approximately 3 months of age on starting the experiment and 15 months of age at the end. The LH rats were housed in groups of four and the LE rats were housed singly. They were fed approximately 10 g laboratory chow per rat per day. No attempt was made to control the food consumption of the individual rats in the group housing, although they were weighed regularly during the course of the studies. Water was available ad libitum.

Apparatus

The apparatus consisted of two sets of four experimental chambers (Campden Instruments, Model 4102). The chambers were 26.5×22×20 cm, and were fitted with two retractable levers and a food pellet dispenser. Food pellets (45 mg, Noyes) were delivered to a tray placed centrally between the two levers. Access to the tray was by opening a hinged Perspex flap. The food tray could be illuminated by a 24 V, 1 W lamp, while a second 24 V, 2.8 W lamp placed centrally in the roof of the chamber served as a houselight. Each chamber was housed in a separate soundproof box with a ventilator fan providing low-level background noise. Each set of chambers was controlled by a microcomputer running the Spider programming language (Paul Fray Ltd, Cambridge, UK). Programs for controlling the apparatus and collecting the data were written by the author.

Training

The initial stages of training were similar for both experiments. Twenty-four hours after the food was removed from their home cages, the subjects were provided with food placed in the food tray

of the experimental chambers for 30 min. On the second day, single 45 mg food pellets were delivered once per minute for a period of 30 min. Thereafter the rats were trained to press both levers under continuous reinforcement (CRF). Only one lever was present during each training session. Training under CRF continued until all the rats had made a minimum of 100 presses on both levers during a 20-min session (a maximum of ten sessions).

Testing

Experiment 1: random reinforcement

Each session began with the non-contingent delivery of a food pellet. Access to this pellet was by opening the hinged flap, at which point one of the two levers was selected randomly with equal probability as being the one next to provide a food pellet ("correct"). This lever remained "correct" until the delivery of the food pellet under a random ratio (RR) schedule, accompanied by illumination of the tray-light and extinguishing of the house-light. Responses on the "incorrect" lever were recorded but had no programmed consequence. On delivery of the food pellet, the computer again randomly reselected which lever was to provide the next reinforcer. No stimulus was provided to distinguish the "correct" and "incorrect" levers. On half the occasions (determined randomly by the computer), food delivery was replaced by a "no-food" event, i.e. the tray-light was turned on and the houselight turned off, but no food was delivered. The subject was still required to open the food tray to advance the schedule. Training proceeded without including "no food" events in two steps, RR2 for ten sessions and RR5 for six sessions. "No-food" events were then included for 12 sessions with RR5, and then a further 12 sessions of RR10 before drug testing began. The session length was a maximum of 100 trials (food delivery and "no-food" events combined) or 30 min. During training, because of the relatively short session duration and small amount of food delivered, two sessions were occasionally run on the same day, a.m. and p.m.

Experiments 2 and 3: FR21-switch

In this procedure, a food pellet was delivered contingent upon the rats making successive responses on the two different levers, either left-right or right-left (a switch). Only switches made after the completion of a fixed ratio of responses (FR) were reinforced. In experiment 2, this ratio was progressively increased during training from FR1 (two sessions), through FR2 (six sessions), FR5 (14 sessions) and FR11 (three sessions) to FR21 responses (for 15 sessions before the start of drug testing). In experiment 3, increase steps were from FR1 (two sessions), FR2 (three sessions), FR5 (15 sessions), FR11 (five sessions) to FR21 (for 14 sessions). The responses making up the ratio could be made on either lever in any order. Further repeat responses made after completion of the ratio were recorded but had no programmed consequences. Delivery of the reinforcer was signalled by the sound of the operation of the food dispenser, turning off the houselight and turning on the traylight. After the first entry into the food tray, the traylight was turned off and the houselight turned on, and further lever-press responses contributed to the next ratio. The session length was 60 min.

Drugs

The drugs used were *d*-amphetamine sulphate, scopolamine hydrobromide, atropine sulphate, phencyclidine hydrochloride (PCP) and caffeine (all Sigma Chemical Company), ethanol (Kemetyl and Pharmco), (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI, RBI) and lysergic acid diethylamide tartrate (LSD, NIDA). In experiment 1, the drugs were tested in the order: amphetamine, PCP, DOI, scopolamine, caffeine, ethanol and atropine, with a final amphetamine retest. In experiment 2, the drugs were tested in the order: PCP, amphetamine, LSD, atropine and ethanol. Caffeine was the only compound tested in experiment 3.

In experiment 1, the drugs were administered 15 min prior to testing and in experiments 2 and 3, 5 min before testing. With the exception of ethanol and caffeine, the vehicle was 0.9% saline in a volume of 1 ml/kg. Caffeine was usually dissolved in distilled water in a volume of 1 ml/kg, but the dose of 30 mg/kg caffeine was administered in a volume of 3 ml/kg in warmed distilled water due to limited solubility. Ethanol was administered in distilled water, in a volume of 5 ml/kg. The solution was prepared by weighing out 5 g ethanol and then making up the volume to 25 ml by the addition of distilled water. Details of the routes of administration are provided in the results section. Vehicle control treatments were administered at the same time and by the same route of administration on the day preceding the drug test day. In all the experiments, the lowest three doses were administered in a Latin square design, using doses derived from the literature or other studies carried out in the laboratory. On occasions when a fourth or fifth dose was employed, this was administered to all the subjects on the same day after completion of the Latin-square. Whenever practicable the dose was increased to obtain a roughly equal reduction in response rate.

Measurements and statistics

In Experiment 1, a number of different measures were taken including:

- Response rate: total number of responses/session length.
- Percent switching: total number of occasions on which the rat made sequential responses on alternate levers/total number of opportunities for sequential responses.
- Perseveration: total number of responses made on the levers after initiation of a "no-food" event, prior to opening the food tray as a percentage of the total number of responses.
- Sensitivity Index (SI; Frey and Colliver 1973): calculated from win-stay (percentage of occasions on which the rat pressed the same lever after collecting the food as it had pressed to deliver the food) and lose-stay (percentage of occasions on which the rats pressed the same lever after a "no-food" event as it has pressed immediately prior to the "no-food" event) using the formula:

$$\mathrm{SI} = \frac{\text{Win-Stay} - \text{Lose-Stay}}{2(\text{Win-Stay} + \text{Lose-Stay}) - (\text{Win-Stay} + \text{Lose-Stay})^2}$$

Each of the measures was subjected to a repeated measures analysis of variance with one factor, Treatment. Comparisons between drug treatment and vehicle (mean of the control days) were carried out using Bonferroni *t*-tests.

In experiments 2 and 3, two measures were analysed: the rate of responding, calculated as the total number of responses divided by the session length, and the percentage switching. Rate of responding was analysed by a repeated measures ANOVA with a single factor, Treatment. To analyse the percentage switching, the fixed ratio was divided into bins, each consisting of triads of responses providing two response pairs, i.e. 1–2-3, 3–4-5, 5–6-7, 7–8-9 etc. In bin 1, the percentage switches from left to right or vice versa were calculated for response pairs 1–2 and 2–3, in bin 2 for 3–4 and 4–5 etc. In this way, ten values for percent switching could be calculated during the course of the ratio. A mean value for the control days was calculated to provide a baseline, and together with the data for each drug dose, these values were then submitted for analysis of variance using a two-factor, repeated measures design, with factors Bin and Treatment. ANOVAs were carried out using the program BMDP. Comparisons between treatments at each bin were carried out using Bonferroni *t*-test. A significance level of 5% was used throughout.

Ethics

Experiment 1 was carried out using procedures approved by the AstraZeneca IACUC in accordance with US law, and experiments 2 and 3 using procedures approved by Södra Stockholms Djuretisknämnd in accordance with Swedish national law.

Results

Experiment 1: random reinforcement procedure

Amphetamine

Only a single dose of 0.8 mg/kg *d*-amphetamine SC was used in this study since the effects of this drug have been extensively documented previously. *d*-Amphetamine reduced the rate of responding [see Table 1, $F(1,7)=21.8$, $P<0.01$]. The drug also increased the percentage switching [$F(1,7)=17.6$, $P<0.01$] and reduced perseveration [$F(1,7)=7.3$, $P<0.05$]. *d*-Amphetamine had no effect on SI.

Because the baseline shifted over the 9 months in which the study was carried out, the 0.8 mg/kg dose of *d*-amphetamine was retested at the end of the study. When retested, the effects of *d*-amphetamine were almost identical to the first time (Table 1). There was a small but consistent reduction in response rate [$F(1,7)=28.2$, $P<0.001$], an increase in switching [$F(1,7)=12.2$, $P<0.05$], and a reduction in perseveration [$F(1,7)=14.9$, $P<0.01$]. There was no significant effect on SI.

Caffeine

An overall significant effect of caffeine on response rate, at doses of 3, 10 and 30 mg/kg, SC, was found after analysis of variance [$F(3,21)=6.5$, $P<0.01$], but none of the three doses differed significantly from vehicle, the significance most likely arising from the inverted-U shaped effect function (Table 1). Caffeine significantly increased switching at the highest dose tested, 30 mg/kg, but had no significant effect at the lower two doses [$F(3,21)=7.0$, $P<0.01$]. Caffeine did not affect perseveration or SI.

PCP

PCP was tested at doses of 1.0–6.0 mg/kg, SC. The highest dose tested had a profound effect on response rate [Table 1, $F(3,21)=19.1$, $P<0.001$], whereas there was no significant effect of the lower two doses. PCP also increased the frequency of switching [$F(3,21)=6.4$, $P<0.01$], but did so only at the highest dose tested. There was no significant effect of PCP on perseveration or on SI.

DOI

DOI was tested at doses of 0.1, 0.3, 1.0, 2.0 and 4.0 mg/kg, SC and had relatively limited effects on behaviour. After initial administration of the lower three doses, doses of 2.0 mg/kg and then 4.0 mg/kg were added until inspection of the data revealed a reduction in response

Table 1 The effects of the amphetamine, caffeine and phencyclidine (*PCP*) on four measures derived from the random reinforcement procedure used in experiment 1. The measures are described in full in the text. The data shown are means and SEM. All drugs were tested using a repeated measures design. The SEM gives an indication of the variability within the group of eight subjects but does not provide an indication of the statistical significance of the effect of the drugs

	Response rate (resp/s)		Switching (% opportunities)		Perseveration (% responses)		SI	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Amphetamine								
Vehicle	1.46	±0.20	24.5	±3.7	17.1	±3.0	0.55	±0.30
0.8 mg/kg	1.25	±0.20*	31.5	±4.2*	8.3	±2.4*	0.52	±0.33
Amphetamine – retest								
Vehicle	1.72	±0.18	14.8	±1.0	17.4	±2.8	0.38	±0.12
0.8 mg/kg	1.32	±0.13*	21.4	±2.7*	8.9	±2.1*	0.38	±0.12
Caffeine								
Vehicle	1.50	±0.15	16.3	±1.3	17.0	±2.5	0.40	±0.12
3 mg/kg	1.62	±0.17	16.3	±1.6	16.8	±2.8	0.32	±0.15
10 mg/kg	1.46	±0.18	17.0	±1.6	13.9	±3.2	0.44	±0.14
30 mg/kg	1.35	±0.15	20.0	±2.0*	15.8	±3.4	0.42	±0.14
PCP								
Vehicle	1.37	±0.15	22.6	±3.1	17.9	±3.1	0.52	±0.10
1.0 mg/kg	1.61	±0.49	23.2	±3.4	18.6	±3.0	0.44	±0.14
3.0 mg/kg	1.04	±0.30	28.3	±4.5	13.4	±3.6	0.50	±0.12
6.0 mg/kg	0.34	±0.13*	34.0	±4.4*	13.5	±2.9	0.47	±0.11

* Significant difference from the vehicle value assessed by Bonferroni *t*-tests following overall significance in the analysis of variance

Table 2 The effects of DOI, scopolamine, atropine and ethanol on four measures derived from the random reinforcement procedure used in experiment 1. For further details see legend to Table 1

	Response rate (resp/s)		Switching (% opportunities)		Perseveration (% responses)		SI	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
DOI								
Vehicle	1.56	±0.15	17.8	±2.2	19.1	±3.5	0.43	±0.11
0.1 mg/kg	1.51	±0.16	17.7	±2.7	15.8	±2.7	0.41	±0.09
0.3 mg/kg	1.55	±0.21	19.5	±3.0	18.0	±3.7	0.36	±0.12
1.0 mg/kg	1.22	±0.22	21.0	±4.3	18.6	±3.5	0.46	±0.08
2.0 mg/kg	1.25	±0.20	17.7	±1.9	22.4	±4.0	0.38	±0.11
4.0 mg/kg	0.73	±0.28*	22.5	±4.1	13.9	±4.7	0.45	±0.10
Scopolamine								
Vehicle	1.68	±0.16	17.1	±2.1	18.7	±3.6	0.42	±0.11
0.01 mg/kg	1.26	±0.09*	16.5	±1.5	18.6	±3.2	0.46	±0.15
0.03 mg/kg	0.58	±0.06*	17.2	±1.8	18.0	±3.6	0.38	±0.11
0.1 mg/kg	0.24	±0.03*	28.7	±4.8*	14.2	±4.3	0.11	±0.16
0.3 mg/kg	0.17	±0.03*	35.0	±4.8*	12.9	±2.5	–0.03	±0.11
Atropine								
Vehicle	1.69	±0.19	14.7	±1.5	18.9	±3.2	0.40	±0.12
0.1 mg/kg	0.80	±0.13*	15.9	±1.5	13.9	±4.2	0.25	±0.12
0.3 mg/kg	0.49	±0.06*	16.3	±1.8	13.0	±4.0	0.22	±0.09
1.0 mg/kg	0.41	±0.07*	16.9	±1.9	10.8	±1.9	0.23	±0.14
Ethanol								
Vehicle	1.60	±0.16	14.8	±1.3	20.4	±3.5	0.45	±0.10
0.1 g/kg	1.50	±0.16	15.0	±1.3	20.2	±3.8	0.53	±0.10
0.3 g/kg	1.54	±0.13	14.2	±1.1	18.1	±3.3	0.50	±0.11
1.0 g/kg	0.91	±0.22*	20.7	±3.0*	12.9	±3.4*	0.49	±0.12

rate. This was confirmed by statistical analysis [$F(5,35)=5.8$, $P<0.001$]. Only the highest dose used differed significantly from vehicle. There were no significant effects of DOI on the other measures (Table 2).

Scopolamine

Scopolamine was tested at doses of 0.01–0.3 mg/kg SC. All four doses produced a significant reduction in response rate [$F(4,28)=80.1$, $P<0.00$, Table 2]. Scopolamine also increased switching [$F(4,28)=10.7$, $P<0.001$], but did so only at the two highest doses, 0.1 and 0.3 mg/kg. There was no effect of scopolamine on perseveration. Scopolamine also reduced SI [$F(4,28)=3.4$, $P<0.05$]. However, despite SI reaching 0, i.e. the rats showed no sensitivity to the preceding reinforcement, none of the individual doses differed significantly from vehicle. The reduction in SI was primarily due to a reduction in win-stay from 0.87 after vehicle treatment to 0.66 after 0.3 mg/kg scopolamine [$F(4,28)=2.7$, $P=0.05$], as there was no consistent effect on lose-stay (0.61 after vehicle to 0.65 after 0.3 mg/kg scopolamine).

Atropine

Atropine was administered SC at doses of 0.1, 0.3 and 1.0 mg/kg. The drug significantly reduced the rate of responding at all three doses tested [$F(3,21)=36.2$, $P<0.001$, see Table 2]. Atropine did not increase switching, although there was a strong trend towards a reduction in perseveration [$F(3,21)= 3.0$, $P=0.055$]. Atropine had no significant effect on SI.

Ethanol

Ethanol was administered IP at doses of 0.1, 0.3 and 1.0 g/kg. The drug significantly reduced response rate at 1.0 g/kg [post hoc tests following $F(3,21)=20.7$, $P<0.001$]. At this same dose, ethanol also significantly increased switching [$F(3,21)=7.4$, $P<0.01$] and reduced perseveration [$F(3,21)=5.1$, $P<0.01$]. However, it had no significant effect on SI. Thus in this procedure ethanol had an effect very similar to amphetamine and caffeine.

Experiments 2 and 3: fixed ratio-switch

Amphetamine

Amphetamine was administered at doses of 0.4, 0.8 and 1.6 mg/kg IP. The drug increased switching at all three doses tested [$F(27,162)=2.15$, $P<0.01$, Fig. 1]. Post hoc tests revealed that only three data points did not differ significantly from control, bin numbers 8 and 10 at the 0.4 mg/kg dose, and bin number 10 at the 0.8 mg/kg dose. These doses of *d*-amphetamine did not significantly affect

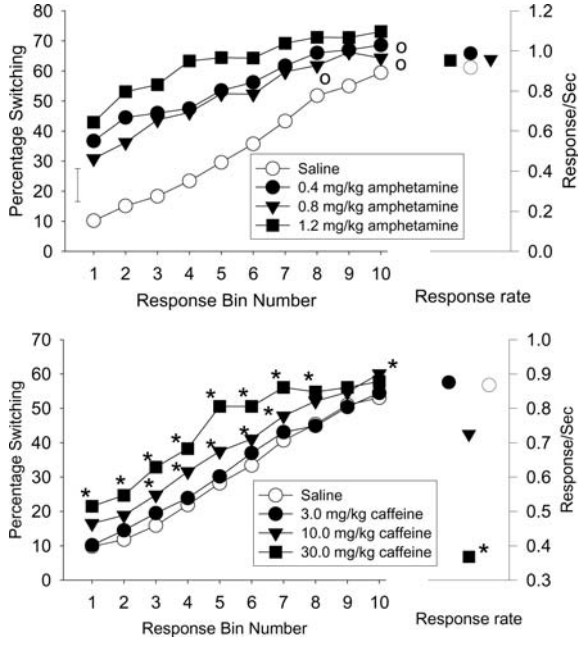

Fig. 1 The effects of amphetamine and caffeine on rats responding under a fixed ratio 21, switch schedule of reinforcement. The *left hand panels* show the percentage switching as a function of progression to completion of the fixed ratio. *Bin 1* refers to the first to third responses (i.e. first and second response pairs), *bin 2* to the third to fifth responses (i.e. third and fourth response pairs) and so on until *bin 10*, which refers to responses 19–21 (penultimate and final response pairs). The *right hand panels* show the effects of the drugs on the rate of responding over the course of the session. The horizontal displacement of the symbols is for display purposes only. In the *upper left panel* lack of statistical significance ($P>0.05$) is indicated by the symbol "0". All other data points in this panel are significantly different from the corresponding vehicle points (*open symbols*). The *vertical bar* in the *upper left hand panel* shows the critical difference used for calculating statistical significance of the interaction term. In the other three panels a statistically significant difference from vehicle control is indicated by * ($P<0.05$)

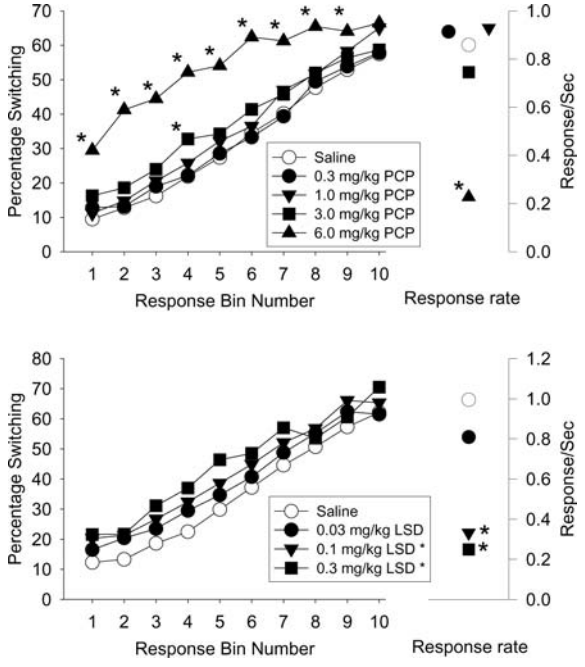

Fig. 2 The effects of PCP and LSD on rats responding under a fixed ratio 21, switch schedule of reinforcement. The *left hand panels* show the percentage switching as a function of progression to completion of the fixed ratio and the *right hand panels* show the effects of the drugs on the rate of responding over the course of the session. In all four panels a statistically significant difference from vehicle control is indicated by * ($P<0.05$). For other details, see legend to Fig. 1

response rate. Thus amphetamine increased switching at doses that did not increase response rate.

Caffeine

Caffeine was the only drug tested in experiment 3, at doses of 3.0, 10.0 and 30.0 mg/kg IP. Caffeine increased response switching (Fig. 1). This observation was supported by a statistically significant Treatment by Bin interaction [$F(27,189)=2.19$, $P<0.01$]. Post hoc tests revealed that at the 10.0 mg/kg dose a statistically significant increase in switching was observed from bin 3 to bin 7 (i.e. from response number 5 to 15) and in the final bin (responses 19, 20 and 21), and at the 30.0 mg/kg in all bins up to bin 8, i.e. from response number 1 to response number 16, but not in the two last bins. Caffeine significantly reduced response rate [$F(3,21)=31.7$, $P<0.001$], an effect which only reached statistical significance at the dose of 30.0 mg/kg. Caffeine increased switching at a dose that did not significantly affect response rate.

PCP

PCP was administered at doses of 0.3, 1.0, 3.0 and 6.0 mg/kg SC. PCP increased the probability of switching at two doses, 3.0 and 6.0 mg/kg [$F(36,193)=2.79$, $P<0.001$, Fig. 2]. The effect of 3.0 mg/kg was quite small, only reaching statistical significance in one bin (response numbers 7, 8 and 9). The effect of 6.0 mg/kg was much greater, reaching statistical significance in all bins except the last. PCP also reduced the response rate significantly [$F(4,24)=17.2$, $P<0.01$]. Post hoc tests revealed that this effect was confined to the dose of 6.0 mg/kg. Thus PCP significantly increased switching and significantly reduced response rate at the same dose.

LSD

LSD was administered at doses of 0.03, 0.1 and 0.3 mg/kg SC. There was a small but significant increase in switching at the two highest doses, 0.1 and 0.3 mg/kg (Fig. 2). However, unlike with PCP, this was reflected by a significant main effect of treatment in the ANOVA [means: Sal: 34.8%, 0.03 mg/kg LSD: 39.3%, 0.1 mg/kg

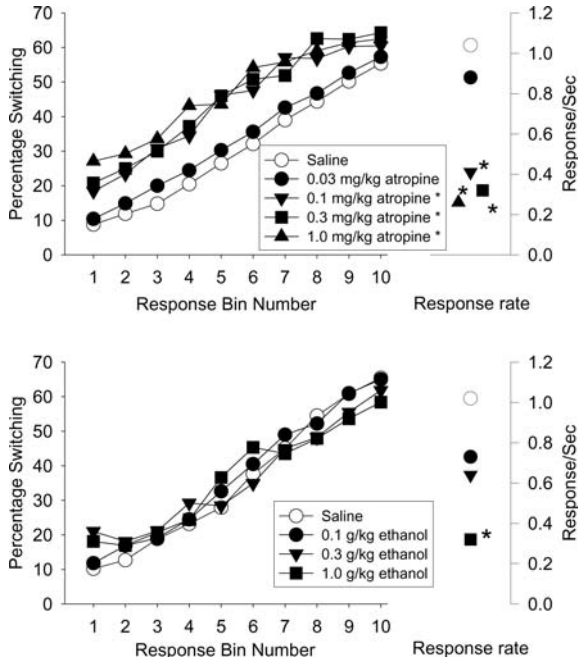

Fig. 3 The effects of atropine and ethanol on rats responding under a fixed ratio 21, switch schedule of reinforcement. The *left hand panels* show the percentage switching as a function of progression to completion of the fixed ratio and the *right hand panels* show the effects of the drugs on the rate of responding over the course of the session. In all four panels a statistically significant difference from vehicle control is indicated by * (P<0.05). For other details, see legend to Fig. 1

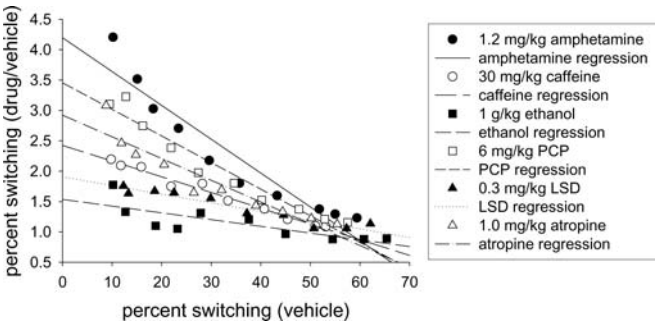

Fig. 4 The maximum effects of the six test drugs on percentage switching under the fixed ratio 21, switch procedure, expressed as function of the baseline percentage switching. The *horizontal axis* shows the percentage switching in each of the ten bins after vehicle treatment (derived from the open symbols in Figs. 1, 2 and 3). The *vertical axis* shows the percentage switching after treatment with the dose of test drug indicated in the panel divided by the percentage switching in the corresponding bin after vehicle treatment. The *straight lines* represent linear regression functions calculated by the graphical package Sigmaplot through the symbols. Further details of these regressions are provided in Table 3

Table 3 Slopes and correlations of the regression plots of the percent change in switching (drug/vehicle) plotted against the percent switching after vehicle treatment. The dose of each drug selected was the one giving the maximum effect. Note that the same

	Slope	r^2
1.2 mg/kg amphetamine	–0.056	0.91
6.0 mg/kg PCP	–0.044	0.94
1.0 mg/kg atropine	–0.036	0.88
30.0 mg/kg caffeine	–0.026	0.98
0.3 mg/kg LSD	–0.014	0.92
1.0 g/kg ethanol	–0.011	0.63

LSD, 42.4%, 0.3 mg/kg LSD, 44.8%, crit dif = 6.1%, F(3,18)=6.6, P<0.01] rather than a Treatment by Bin interaction. These two doses of LSD also significantly reduced the response rate [post hoc tests following F(3,18)=24.3, P<0.001], so that LSD increased switching and reduced response rate at the same doses.

Atropine

Atropine was administered at doses of 0.03, 0.1, 0.3 and 1.0 mg/kg SC There was a considerable increase in switching produced by the three highest doses of atropine (Fig. 3). This observation was supported by a statistically significant main effect of Treatment [means: Sal, 30.4%, 0.03 mg/kg atropine, 33.5%, 0.1 mg/kg atropine 43.6%, 0.3 mg/kg atropine, 45.2% and 1.0 mg/kg atropine, 47.0%, critical difference=9.8%, F(4,24)=10.6, P<0.001]. These three doses of atropine also significantly reduced the rate of responding [post hoc tests following F(4,24)=30.5, P<0.01]. Like LSD, atropine increased switching and reduced response rate at the same dose.

Ethanol

Ethanol was administered orally at doses of 0.1, 0.3 and 1.0 g/kg. The drug had no significant effect on the percentage of switching either as an interaction with Bin or as a main effect of Treatment (Fig. 3). However, ethanol did reduce the rate of responding, although the inter-subject variability was such that this only reached statistical significance at the highest dose tested, 1.0 g/kg [post-hoc tests following F(3,15)=4.2, P<0.05].

Comparison between drugs

In Fig. 4, the increase in switching (expressed as percent switching under the drug divided by the percent switching in the corresponding bin after vehicle treatment) produced by the dose of drug exerting the maximum effect has been plotted against the baseline performance (i.e. percent switching after vehicle treatment during the corresponding bin). The slopes of the regression lines and the correlation coefficients are listed in Table 3. From Fig. 4, it is clear that amphetamine exhibits the strongest inverse relationship between the baseline percent switching and the increase produced by the drug. Ethanol, which did not significantly increase switching, shows the weakest effect. PCP shows "probability dependency" somewhat weaker than amphetamine, atropine and caffeine lie

intermediate, whereas LSD has an effect almost as small as that of ethanol.

Discussion

The effects of amphetamine on switching reported here were similar to those previously reported in the literature. In the random ratio procedure, the single dose of 0.8 mg/kg *d*-amphetamine significantly increased switching as previously reported (Evenden and Robbins 1983a, 1983b). It also reduced perseveration and slightly reduced response rate, and had no effect on the Sensitivity Index. In previously published studies, which included a wider range of doses, this dose of drug had no significant effect these measures. In the FR-Switch procedure, the effects of amphetamine were similar to published data in this dose range. Evenden and Doggett (1989) found dose-dependent increases in switching of about the same magnitude, with no effect on average response rate. The second psychomotor stimulant tested was caffeine, which increased switching in both procedures at 30 mg/kg. In the FR-switch procedure, this was accompanied by a significant reduction in the rate of responding. In that procedure caffeine also increased switching at a dose of 10 mg/kg, which had no effect on response rate. Thus in both procedures, like amphetamine, caffeine could increase switching without any effects on response rate, demonstrating a certain behavioural selectivity. There are no previously published reports of the effects of caffeine in either of these procedures. However, in a related procedure, measuring tracking of a visual stimulus as it moved from one lever to another, Evenden et al. (1993) also found that caffeine increased response switching.

In both procedures, PCP consistently increased switching only at doses that markedly reduced response rate. PCP has not previously been tested in this type of procedure. Thompson and Moerschbaecher (1984) did find that this drug increased errors in the response chain learning and performance procedure in monkeys providing further confirming evidence that PCP disrupts behavioural organisation, although from a rather different procedure. Unfortunately, it was not possible to test the same drug representing 5-HT_2 agonists in both procedures. In the random reinforcement procedure the selective 5-$HT_{2A/2C}$ agonist, DOI, had no significant effects on switching although the test dose was increased up to a level (4.0 mg/kg), which produced a substantial reduction in response rate (approximately 50%). LSD did increase switching in the FR-switch procedure, but again, only at doses which markedly reduced response rate. The difference between LSD and DOI may be related to the broader pharmacological actions of LSD which has affinity for dopaminergic and adrenergic receptors as well as serotonergic receptors (Whitaker and Seeman 1978, 1979). Affinity for 5-HT_{2A} receptors appears to be sufficient for psychotomimetic effect in humans (Glennon 1990). Unlike the other psychotomimetic drugs used in this study, DOI does not reliably increase spontaneous locomotor activity in habituated subjects, (Hillegaart et al. 1996). The lack of effect of DOI on switching would suggest that stimulation of 5-HT_{2A} or 5-HT_{2C} receptors does not affect this behaviour.

Anticholinergics were exemplified by scopolamine and atropine. In the random ratio procedure scopolamine increased switching, but only at doses which suppressed responding. Atropine did not increase switching, although it did reduce the rate of responding at all three doses tested. Uniquely, scopolamine also dose-dependently disrupted response choice following food or "no-food" as measured by SI. In the FR-switch procedure, atropine did increase switching, but again, at doses which markedly reduced response rate. Evenden (1986) tested the effects of scopolamine using an FR21-switch procedure in the pigeon. The average results were very similar to those demonstrated here in the rat, but in the single subject exhibiting a terminal baseline frequency of switching greater than 50%, scopolamine reduced the frequency of switching, suggesting that scopolamine may drive switching towards the 50% level, i.e. randomised responding. In the present experiment, there was no such tendency following atropine even though one subject exhibited a terminal baseline frequency of switching of over 95%. However, the reduction of SI following scopolamine treatment in the random ratio procedure would lend weight to the suggestion that the response selection of the rats did become more independent of its consequences and/or external controlling stimuli at higher doses of the drug.

Ethanol was not expected to increase switching, and was included in this study as a negative control. In the FR-switch procedure, after IP administration, the drug had no significant effect other than to reduce the rate of responding. However, in the random reinforcement procedure the dose of 1.0 g/kg given by the oral route not only reduced response rate, but also significantly increased switching and reduced perseveration. The reduction in response rate was somewhat more than with psychomotor stimulants but clearly less than those seen with PCP and the anticholinergics. Although ethanol may not be an appropriate negative control, there are findings of drugs which reduced response rate, but had no effect on switching: α-flupenthixol, and chlordiazepoxide in the random reinforcement procedure (Evenden and Robbins 1983a) and α-flupenthixol in the FR-switch procedure (Evenden and Doggett, unpublished). These results, together with those of DOI and atropine in the present study, are important, since they confirm that reductions in response rate are not inevitably accompanied by increases in switching secondary to a generalized disruption of responding.

A direct comparison of the effect of drugs on response switching in the FR-switch procedure can be seen in Fig. 4, using an analysis based upon the rate dependency hypothesis. From numerous experimental studies, it is clear that the effect of amphetamine on response rate is dependent on the baseline rate of responding: the lower the baseline rate, the greater the increase in rate produced

by the drug (reviewed by Dews and Wenger 1977). Robbins and Evenden (1986) extended this analysis to probabilistic measures such as response switching, stating that the lower the baseline percentage of switching, the greater the increase produced by amphetamine (the so-called "probability dependency" hypothesis). The results in Fig. 4 confirm that the effect of amphetamine was clearly baseline dependent, as were those of PCP and atropine. The effect of caffeine, although selective for switching versus response rate, was clearly differentiated from that of amphetamine over the dose range studied. The small effects of LSD and ethanol were not evidently baseline dependent. LSD and ethanol have both been reported to produce rate-dependent effects, although in both cases less marked than amphetamine (Leander et al. 1976; Harris et al. 1978).

Only a limited number of clinical studies on behavioural organisation appear to have used methods similar to the present study. Frith and Done (1983) found that acute schizophrenics with negative symptoms treated with antipsychotic medication showed an excess of "LRLR" tetragrams in a two-choice randomised guessing task somewhat similar to the random reinforcement task for rats. In contrast, chronically medicated schizophrenics with intact cognition showed an excess of alternations, whereas those in a defect state showed an excess of repetitive tetragrams (i.e. RRRR or LLLL). Lyon et al. (1986) obtained similar results using a group of Danish neuroleptic-treated schizophrenic outpatients. A second test, somewhat different in nature, but which may address the same process, is the task switching procedure of Rogers and Monsell (1995), in which subjects are required to switch between classifying a series of visual stimulus pairs along one of two dimensions. In this procedure, although showing slower decision making than controls, schizophrenics were faster in disengaging from the previous task set (Meirin et al. 2000), i.e. switching. In another study, methylphenidate enhanced the ability of children with attention deficit/hyperactivity disorder to switch between the two tasks (Kramer et al. 2001). There are obvious differences in design and potential interpretation between the clinical and the rodent studies but some interesting commonalities may be emerging.

In conclusion, at least two critical criteria should be fulfilled if changes in response switching induced by psychotomimetic drugs are a general animal model of the behavioural disorganisation in schizophrenia. First, even though the effects of psychotomimetic drugs differ to some extent in humans, they should have similar effects in this model. Since DOI had no effect, and LSD only a small effect, psychotomimetics as a class do not all share similar effects on the organisation of behaviour as measured by response switching. Rather, the similar effects on response switching of caffeine and amphetamine, which have different pharmacological mechanisms of action, suggest that they may be accounted for by the common psychomotor stimulant activity of the two drugs. Nonetheless, since amphetamine, PCP and the anticholinergics did increase switching this behavioural index may still have some utility for screening antipsychotic drugs. Thus, second, at least for those psychotomimetics that do affect response switching, this increase in switching should be blocked by a range of typical and atypical antipsychotics. This criterion has not been addressed in the present manuscript. A small number of pilot studies have been carried out, some of which support the hypothesis, but a more comprehensive program of work is needed to provide a definitive answer.

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