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Effects of d-Amphetamine and Prefrontal Cortical Cooling on Delayed Matching-to-Sample Behavior[1]

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BAUER, R. H. AND J. M. FUSTER. *Effects of d-amphetamine and prefrontal cooling on delayed matching-to-sample behavior.* PHARMAC. BIOCHEM. BEHAV. 8(3) 243–249, 1978. – The interaction was examined between d-amphetamine (d–A) and dysfunction induced by localized cooling of the dorsolateral prefrontal cortex. Saline or d–A (0.1, 0.2, or 0.4 mg/kg) was administered to monkeys in two conditions; normal cortical temperature (no cooling – NC) and frontal cooling (FC). Errors, reaction time (RT), eye movements, and motor activity were recorded during performance of a delayed matching-to-sample task with intratrial delays of 1–32 sec. Although d–A and FC had little effect on percentage of correct responses at the shortest delay, each of the two treatments significantly decreased correct responses at longer delays; drug and FC combined produced a significantly greater decrease than either treatment alone. Motor activity and eye movements were increased by either d–A or FC; the two treatments combined had an even greater effect. In the NC condition, two-choice RT was decreased by the drug; it was increased by drug-FC combinations. These findings indicate that d–A and FC potentiate each other in their behavioral effects.

Frontal cortex Short-term memory Monkeys d–Amphetamine Motor activity

A PREVALENT method for analysing the behavioral effects of ablating the prefrontal cortex is the administration of drugs [10]. In monkeys, d-amphetamine (d–A) reduces the hyperactivity resulting from prefrontal ablations [4,7] but does not reduce the delayed-response deficit produced by these lesions [23]. However, comparing the behavioral effects of drugs in ablated and non-ablated animals bears more directly on the question of postablation changes in remaining brain structures than on frontal lobe functions per se. For example, in the rat d–A potentiates hyperactivity produced by frontal ablations shortly after ablation, and this effect increases or decreases with time [10,15]. On the other hand, monkeys that have fully recovered from the delayed matching-to-sample deficit induced by prefrontal ablation are more resistant to the effects of d–A in this task than nonablated monkeys [12]. Since the behavioral effects of d–A are thought to be due to increased release or decreased reuptake of norepinephrine and dopamine at synapses [2, 6, 8, 14], both behavioral recovery and differential drug reactions following frontal ablations may depend on alteration in catecholamine processes in remaining structures [10,12].

A number of psychopharmacological studies suggest that, in the intact animal, brain catecholamines are important for adequate performance of tasks that require short-term memory. In normal cats, L–DOPA increases endogenous levels of brain dopamine and reduces errors in a delayed-response task [18]. α–Methyltyrosine, an inhibitor of catecholamine synthesis, reduces brain norepinephrine and dopamine, while increasing delayed-response errors [17]. Neither L–DOPA nor α-methyltyrosine alter performance in a simultaneous visual discrimination task [17,18]. Endogenous levels of brain dopamine are also positively correlated with delayed-response performance in cats [18]. On the basis of this evidence, it has been suggested that catecholamines are important for short-term memory [17,18].

It has recently been shown that cooling the dorsolateral prefrontal cortex (frontal cooling – FC) produces a reversible deficit in delayed matching-to-sample performance. In conjunction with ablation studies, this finding suggests that the prefrontal cortex is involved in short-term memory. Motor activity is also increased by FC. The monkeys are fully recovered when tested 24 hr later without cooling. However, unlike the results of ablations, these cooling effects do not decrease on repeated application over an extended period (over 6 months) [3,9]. Thus, cooling results in a prefrontal dysfunction but appears to circumvent the compensatory changes which occur following permanent damage to neural tissue.

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The major purpose of the present study was to compare the effects of FC and d–A, alone and in combination, on delayed matching-to-sample performance. In addition to correct responses, motor activity, eye movements, and response latencies were recorded. Since previous results indicate that FC and d–A increase delayed matching-to-sample errors and motor activity, one might expect that the two treatments combined would have a greater effect than either treatment alone. However, it has been suggested that the prefrontal cortex is predominantly adrenergic [10,12]. If FC induces a partial dysfunction of adrenergic synapses, d–A might, because of its adrenergic effects, reverse some of the behavioral consequences of FC.

METHOD

Animals

Two adult, male rhesus monkeys, weighing approximately 6 kg, served as subjects. Throughout the experiment they were housed in individual cages. They were food- and water-deprived for at least 20 hr prior to each testing session.

Apparatus

The apparatus has been described in greater detail elsewhere [3]. Briefly, the monkeys sat in a primate chair facing a panel containing three translucid stimulus-response buttons (2.5 cm in diameter). The three buttons formed an isosceles triangle (one on top and two below). Each button could be illuminated with a red or green light by rear projectors. Light pressure on each button activated a microswitch. Reaction time (RT) was recorded to the nearest 0.01 sec by means of an electronic timer.

The floor of the primate chair rested on springs at each corner, and a permanent magnet was attached to the chair. A relay coil was mounted 0.5 mm from the magnet. Thus the monkey's movements resulted in an electromagnetic voltage change in the coil. The signal was amplified and fed into a level detector and a digital counter. This system was sensitive to both velocity and magnitude of movement.

Delayed Matching-to-Sample Task

Training in the matching-to-sample task has been described in detail previously [3,16]. In this task a trial was initiated by transillumination of the top button with one of two sample colors (red or green). By pressing the sample button the animal terminated the color and initiated a delay. At the end of the delay the colors appeared simultaneously on the two lower buttons. By pressing the lower button with the previously presented sample-color the monkey terminated the colors on the lower buttons and received 0.8 ml of grape juice. An incorrect response or failure to respond within 4.0 sec terminated the trial without reinforcement. From trial to trial the colors on each button changed in random order.

Surgery

Upon completion of training, cooling probes were placed bilaterally on the surface of the dura directly over sulcus principalis. Each probe consisted of a gold-plated copper cylinder (18 mm in diameter and 17 mm high). Each probe was implanted with one end in contact with the dura and the other end protruding through the skull. A thermistor was placed subdurally directly under each cooling probe. Stainless steel screws (2.2 mm in diameter) were placed in the orbital ridge of the left eye for recording eye movements. Wires from the thermistors and eye-movement electrodes were soldered to a miniature plug. The probes, thermistors, and plug were permanently attached to the skull by means of screws and dental acrylic.

Upon completion of the experiment, the area covered by the probes was determined. The placements were almost identical to those reported previously [3]. Briefly, the probes covered the anterior two-thirds of the sulcus principalis and its banks. Thus, major portions of Brodmann's cortical areas 9 and 10 were cooled.

Cortical Cooling

Prior to each testing session, thermoelectric coolers were attached to the cooling probes [3,9]. The coolers consist of alternating plates of two dissimilar metals and operate on the basis of the Peltier effect. Direct current passing through the plates creates a cold sink that extracts heat from the underlying cortex. The cortex can be maintained at a constant temperature by thermostatic control from the thermistors.

Eye Movements

Eye-movement potentials were amplified by a Tektronix Model 122 preamplifier (bandwidth 8–250 Hz) and a DC power amplifier. The resulting signal was fed into a level detector and then to a digital counter. This system was sensitive to both velocity and magnitude of the movements.

Testing Procedure

The monkeys received daily sessions of 120 trials each. Delays of 1, 6, 16 and 32 sec were used, and each delay was given in six blocks of five trials each. These blocks were presented in random order, with the exception that the two longest delays never occurred in sequence. Physiological saline, 0.1, 0.2, or 0.4 mg/kg d–A in a 0.2% solution was injected intramuscularly approximately 10 min before testing. The frontal cortex was cooled to 20°C or the coolers were attached but inoperative (normal brain temperature – NC). Each animal was given three sessions in each condition. Thus, the experimental design was a 2 (Animal) × 2 (Cooling condition) × 4 (Dose) × 4 (Delay) complete factorial. Across sessions each condition followed every other condition approximately an equal number of times. To insure that there were no carry-over effects of the drug, at least one non-drug session was given after drug treatment; the data thereof are not reported.

RESULTS

Percentage of Correct Responses

Mean percentage of correct responses in NC and FC as a function of drug dose and delay is presented in Fig. 1. This figure indicates that FC produces a delay-dependent decrease in the number of correct responses. Similarly, d–A appears to produce a dose- and delay-dependent decrease in percentage correct. In general, the d–A induced deficit is more pronounced when the drug is associated with FC.

Since there was heterogeneity of variance across delays, the percentage of correct responses for each daily block of 30 trials – per animal, condition, and delay – was

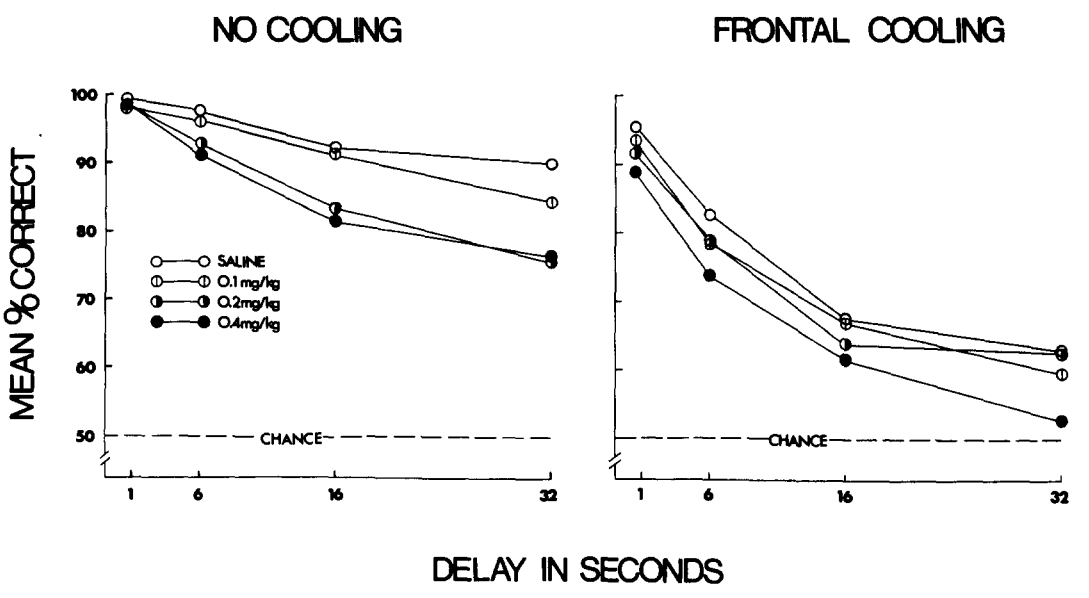

FIG. 1. Percentage correct at normal brain temperature and during bilateral prefrontal cooling as a function of dose and delay (SEMs ranged from 0 to 5.04).

subjected to an arcsin transformation. The transformed data were analysed by a 2 (Animal) x 2 (Cooling condition) x 4 (Dose) x 4 (Delay) mixed factorial analysis of variance, with three sessions within each animal. The last three factors were treated as repeated measures variables. There were no systematic changes within or across sessions; consequently these sequence effects were disregarded in this and subsequent analyses. This analysis showed that the main effects for Cooling, $F(1,4) = 979.52$, $p<0.001$, drug Dose, $F(3,12) = 8.11$, $p<0.003$, and Delay, $F(3,12) = 219.87$, $p<0.001$, were significant (for this and subsequent analyses $p<0.05$ was considered the lowest level of significance). A significant Cooling x Delay interaction, $F(3,12) = 6.79$, $p<0.006$, indicates that the delay-dependent decrease in percentage of correct responses is accentuated by FC. The Cooling x Dose x Delay interaction was significant, $F(9,36) = 2.76$, $p<0.02$, and suggests that the decrease across delays was greater with combined cooling and drug treatment than either treatment alone.

The left panel of Fig. 1 suggests that without cooling d–A produced a greater effect at longer delays than at shorter delays. Therefore, a 2 (Animal) x 4 (Dose) x 4 (Delay) mixed factorial analysis of variance (with three sessions within each animal) was conducted on the transformed NC data. This analysis showed that the drug significantly reduced the percentage of correct responses, $F(3,12) = 10.02$, $p<0.001$. More importantly, the interaction between drug and delay was significant, $F(9,36) = 4.97$, $p<0.001$, indicating that d–A had less effect at shorter delays than at longer delays. Individual comparisons of percentage correct – averaged across delays – by Tukey's (a) test showed that, as compared to saline controls, errors were increased significantly by 0.2 and 0.4 mg/kg d–A (all individual comparisons reported were based on the mean of each treatment group averaged across delays).

Similar analysis of the FC data indicated that neither the main effect for Dose, $F(3,12) = 3.06$, $p<0.07$, nor the Dose x Delay interaction, $F(9,36) = 0.58$, were significant. Tukey's test showed that there were significantly more errors with 0.4 mg/kg than 0.1 mg/kg and saline.

Reaction Time

Figure 2 presents mean RT on the top button (sample RT) and mean RT on the lower buttons (choice RT) during NC and FC as a function of drug dose and delay. For purposes of reducing and normalizing RT data, mean sample RT and mean choice RT for each monkey, condition, and delay were computed in blocks of five trials. These means were subjected to reciprocal transformation and the reciprocals for sample RT and choice RT analysed separated by 2 (Animal) x 2 (Cooling condition) x 4 (Dose) x 4 (Delay) mixed factorial analyses of variance.

Sample RT increased as a function of the delay, $F(3,48) = 21.83$, $p<0.001$. Other main effects and interaction terms were not significant.

As shown in the lower panels of Fig. 2, choice RT was longer during FC than NC and increased as a function of the delay. This was supported by significant main effects for Cooling, $F(1,16) = 120.88$, $p<0.001$ and Delay, $F(3,48) = 284.88$, $p<0.001$. The main effect for Dose was significant, $F(3,48) = 7.29$, $p<0.001$. Significant Dose x Delay, $F(9,144) = 3.82$, $p<0.001$ and Cooling x Delay, $F(3,48) = 12.31$, $p<0.001$, interactions suggest that d–A and FC had little effect on choice RT at short delays but, in general, these treatments increased choice RT at longer delays.

Since it appeared that the effect of d–A on choice RT was different in NC than FC, separate analyses of variance were conducted on the NC and FC data. In NC the drug significantly reduced choice RT, $F(3,48) = 4.37$, $p<0.008$. Tukey's test indicated that, as compared to saline control, choice RT was faster with 0.4 mg/kg. However, during FC the drug significantly increased choice RT, $F(3,48) = 3.90$, $p<0.02$. Furthermore, a significant Dose x Delay interaction, $F(9,144) = 2.32$, $p<0.02$, and Tukey's test indicated that 0.1 and 0.2 mg/kg increased this RT to a greater degree as a function of the delay than saline or 0.4 mg/kg.

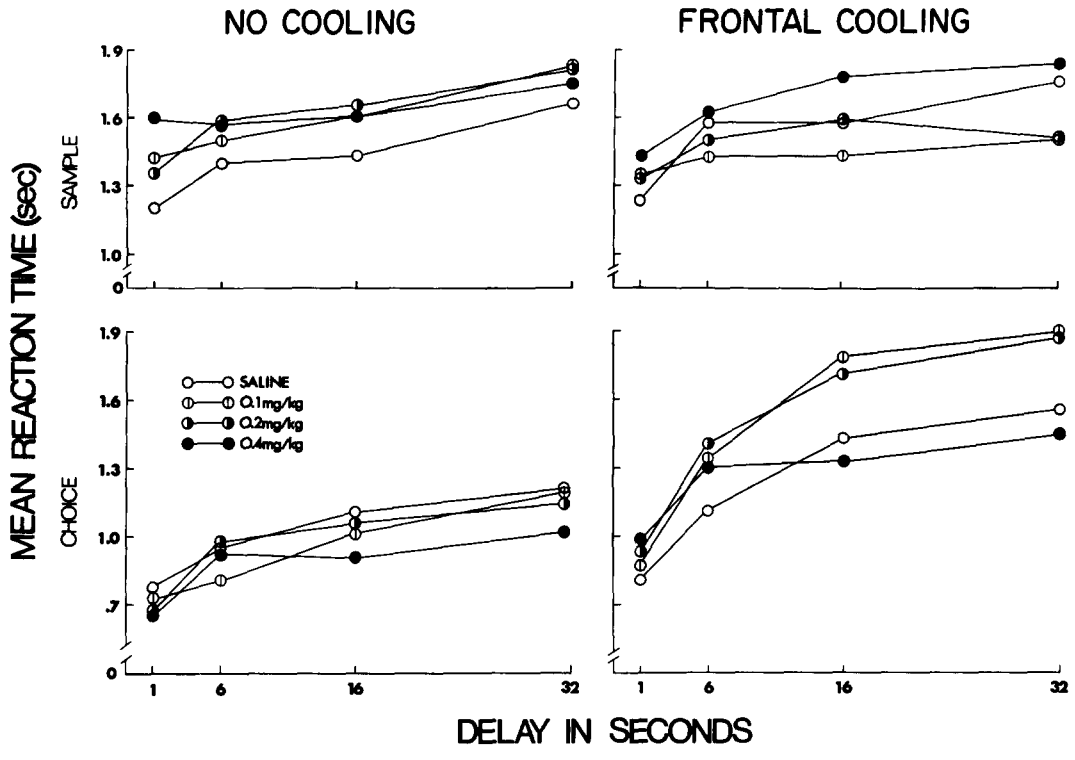

FIG. 2. Sample reaction time (upper panels) and choice reaction time (lower panels) at normal brain temperature and during frontal cooling as a function of dose and delay (sample SEMs ranged from 0.08 to 0.23; choice SEMs ranged from 0.03 to 0.19).

Eye Movement

Eye movements during the intertrial interval and the intertrial delay were first converted to counts per second. For the purpose of reducing these data, the means for each monkey, condition, and delay were computed in blocks of five trials. The means for the intertrial interval and for the delay were analysed separately by 2 (Cooling condition) x 4 (Dose) analyses of variance.

Figure 3 presents mean eye-movement counts per second during the intertrial interval (upper panels) and the delay (lower panels) as a function of drug dose. Analysis of the intertrial interval data showed that eye movements were increased by FC, $F(1,572) = 744.96$, $p<0.001$ and d–A, $F(3,572) = 121.76$, $p<0.001$. Combined FC and d–A treatment appeared to have a greater effect on eye movements than either treatment alone. This was supported by a significant Dose x Cooling interaction, $F(3,572) = 12.25$, $p<0.001$. Tukey's test indicated that in the saline condition eye movements were significantly higher during FC than NC. In NC eye movements were higher with each d–A than saline and were higher with 0.2 and 0.4 mg/kg than 0.1 mg/kg. During FC there were significantly more movements with each drug dose than saline and more with 0.4 mg/kg than 0.1 or 0.2 mg/kg.

In the intratrial delay both cooling, $F(1,572) = 172.23$; $p<0.001$ and the drug, $F(1,572) = 7.83$, $p<0.001$, increased eye movements. However, a significant Dose x Cooling interaction, $F(3,572) = 16.51$, $p<0.001$, indicates that both treatments combined produced a greater effect than either treatment alone. Comparisons between individual treatment means showed that during NC eye movements were significantly enhanced with 0.2 and 0.4 mg/kg than saline or 0.1 mg/kg. During FC the only significant difference was between saline and 0.4 mg/kg.

Motor Activity

The upper panels of Fig. 4 present mean motor activity (counts per second) during NC and FC as a function of dose. The lower panels of this figure show mean activity per second in the intratrial delay. Mean activity in blocks of five trials for each monkey, condition, and delay was computed and the means for activity in the intertrial interval and delay analysed separately by 2 x 4 analyses of variance.

Motor activity in the intertrial interval was increased by drug treatment, $F(1,572) = 13.68$, $p<0.001$ and cooling, $F(1,572) = 130.84$, $p<0.001$. A significant Dose x Cooling interaction, $F(1,572) = 9.57$, $p<0.001$ and inspection of the upper panels of Fig. 4, indicate that d–A was more effective in altering activity during NC and FC. Tukey's test showed that during NC all doses were significantly different from each other. During FC activity was higher following 0.4 mg/kg than all other doses.

Analysis of motor activity during the delay showed that activity was higher during FC than NC, $F(1,572) = 41.60$, $p<0.001$. A significant Dose x Cooling interaction, $F(1,572) = 7.83$, $p<0.001$, indicates that activity during NC was increased by d–A but with FC the drug reduced activity slightly.

Separate analysis of motor activity in the delay with NC showed that d–A resulted in a dose related increase,

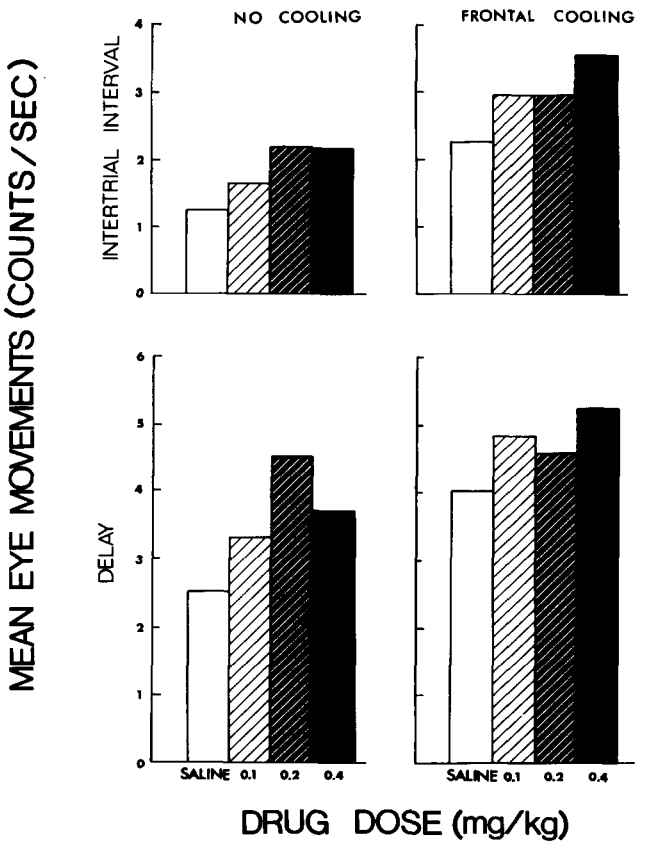

FIG. 3. Eye movements in the intertrial interval (upper panels) and the intratrial delay (lower panels) as a function of dose (intratrial interval SEMs ranged from 0.02 to 0.07; intratrial delay SEMs ranged from 0.11 to 0.36).

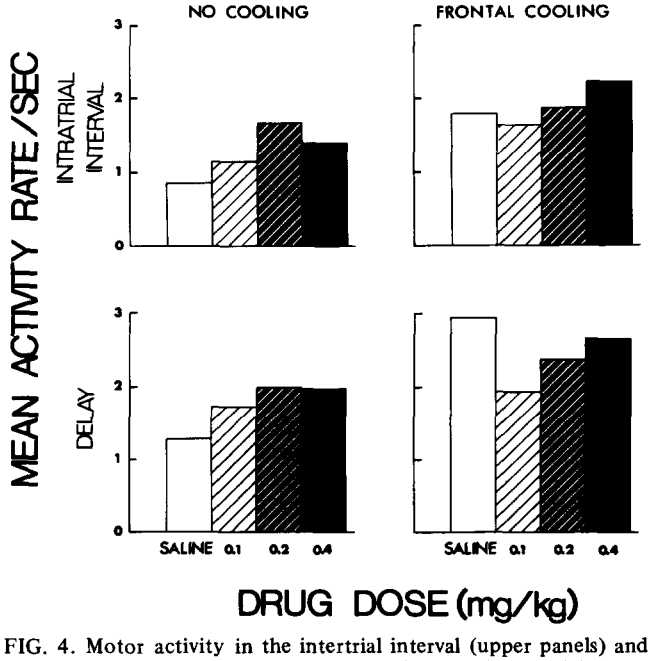

FIG. 4. Motor activity in the intertrial interval (upper panels) and the intratrial delay (lower panels) at each dose (intratrial interval SEMs ranged from 0.02 to 0.14; intratrial delay SEMs ranged from 0.09 to 0.43).

$F(3,572) = 3.10$, $p<0.03$. Tukey's test revealed that during NC activity was significantly greater with 0.2 and 0.4 mg/kg than saline. In general, low doses reduced activity during FC, $F(3,572) = 3.40$, $p<0.008$. During FC the only significant individual comparison was the lower activity with 0.1 mg/kg as comprared to saline.

DISCUSSION

Percentage of correct responses, sample RT, eye movements, and general motor activity were affected in a similar manner by d–A and FC. In general, the combination of the two treatments induced changes in the same direction but of a greater magnitude than either treatment alone. Similarity and mutual potentiation from the two treatments suggest that both affect the same neural processes. There is evidence that both cooling and d–A depolarize and inactivate cortical neurons [1,5]. Thus, to the extent that the primary action of d–A is on catecholamine synapses [2, 6, 8, 14] and that adrenergic synapses are numerous in prefrontal cortex [10, 12, 20], the effects of both cooling and the drug could be principally, if not exclusively, the result of excessive depolarization and inactivation of neurons in the prefrontal cortex. But, of course, similarity or potentiation of behavioral effects does not necessarily imply that both treatments act by the same mechanisms or on the same structures. At least one alternative interpretation seems plausible, based on evidence that the prefrontal cortex has reciprocal connections with other structures [15,20] which are inhibited or excited by d–A [5,14]. Inordinate activation or inhibition of these structures, whether by release from prefrontal influences or by the action of d–A, would result in similar and synergistic effects.

Studies comparing the behavioral effects of d–A in frontally ablated rats at various times after ablation show that the effectiveness of the drug changes with time after ablation [10,15]. Furthermore, d–A has little effect on delayed-matching performance in monkeys that have fully recovered from the deficit produced by frontal ablation [12]. Thus, the effects of d–A on frontally ablated animals may be similar to those obtained under FC but only for a period immediately following ablation. Since FC is applied intermittently and for relatively brief periods, FC probably does not result in compensatory changes, as may be the case with frontal ablations, where remaining structures may take over functions previously performed by the ablated tissue [3, 10, 12]. Consequently, findings from the present and previous studies are consistent with the notion that differences in the drug's effect as a function of time after ablation are due to a pharmacological action on structures other than the frontal cortex and consistent with the supposition that compensatory changes do not occur with FC.

Altering brain catecholamines in cats produces systematic changes in delayed-response performance and on the basis of this evidence it has been suggested that catecholamines are important for short-term memory [17,18]. However, before one can infer that any treatment alters this type of memory, it must at least be shown that the treatment effect increases in proportion to the length of the intratrial delay. Therefore, testing at more than one delay is necessary to establish this relationship. In the cat studies mentioned only one delay (5 sec) was used between the cue (baiting a food cup) and the response; thus, with regard to

memory the data are inconclusive. Since in the present study the d–A induced deficit was less evident at short delays than at long delays, it would appear that the drug enhances the loss of information from short-term memory. Inasmuch as the primary action of d–A is on catecholaminergic synapses [2, 6, 8, 14], the present results provide a more substantial basis for suggesting that catecholamines are implicated in short-term memory.

Our data are apparently inconsistent with the previous report that in normal monkeys d–A increases delayed matching-to-sample errors to approximately the same degree at all delays [11]. However, a slight delay-dependent effect in the same direction as that found here can be observed in Fig. 1 of that report. In addition, there are methodological differences (e.g., the statistical analyses, the intertrial interval, the testing environment, and the baseline performance level) that could account for the discrepancy between the two studies.

It has been reported that both d–A and frontal ablations increase reactivity to novel stimuli [8,13]. Furthermore, monkeys with prefrontal dysfunction are especially prone to commit delayed-matching and delayed-response errors when novel stimuli are interjected in the intratrial delay [9, 19, 21]. Conversely, reducing the number of irrelevant stimuli in the testing environment improves delayed-response performance [21,22]. Since the possibility of distraction by irrelevant stimuli is likely to increase as the delay becomes longer, the delay-dependent deficit produced by d–A and FC might be due to increased distraction or retroactive interference from irrelevant stimuli. Greater distractibility may also explain the greater incidence of eye movements induced by the treatments, i.e., enhanced eye movements may simply reflect increased orientation to irrelevant stimuli in the testing environment.

Retroactive interference from motor responses can also increase delayed-matching errors [16], but it seems unlikely that this type of interference accounts for the treatment-induced deficits. Although motor activity was increased by the treatments, there was no consistent relationship between motor activity and errors. Moreover, d–A is reported to reduce the hyperactivity resulting from prefrontal ablation without altering the number of delayed-response errors [23]. Findings of the present study are in accord with this. It should also be pointed out that increased motor activity may be due to frustration arising from frequent errors. Thus, on the basis of our data, it cannot be determined if greater activity results in increased errors or vice versa.

The finding that neither d–A nor FC altered sample RT suggests that differences in exposure time to the relevant cues are not responsible for differences in percentage of correct responses. In addition, if either treatment impaired some aspect of sensory processing or attention to the sample, one would expect errors to increase with short as well as long intratrial delays.

Although 0.1 mg/kg d–A has little effect on food and water intake in monkeys, higher doses decrease intake [24]. However, increased deprivation does not reduce the number of errors resulting from d–A [11]. In the present study, response latencies were not increased by d–A, as would be expected if motivation were reduced and, in fact, choice RT was reduced. Thus, although the drug may decrease motivation, it is not clear that such an effect accounts for the increase in errors. Since FC does not appear to alter motivation for food or water [3], the greater effect of combined FC and d–A treatment is probably not due to lesser motivation.

In summary, results of the present study provide further support for the conclusion that catecholamine systems and the dorsolateral prefrontal cortex are involved in short-term memory. Increased distractibility or retroactive interference may account, at least in part, for the short-term memory deficit induced by FC and d–A. Although the two treatments combined generally produce greater behavioral effects than either treatment alone, the basis for this mutual potentiation requires further investigation.

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