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A performance-dependent adjustment of the retention interval in a delayed non-matching-to-position paradigm differentiates effects of amnestic drugs in rats

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Abstract

Operant delayed non-matching-to-position (delayed non-matching-to-position) tasks have been widely used as tests of working memory in rats, but have suffered some loss in sensitivity to differentiating selective mnemonic from non-mnemonic deficits due to floor and ceiling effects. To circumvent this problem, a novel delayed non-matching-to-position was developed in which the retention interval was adjusted on a trial-by-trial basis to hold performance accuracy at an intermediate value. The present study assessed the effects of three amnestic drugs in this delayed non-matching-to-position. Rats were administered (i.p.) NMDA receptor antagonist ((5*R*,10*S*)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d,] cyclohepten-5,10-imine (Dizocilpine or MK-801), muscarinic receptor antagonist (−)-scopolamine hydrobromide (scopolamine), or cannabinoid receptor agonist ((*R*)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone) (WIN 55, 212-2). At high doses, both MK-801 (0.12–0.25 mg/kg) and scopolamine (0.25 mg/kg) produced deficits not selective to working memory. At low doses, scopolamine (0.06–0.12 mg/kg) and MK-801 (0.06 mg/kg) produced no deficits in any mnemonic or secondary measures. WIN 55, 212-2 produced deficits at 2.0 mg/kg that were consistent with a specific impairment of working memory. Using this particular delayed non-matching-to-position revealed that consistent changes in performance accuracy at the short retention interval were evident for scopolamine and MK-801, at times in the absence of changes in response tendency, which are consistent with an interpretation that these drugs produce general deficits in reference or procedural memory. In contrast, cannabinoid-induced deficits in choice accuracy support previous reports of delay-dependent deficits. Together, these data suggest that this delayed non-matching-to-position task is able to differentiate deficit patterns of amnestic drugs, and isolate the effects of motivational side effects of drugs from working memory measurement.

Keywords: Acetycholine; Cannabinoid; Glutamate; Learning; Short-term memory

1. Introduction

Cholinergic muscarinic receptor antagonists, glutamate NMDA receptor antagonists, and cannabinoid receptor agonists have each been characterized as having disruptive effects upon working memory (e.g. Sarter et al., 1992; Hampson and Deadwyler, 1998; Izquierdo and Medina, 1995). However, it has been debated as to whether it is possible to distinguish the selective effects on working memory from effects resulting from non-mnemonic side effects of these drugs, a problem potentially limiting the predictive utility of rodent models of human amnesias in preclinical studies of cognition-enhancing pharmaceuticals (e.g. Dawson et al., 1992).

Even in one of the most sophisticated and sensitive rodent working memory paradigms available, the delayed non-matching-to-position task, muscarinic receptor antagonist scopolamine and NMDA receptor antagonist ((5*R*,10*S*)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d,] cyclohepten-5,10-imine (Dizocilpine or MK-801)) have consistently produced deficits in delayed non-matching-to-position choice accuracy that are generally characterized as not specific to working memory (e.g. Dunnett, 1985; Robinson, 1997; Tan et al., 1989). This pattern of deficits is termed "delay-independent", because performance is disrupted even at short retention intervals when remember-

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ing is not required for accurate performance. The best studied cannabinoid receptor agonist, (−)-Δ^9-tetrahydrocannabinol has been shown to produce either "delay-dependent", memory-specific, deficits in one experiment (Hampson et al., 1993), or delay-independent in another (Mallet and Beninger, 1996). When considered together, these experiments fail to make a strong case that selective effects of "amnestic" drugs in the delayed non-matching-to-position task have been demonstrated.

One explanation for this situation may lie in limitations of the delayed non-matching-to-position itself. The first is that in the delayed non-matching-to-position procedure, as it is usually conducted, the duration of the retention interval is a within-subject, within-session independent variable. In normal animals, choice accuracy is at a high level at the shortest retention intervals, and drops off to somewhat above chance at longer retention intervals. For an effect to be characterized as a selective memory impairment, a choice accuracy deficit must increase as a function of the duration of the retention interval. Statistically speaking, this requires a significant drug dose × retention interval interaction in the analysis of variance. Secondly, because the percent correct measure in the two choice tasks has a ceiling at 100% correct and a nominal floor at the 50% correct "guessing" point, the greatest between-subject variance occurs as choice accuracy decreases from 100% with the increasing retention interval. This creates a violation of the assumption of equal spread of variances at each observation. Statistical transformations can equalize the variance across delays, but generally sacrifice some power in doing so (see Ringo, 1988; Wixted, 1990).

A promising alternative to performing statistical transformations on the data has been to address these limitations in the rodent delayed non-matching-to-position procedure. A performance-dependent adjustment in retention interval, where choice accuracy is held at approximately 75% or greater, has been shown to be an effective means of overcoming loss of statistical validity resulting from floor and ceiling effects (Wenger et al., 1993; Robinson and Mair, 1992).

In a recent study by the present authors, the retention intervals in a delayed non-matching-to-position were adjusted within-session between a 1.0 s retention value and a longer value of varying duration (Robinson et al., in press). The subjects were exposed to a long retention interval on a given trial when the overall within-session accuracy at both long and short retention intervals exceeded 75% correct, and the short 10.0 s retention interval when overall accuracy was 75% or less. This had the effect of maintaining overall choice accuracy at approximately 75% correct. It was shown that the proportion of trials over the course of the session in which the long retention interval was presented decreased in response to the lengthening of the value of longer retention interval. Secondly, other non-mnemonic measures of delayed non-matching-to-position performance, such as discrimination accuracy, accuracy at a 1.0 s retention interval, and the number of trials completed per session were not altered. In a second experiment in that paper, a non-mnemonic independent variable, deprivation level, was systematically manipulated to assess the effects of motivational changes upon the measures. In contrast to the first experiment, the number of trials completed per session decreased, but the proportion of trials in which the rat was exposed to a long-delay was not. These experiments suggested that it was possible to dissociate a selective reduction of retention capacity of the drugs from performance deficits resulting from motivational and perhaps other non-mnemonic effects of the drugs.

The present study represents the first study of the effects of amnestic drugs in this adjusting delayed non-matching-to-position procedure. We chose to compare three amnestic drugs, (−)-scopolamine hydrobromide (scopolamine), MK-801, and ((*R*)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone) (WIN 55, 212-2) in this procedure. Scopolamine was chosen because of its use as a pharmacological model of Alzheimer's disease (Hagan and Morris, 1988). MK-801 was chosen because of its known disruptive effects upon long-term potentiation in the hippocampus (Abraham and Mason, 1988). WIN 55, 212-2 because of its similarity to a psychoactive ingredient in marijuana, Δ^9-tetrahydrocannabinol, which has reported effects on working memory in human marijuana smokers (Hollister, 1986; Mendihiratta et al., 1988; Miller and Cornett, 1978) and has been shown to disrupt long-term potentiation in the hippocampus (Terranova et al., 1995). The present study evaluated whether non-mnemonic side effects would still be evident under this adjusting delay procedure, or if they were evident, whether their influence was dissociable from specific effects of the drugs on remembering.

2. Methods

2.1. Subjects

The subjects for the scopolamine and MK-801 experiments were 20 male, Sprague–Dawley rats, approximately 120 days old at the beginning of behavioral training. The subjects for the WIN 55, 212-2 experiment were 10 other male, Sprague–Dawley rats, also approximately 120 days old at the beginning of behavioral training and pretrained to a level comparable to the other group. They were housed individually in plastic tub cages in a humidity and temperature controlled vivarium, and were maintained on a 7 a.m.-on/7 p.m.-off light–dark cycle. The experiments were conducted Monday–Friday, during which subjects were maintained on a 23.5 h water restriction schedule. The subjects were allowed free-access to water on weekends. All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Ani-

mals (US Public Health Service, 1985) and with the approval of the SUNY Stony Brook IACUC.

2.2. Apparatus

The subjects were tested in computer controlled operant test chambers, equipped with one rear-mounted and two front-mounted response levers (described in detail previously in Mao and Robinson, 1998). A cue lamp was in place over each, and water reinforcers were delivered into a front water aperture.

2.3. Behavioral testing

A delayed non-matching-to-position trial consisted of three phases. (1) Sample phase: One of the front cue lamps was illuminated for 10 s. Assignment of the sample stimulus side was random, except in the case where the choice response on the previous trial was incorrect. In this case, the sample on the following trial was the same as on the previous trial. This "correction rule" discouraged the formation of position biases. A press on the cued lever within that 10 s was following the offset of that sample cue and by the illumination of the rear cue lamp. (2) Retention phase: A retention interval consisting of either a 1.0 s or a 11.0 s delay was presented. Within-session, the 1.0 s delay was presented if the running proportion correct responses for the 1.0 and 11.0 s delay trials combined was 0.75 or less. The longer 11.0 s delay value was presented on a trial if the running proportion correct responses was 0.76 or greater. (3) Choice phase: The first press on the rear cue following the completion of the retention interval illuminated both front cue lamps. A press on the lever not pressed (a "non-match to position") during the sample phase produced a 0.1 ml water reward followed by a 10 s intertrial interval. A press on the same lever pressed during the sample phase produced only the intertrial interval.

Both groups of subjects were extensively pretrained for approximately three months through a series of pretraining programs, described in Mao and Robinson (1998), then to greater than 90% choice accuracy at a 1-s delay in the delayed non-matching-to-position procedure. They were then exposed to the adjusting delay procedure.

2.4. Measures

The primary measure of working memory was the proportion of responses at the 11.0 s retention interval. As detailed above, overall (1.0 and 11.0 s delay trials) accuracy was held near 75% by assigning short delay trials to bring accuracy temporarily above 75% when in fell below, and long-delay trials to counter this by bringing accuracy back down to 75% or below. The assumption was that the 11.0 s trial required remembering whereas the 1.0 s trials required little remembering. This derived measure reflecting this distribution is the proportion of the total delays that were at a long-delay, and could vary from one to zero. A proportion of trials at the long-delay of 1.0 would indicate perfect accuracy at both the 1.0 s and long-delay trials. This 11.0 s longer retention interval was determined to be optimal by Robinson et al. (in press) for revealing large changes in the proportion of trials at the long-delay measure in response to small changes in retention capacity.

Two other standard secondary measures were analyzed. The first was accuracy at the sample phase discrimination, which reflects whether the rats pressed the lever under the cue lamp when lit during the sample phase. This measure assessed reference memory, that is, a well-learned discrimination. Another secondary measure analyzed was number of trials completed per session, which is a relatively sensitive but non-specific measure that is altered by many different side effects that changes the rate that the subjects complete trials.

2.5. Preparation of drugs

WIN 55, 212-2 (RBI, Natick, MA, USA) was prepared by first mixing the 100 mg of powdered WIN 55, 212-2 with 1.0 ml of dimethysulfoxide. Then a small drop of emulphor (GAF, Rochester, NY) was added. Finally, normal saline was added slowly to produce an injection solution. A vehicle solution of dimethysulfoxide and emulphor equal to that of the 2.0 mg/kg dose of WIN 55, 212-2 was used. Scopolamine and MK-801 were dissolved in normal saline, and normal saline served as a vehicle.

2.6. Drug injections

The doses of drugs were chosen because they have been shown to disrupt performance in previous operant delayed non-matching-to-position working memory paradigms (e.g. Hampson and Deadwyler, 1999; Robinson, 1997). Drugs were administered on Tuesday and Thursday drug administration test days. Intervening baseline performance days assessed after effects. The drug doses were administered in a quasi-latin square order so that each subject received at least one injection of each dose of the drug and one injection of saline. WIN 55, 212-2 was administered 40 min prior to the start of the session. Scopolamine and MK-801 were administered 20 min prior to the start of the session.

3. Results

Fig. 1 shows the proportion of trials at the long-delay measure as a function of dose of drug for scopolamine, MK-801, and WIN 55, 212-2. For all drugs, the proportion of trials at the long-delay increased as a function of dose of drug (scopolamine: $F(4,76) = 4.6$, $P < 0.0002$; MK-801: $F(3,72) = 10.5$, $P < 0.0001$; WIN 55, 212-2: $F(4,36) = 3.1$, $P < 0.03$). Dunnett's test revealed that the 0.25 and

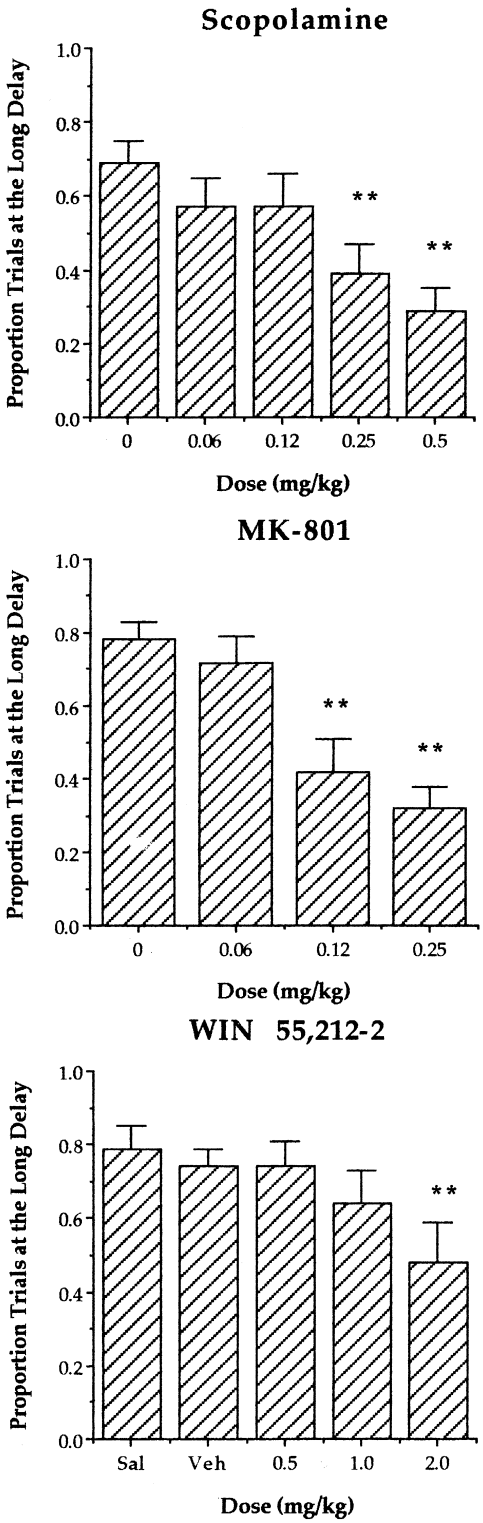

Fig. 1. The proportion responses at the 1.0 s retention interval measure as a function of dose of drug. $^{*}P < 0.05$ by Dunnett's test. $^{**}P < 0.01$ by Dunnett's test. For all the figures, the means ± S.E.M are shown.

0.5 mg/kg group was significantly different than the saline control group ($P < 0.01$) for scopolamine, the 0.12 and 0.25 mg/kg group was significantly different than the saline control group ($P < 0.01$) for MK-801, and the 2.0 mg/kg group was significantly different than the saline and vehicle control groups ($P < 0.01$) for WIN 55, 212-2.

Fig. 2 shows the proportion correct as a function of dose of drug at the 1.0 and 11.0 s retention interval for

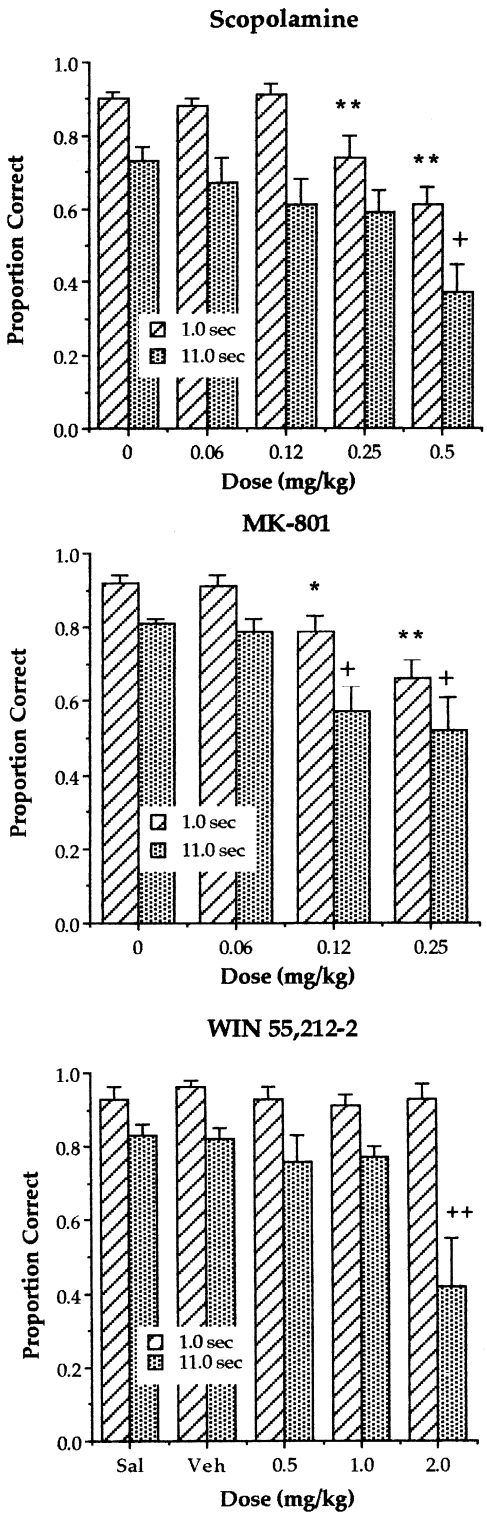

Fig. 2. The proportion correct as a function of dose of drug at the 1.0 and 11.0 s retention interval for scopolamine, MK-801, and WIN 55,212-2. *, $+P < 0.05$ by Dunnett's test. **, $++P < 0.01$ by Dunnett's test.

scopolamine, MK-801, and WIN 55, 212-2. For scopolamine, accuracy was significantly reduced at both the 1.0 s retention interval ($F(4,76) = 9.8$, $P < 0.0001$) and the 11.0 s retention interval ($F(4,75) = 4.2$, $P < 0.004$). Dunnett's test revealed that the 0.25 and 0.5 mg/kg group was

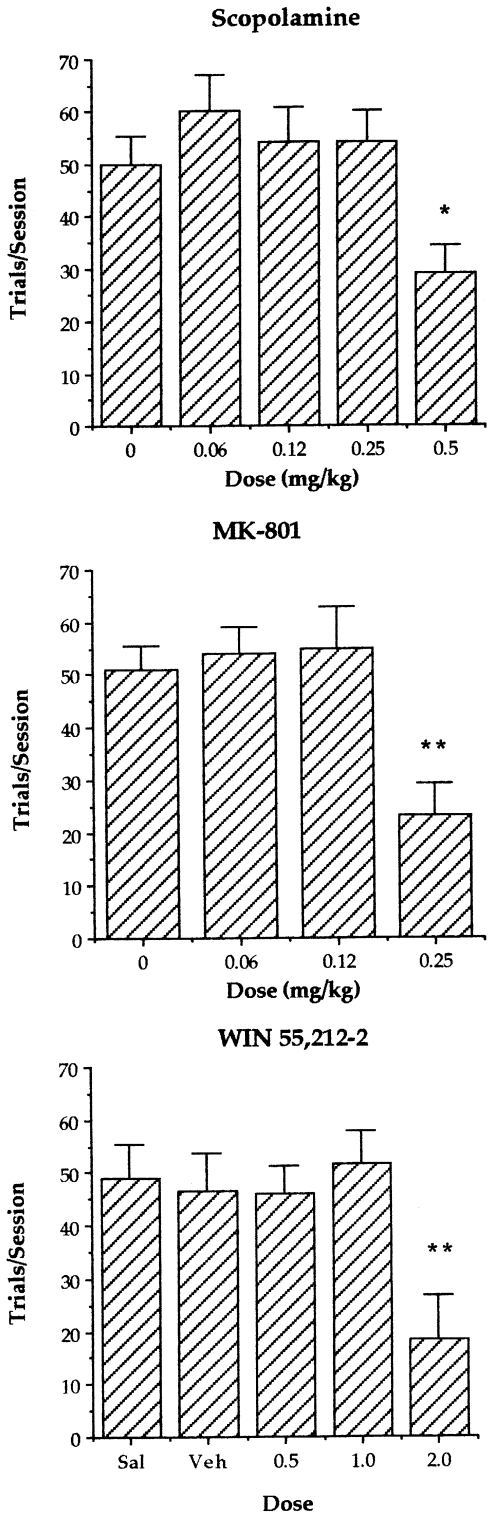

Fig. 3. The number of trials completed per 40 min session as a function of the dose of drug. $^{**}P < 0.01$ by Dunnett's test.

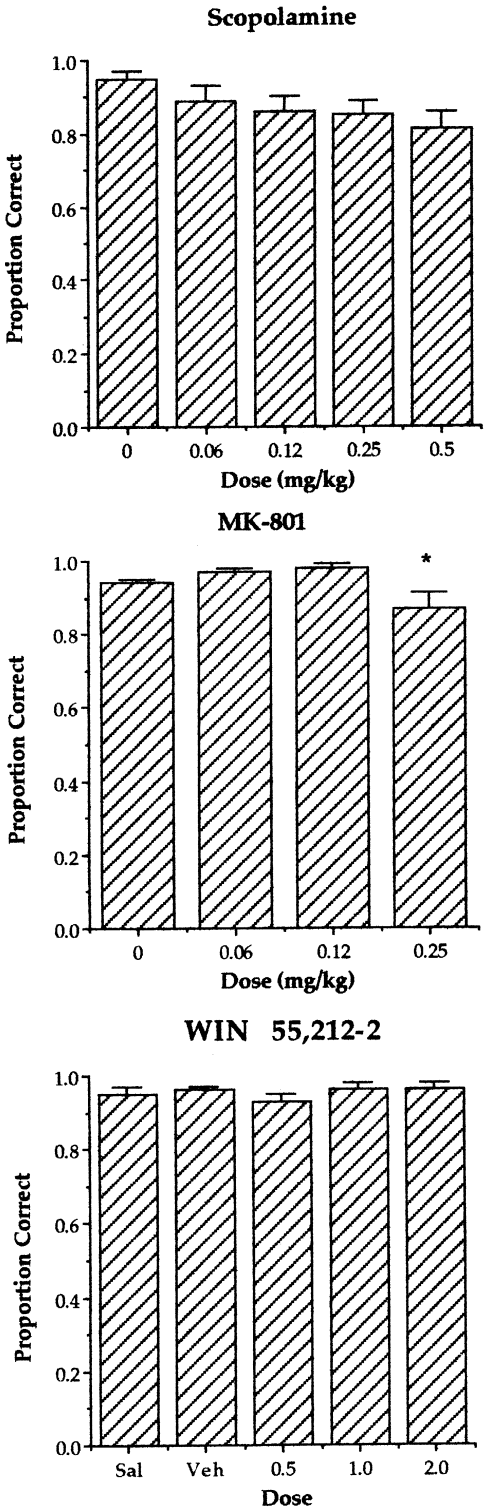

Fig. 4. The accuracy of sample phase light–dark discrimination responses as a function of the dose of drug. $^{*}P < 0.05$ by Dunnett's test.

significantly different than the saline control group ($P < 0.01$) at the 1.0 s retention interval, and the 0.5 mg/kg was significantly different than the saline control group ($P < 0.05$) at the 11.0 s retention interval. MK-801 also significantly reduced accuracy at both the 1.0 s retention

interval ($F(3,72) = 10.2$, $P < 0.0001$) and the 11.0 s retention interval ($F(4,75) = 6.7$, $P < 0.0005$). Dunnett's test revealed that the 0.12 mg/kg ($P < 0.05$) and 0.25 mg/kg ($P < 0.01$) group was significantly different than the saline control group at the 1.0 s retention interval as well as at the 11.0 s retention interval ($P < 0.01$ for both doses). WIN 55, 212-2 produced no significant effect on choice accuracy at the 1.0 s retention interval ($F(4,44) = 0.34$, n.s.), but did impair performance at the 11.0 s retention interval $F(4,44) = 4.74$, $P < 0.003$). Dunnett's test ($P < 0.01$) revealed that the 2.0 mg/kg group was significantly different than the saline and vehicle control groups.

Fig. 3 shows the number of trials completed per 40 min session as a function of the dose of drug. All drugs produced a significant reduction in trials per session (scopolamine: $F(4,76) = 3.1$, $P < 0.02$; MK-801: $F(3,74) = 6.4$, $P < 0.0007$; WIN 55, 212-2: $F(4,45) = 4.11$, $P < 0.007$). Dunnett's test revealed that for scopolamine the 0.5 mg/kg group ($P < 0.05$) was significantly different than the saline control group, for MK-801 the 0.25 mg/kg group ($P < 0.01$) was significantly different than the saline control group, and for WIN 55, 212-2 the 2.0 mg/kg group was significantly different than the saline and vehicle control groups.

Fig. 4 shows the accuracy of sample phase light–dark discrimination responses as a function of the dose of drug. Scopolamine and WIN 55, 212-2 failed to produce a significant reduction in discrimination accuracy (scopolamine: $F(4,76) = 1.9$, $P < 0.11$; WIN 55, 212-2: $F(4,45) = 1.25$, n.s.). In contrast, MK-801 produced a significant deficit ($F(3,74) = 5.0$, $P < 0.004$). Dunnett's test indicated that the 0.25 mg/kg group ($P < 0.05$) was significantly different than the saline control group.

4. Discussion

The present study was conducted to compare the effects of several amnestic drugs in this adjusting delayed non-matching-to-position procedure. Scopolamine and MK-801 produced generally similar patterns of performance disruption. Both reduced the proportion of trials at the long-delay remembering measure significantly at the two highest doses administered for each. This reduction was accounted for by a decrease in choice accuracy at the longer 11.0 s retention interval, but also at the shorter 1.0 s retention interval. These decreases in choice accuracy were accompanied by a significant reduction in the number of trials completed per session only at the highest dose of each. In contrast, WIN 55, 212-2 produced a different pattern of deficits, including a significant reduction of choice accuracy at the 11.0 s retention interval, and a significant reduction of the number of trials completed per session.

Our previous behavioral experiments with this adjusting delayed non-matching-to-position task (Robinson et al., in press) simulated a selective reduction in retention capacity by systematic increases in the length of the second retention interval. When this was performed, the proportion of trials at the long-delay measure changed significantly because of a reduction in accuracy at the longer retention interval, but that accuracy at the 1.0 s retention interval, discrimination accuracy, and number of trials completed per session did not change. In a second experiment, where subjects were given access to water immediately before the start of the session to directly reduce the motivation to respond, the number of trials per session decreased, but none of the other measures were significantly altered. These experiments argued for the selectivity of the proportion of trials at the long-delay measure to changes in retention capacity, and the sensitivity of the trials per session measure to non-mnemonic disruption. Therefore, it is of interest that for at the 0.25 mg/kg of scopolamine and 0.12 mg kg dose of MK-801 (1) the proportion of trials at the long-delay and choice accuracy changes were not accompanied by a change in rate of trial completion, and (2) the changes in the proportion of trials at the long-delay at these doses were largely accounted for by a change in accuracy at the 1.0 s retention interval. In other delayed non-matching-to-position tasks, a reduction of trial completion rate uniformly accompanied choice accuracy deficits (e.g. Robinson and Crawley, 1993a; Robinson, 1997). The presently observed pattern suggests that the previously reported delay-independent deficits produced by these drugs did not result from changes in motivation. Instead, they point to substantial alterations of procedural or reference memory, or other processes leading to a failure to perform the task procedures effectively.

These effects are generally consistent with those of a another report (Stanhope et al., 1995), who also sought to isolate motor/motivational effects from mnemonic effects in a delayed match-to-sample task in rats. These authors reported that MK-801 and another NMDA receptor antagonist, *cis*-4-(Phosphonomethy)piperidine-2-carboxylic acid (CGS 19755), produced similar delay-independent impairments of choice accuracy, a reduction of discrimination accuracy, and a decreased rate of trial completion to those reported here. However, low doses of scopolamine (0.05 and 0.1 mg/kg i.p.) produced delay-dependent deficits in their task, without disrupting the rate of trial completion. It is possible that this difference in the reported effects of scopolamine resulted from the match vs. non-match contingency difference, or another procedural dissimilarity between the two tasks. This could be addressed in a future study in which the adjusting delay procedure is employed in a match-to-sample version of the tasks.

In contrast to scopolamine and MK-801, WIN 55, 212-2 altered the proportion of trials at the long-delay only by influencing accuracy at the 11.0 s delay trials. Our results are consistent with the delay-dependent deficits of a delayed non-matching-to-position by Δ^9-tetrahydrocannabinol reported by Hampson et al. (1993), and by WIN 55, 212-2 (Hampson and Deadwyler, 1999). However, the 2.0 dose

of WIN 55, 212-2 also reduced the trial completion rate, pointing to some additional non-mnemonic alteration(s) that could account for the delay-independent effects reported in another study of Δ^9-tetrahydrocannabinol on a delayed non-matching-to-position task (Mallet and Beninger, 1996). However, given that in our previous study (Robinson et al., in press) showed that a presumed reduction in reward efficacy did not affects the proportion of trials at the long-delay measure, one could also argue that a motivation change can be ruled out as an explanation for the delay-dependent deficits reported here.

In conclusion, the present study demonstrates that this adjusting delayed non-matching-to-position task is able to differentiate deficit patterns of amnestic drugs, and can isolate the effects of motivational side effects of drugs from working memory measures. Future studies can perhaps examine what other behavioral processes are influencing non-mnemonic measures in this delayed non-matching-to-position task, and attempt to isolate specific mnemonic and non-mnemonic effects of these drugs to particular brain systems.

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