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Effects of *d*-Amphetamine and Morphine on Discrimination: Signal Detection Analysis and Assessment of Response Repetition in the Performance Deficits

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Abstract. Signal detection analysis was used to examine the effects of *d*-amphetamine and of morphine on auditory discrimination in female rats. The probability of response repetition in the discrete trial two-choice discrimination procedure was used as an additional behavioral measure. *d*-Amphetamine (0.4–3.2 mg/kg) and morphine (1.88–15.0 mg/kg) decreased the sensitivity measures (A′ and SI) but did not consistently affect the response bias measures (B″ and RI). The probability of response repetition was increased by *d*-amphetamine and was not affected by morphine. It is concluded that the response bias measure B″, derived from signal detection theory, and the empirical response bias measure RI, do not discriminate between the different ways in which *d*-amphetamine and morphine affect discriminative responding, under the conditions of this study.

Key words: Auditory Discrimination – Signal detection – Response Repetition – *d*-Amphetamine – Morphine – Rats

Behavioral effects of drugs may result from drug-induced changes in the control of stimuli over behavior. Different procedures have been used to study drug effects on stimulus control (Thompson 1978). In the usual, discrete trial discrimination procedure, a single response on one lever is reinforced in the presence of a discriminative stimulus, and a single response on the other lever is reinforced in the presence of a different discriminative stimulus. Such a procedure seems to be very useful in studying selective effects on discrimination, because concomitant, non-specific drug effects on response rate would presumably affect responses on both levers equally. Thus, a two-choice discrete trial procedure might enable a measure of drug effects upon stimulus control unconfounded by drug effects upon response rate. However, a reduction of the accuracy of discriminative responding in a discrete trial procedure could result from a reduced ability to discriminate between the two stimuli, or might result from an increased probability that a response on a particular lever is repeated during the next trial, regardless of the discriminative stimulus presented during the trial (response perseveration).

Results consistent with this latter possibility have for instance been obtained by Nielsen (1981) in a discrete trial visual discrimination procedure. It was observed that *d*-amphetamine decreased the discrimination accuracy and increased the number of consecutive responses made on the same lever.

Signal detection theory has been successfully used in animal drug experiments in an effort to measure drug-induced changes in sensitivity separately from drug-induced changes in response bias (the degree to which animals emit one response more frequently than another) (Appel and Dykstra 1977). It was the aim of the present experiment to study the sensitivity of a response bias measure, derived from signal detection theory, to amphetamine-induced response perseveration. A discrete trial two-choice, successive auditory discrimination procedure was used. The probability of response repetition might provide a more direct measure of response perseveration than the response bias measure, derived from signal detection theory. Therefore, in addition to the signal detection measures (i.e. sensitivity and response bias), the probability of response repetition was used as a dependent variable. This probability has been shown to be affected by *d*-amphetamine (Robbins and Watson 1981). In order to investigate the specificity of the effects of *d*-amphetamine, the effects of morphine on sensitivity, response bias and probability of response repetition, were also studied. Morphine was selected because it has been reported that morphine decreased the discrimination accuracy in a discrete trial auditory discrimination (Hernandez and Appel 1979) and because morphine, to our knowledge, does not induce response perseveration.

Materials and Methods

Subjects. Four female Wistar rats (CPB-TNO, Zeist, The Netherlands) were used. They were individually housed in a room maintained on a 12 h light/dark cycle with constant temperature (21 °C). Water was continuously available in the individual home cages. The rats were maintained at 85% of their free-feeding body weight (210–240 g) by augmenting food consumed during the experimental sessions with an additional 5–10 g of laboratory food pellets per day. The rats were fed 2 h after the completion of the sessions, which were conducted 5 days per week, Monday to Friday. The subjects had previously been used in a stimulus generalization study.

Apparatus. The apparatus consisted of a Skinner box (Campden Instruments model 4107) equipped with a food pellet dispenser and two retractable levers, equidistant from the food tray. The Skinner box was housed in a sound resistant chamber (Industrial Acoustics Company). Stimuli were produced by an audio generator (Campden Instruments model 258). The stimulus intensity was 70 dB (measured in

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the centre of the Skinner box). The background noise level was 45 dB. All experimental events were controlled and recorded by a SCAT system, implemented on a PDP 8 computer.

Behavioral Procedure. The animals were trained to respond differentially in a self-paced two-choice discrimination task. Two rats were trained to discriminate between the presence and the absence of a clicking noise [8 clicks per s (cps)], and two rats were trained to discriminate between 8 and 40 cps. All rats were initially trained to press the left lever in the presence of the 8 cps stimulus, during two 30-min sessions. The left lever was inserted into the chamber 2.5 s after the start of the stimulus presentation. Immediately after a left lever press, a reinforcer (one 45-mg food pellet, Campden Instruments) was delivered, the presentation of the auditory stimulus was discontinued and the lever was retracted. The next trial started with the presentation of the auditory stimulus after a 7.5-s period. The animals were trained in the same manner to respond on the right lever in the absence of the auditory stimulus (rat 1 and rat 2), or in the presence of the 40 cps stimulus (rat 3 and rat 4).

Finally both levers were inserted simultaneously, 2.5 s after the start of the stimulus presentation (or 10 s after the end of the previous trial if no auditory stimulus was presented). A left lever response was reinforced in the presence of the 8 cps stimulus (S1) and a right lever response was reinforced in the presence of the alternative stimulus condition (S2). After a correct lever choice it was randomly determined whether S1 or S2 was presented during the next trial, with the exception that the same stimulus was never presented on more than three consecutive trials. After an incorrect lever choice the same stimulus condition was repeated during the next trial. This correction procedure was replaced by a random procedure after the rats reached a criterion of 80% correct responses. All rats reached this criterion in less than 20 sessions. When the animals again responded correctly in 80% of the trials the probability of reinforcement was reduced to 0.5 on each lever, in order to submit the animals to maintained stimulus generalization tests (Blough 1969) along the auditory frequency dimension on Wednesdays and Fridays during 4 weeks (results not reported here). Drugs were tested after 4 weeks of training since the generalization tests.

Pharmacological Procedure. Drugs were administered on Tuesdays and Fridays, and 0.9% saline was administered on Thursdays. All injections were given subcutaneously in a volume of 2 ml/kg of body weight, 30 min before testing. All rats received 0.4, 0.8, 1.6 and 3.2 mg/kg *d*-amphetamine sulfate and 1.88, 3.75, 7.5 and 15 mg/kg morphine hydrochloride. Tests with doses of *d*-amphetamine were conducted first. The sequence in which different doses of a drug were administered was counterbalanced across rats. When the aforementioned tests were completed the rats were tested with 1.1 mg/kg *d*-amphetamine sulfate and with 10.6 mg/kg morphine hydrochloride in order to determine the dose-effect curves more accurately. The drugs were dissolved in 0.9% NaCl immediately before use. Doses refer to the salts.

Analysis of Data. The discrimination performance was defined in a signal detection framework as follows: a response on the left lever in the presence of S1 was arbitrarily designated a hit and a response on the left lever in the presence of S2 was designated a false alarm. The proportion of hits (number of hits/number of S1 trials) and the proportion of false alarms (number of false alarms/number of S2 trials) were computed for each subject and each session. The proportion of hits and the proportion of false alarms were used to calculate the nonparametric sensitivity index A′ and the nonparametric bias index B″, using the formulas of Grier (1971). A′ can take on values between 0.5 (no sensitivity) and 1.0 (perfect sensitivity). B″ ranges from -1.0 to $+1.0$; $B'' < 0$ indicates a bias toward responding on the left lever, $B'' = 0$ indicates no response bias, and $B'' > 0$ indicates a bias toward responding on the right lever. Since B″ might become increasingly insensitive to changes in bias as A′ decreases, the data were also analyzed in terms of the sensitivity measure SI and the response bias measure RI (Frey and Colliver 1973); whereas SI behaves similarly to A′, RI is independent of SI. In addition to the A′ and the B″ measures, and the SI and RI measures, the probability of response repetition and the total number of trials completed during the 30-min sessions were also determined. The probability of response repetition was defined as the number of trials, during which the animal responded on the same lever on which it responded during the immediately preceding trial, divided by the total number of trials minus 1.

Drug testing was conducted during a 5-week period. For every rat the mean A′, the mean SI, the mean probability of response repetition, and the mean number of trials completed during the five saline tests, were used in subsequent analyses. The response bias (B″ and RI) data were analyzed by a method which was similar to the method described by Dykstra and Appel (1974). The difference in response bias between the first and the third saline test day (the measure of normal variability in response bias) was compared to the differences in response bias between the fifth saline test day and the drug test days (the measure of drug-induced variability), in order to determine whether the differences seen after drug administration were greater than changes attributable to normal day-to-day variations.

The effects of drug dose on the different behavioral measures were analyzed by a one-factor repeated measures ANOVA, followed, where appropriate, by multiple *t*-tests between every drug dose and saline (Winer 1971). This ANOVA assumes equality of the covariances for each pair of treatments and equality of the variances for each treatment. If this assumption is violated the test is positively biased, i.e. rejects the null hypothesis more often than would be expected by the nominal significance level. A significant conventional ANOVA ($\alpha = 0.05$) was therefore followed by an ANOVA which was adjusted for positive bias by reducing the degrees of freedom of the conventional F-statistic. The adjusted degrees of freedom were θ (K-1) and θ (N-1) (K-1) [N = number subjects, K = number of treatments, θ was estimated from the variance-covariance matrix (Vitaliano et al. 1981)]. Since the effects of *d*-amphetamine and morphine did not seem to depend upon the nature of the discrimination task (presence versus absence of the 8 cps stimulus, and 8 cps versus 40 cps) the results from both pairs of rats were included in the same one-factor ANOVA.

Results

Three out of four rats did not respond after the administration of 3.2 mg/kg *d*-amphetamine and two rats did not respond after 15 mg/kg morphine. The results of these doses were not included in the statistical analyses. The mean

number of trials (±1 SEM) completed during the 30-min sessions after the administration of saline was 159 ± 4. The mean number of trials was significantly reduced by *d*-amphetamine [F (4/12) = 6.45, $P < 0.01$] and by morphine [F (4/12) = 23.33, $P < 0.001$]. Multiple t-tests showed that 1.6 mg/kg *d*-amphetamine significantly reduced the mean number of trials to 69 ± 33 ($P < 0.001$). The mean number of trials was significantly reduced to 98 ± 22 by 7.5 mg/kg morphine ($P < 0.01$) and was reduced to 41 ± 12 by 10.6 mg/kg morphine ($P < 0.001$).

d-Amphetamine dose-dependently decreased the sensitivity measure A′ [F (4/12) = 20.96, $P < 0.001$] (Fig. 1), and did not significantly affect the change in the response bias measure B″. However, the probability of response repetition was dose-dependently increased by *d*-amphetamine [F (4/12) = 5.86, $P < 0.01$]. Morphine decreased the A′ measure [F (4/12) = 7.22, $P < 0.005$], but neither significantly affected the change in B″, nor the probability of response repetition. Similar results were obtained with the sensitivity measure SI and the response bias measure RI (not shown). *d*-Amphetamine and morphine both decreased the SI measure [F (4/12) = 20.37, resp. 10.99, $P < 0.001$], and did not significantly affect the RI measure.

In certain rats there were B″ values (Fig. 2) and RI values (not shown) which differed by more than two standard deviations from the mean saline value, at certain doses. However, taken together, the results suggest that *d*-amphetamine and morphine did not consistently affect the B″ and RI values, either in the rats trained to discriminate between the presence and the absence of the 8 cps stimulus, or in the rats trained to discriminate between an 8 cps stimulus and a 40 cps stimulus.

The F-values reported above were also statistically significant ($\alpha = 0.05$) when the degrees of freedom were adjusted for inhomogeneity of the variance-covariance matrix.

Discussion

d-Amphetamine and morphine dose-dependently decreased the sensitivity measures A′ and SI in rats which were trained to discriminate between auditory stimuli. The response bias measures B″ and RI were neither significantly affected by *d*-amphetamine, nor by morphine, in a consistent manner. These results agree with the finding that *d*-amphetamine decreases the accuracy of a visual discrimination in rats (Nielsen 1981), and that *d*-amphetamine decreases the accuracy of temporal discriminations and of brightness discriminations without affecting response bias (Appel and Dykstra 1977). The results of the present study extend these findings to an auditory discrimination task in rats. The present results are also consistent with the finding that

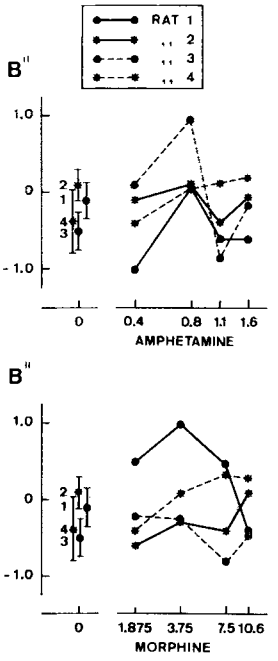

Fig. 2. Effects of *d*-amphetamine and morphine (mg/kg, SC 30 min before testing) on response bias (B″) in rats which were trained to discriminate between the presence and the absence of an auditory stimulus (8 clicks/s) (rat 1 and rat 2), and in rats which were trained to discriminate between 8 clicks/s and 40 clicks/s (rat 3 and rat 4). Bars represent the standard deviation

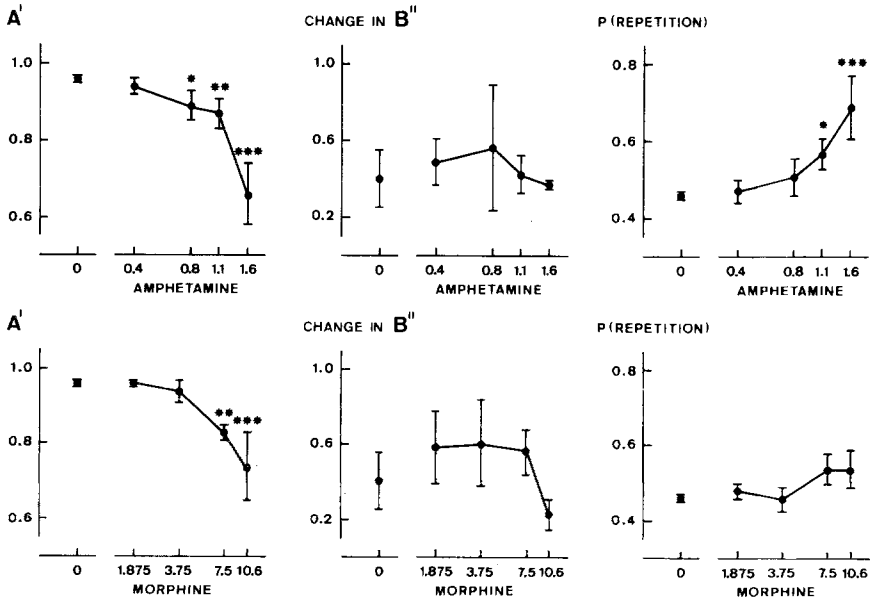

Fig. 1
Effects of *d*-amphetamine and morphine (mg/kg, SC 30 min before testing) on sensitivity (*A′*), on change in response bias (*B″*), and on probability of response repetition in rats ($N = 4$), which were trained to discriminate between auditory stimuli in a discrete-trial two-lever procedure. Bars represent the standard error of the mean. Asterisks indicate the significance of differences from saline (*$P < 0.10$, **$P < 0.05$, ***$P < 0.001$)

morphine decreases the accuracy of an auditory discrimination in rats (Hernandez and Appel 1979), and with the observation that morphine decreases sensitivity in a shock-discrimination task without affecting response bias (Grilly 1981; Hernandez and Appel 1980). In the present experiment it was observed that *d*-amphetamine dose-dependently increased the probability of response repetition. Increased response perseveration after *d*-amphetamine has been reported in studies on discriminination of stimulus duration (Stubbs and Thomas 1974; Rapp and Robbins 1976; Altman et al. 1979), and in a study on visual discrimination (Nielsen 1981). It is important to note that the probability of response repetition was increased by *d*-amphetamine but not by morphine. This finding suggests that the decreased accuracy after *d*-amphetamine might result from amphetamine-induced response perseveration, whereas the decreased accuracy after morphine cannot be ascribed to drug-induced response perseveration. The decreased accuracy after morphine might result from a diminished sensitivity to the discriminative stimuli.

It is concluded that, under the conditions of the present experiment, the response bias measure B″, derived from signal detection theory, and the empirical response bias measure RI, do not discriminate between the different ways in which *d*-amphetamine and morphine seem to affect discriminative responding. Because the "probability of response repetition" measure did discriminate between the effects of *d*-amphetamine and morphine on discriminative responding it might be useful to include a measure of response repetition in discrete trial studies, designed to investigate the effects of drugs on stimulus control. The B″ and RI measures have been used in this study to index changes in lever bias. It is to be expected that a complete lever bias will be observed as the probability of response repetition approaches 1. However, the results of the present study suggest that, at lower levels of response repetition, the response repetition measure is more sensitive to the effects of *d*-amphetamine than the B″ and RI measures, when these latter measures are calculated on the basis of the total number of trials of an experimental session.

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