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# The Effects and Interactions of Scopolamine, Physostigmine and Methamphetamine on Human Memory

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MEWALDT, S. P. AND M. M. GHONEIM. *The effects and interactions of scopolamine, physostigmine and methamphetamine on human memory.* PHARMAC. BIOCHEM. BEHAV. 10(2) 205–210, 1979.—Seventy college age subjects learned and recalled a series of word lists prior to being injected with methamphetamine (0.2 mg/kg or 0.3 mg/kg), scopolamine (8 μg/kg), or a placebo. Following the injection subjects were tested for their free recall and recognition of the words and they completed a short-term digit recall task. Subjects who had previously received scopolamine were next injected with either methamphetamine (0.2 mg/kg or 0.3 mg/kg), physostigmine (32 μg/kg), or placebo, while other subjects received a placebo injection. The above memory procedure was then repeated with a second series of word lists. In addition, subjective feelings were measured with a questionnaire. Scopolamine and methamphetamine did not affect recall of information learned prior to injection. Scopolamine did, however, impair performance in both the digit recall task and in the second series of memory tests. Physostigmine and methamphetamine alleviated most of the memory deficits and sedation produced by scopolamine. Methamphetamine alone produced subjective arousal and a small improvement in recall of words learned after injection and a large increase in incorrect responding.

Methamphetamine Scopolamine Physostigmine Memory Subjective moods Arousal

PREVIOUS studies in our laboratory demonstrated that scopolamine impairs memory functions through interference with storage processes while the retrieval mechanisms are left virtually intact [10]. Physostigmine counteracted the memory defect produced by scopolamine [11] which led us to conclude that the latter drug probably affects human memory through cholinergic blockade. Physostigmine antagonized also the sedative effect of scopolamine; therefore, it is possible that at least part of the improvement in memory when the two drugs are used may be due to a general arousal effect leading to better acquisition of information.

Methamphetamine is a strong central nervous system stimulant. It is closely related chemically and pharmacologically to amphetamine but its central effects are more pronounced than those of amphetamine and are accompanied by less prominent peripheral actions [14]. It was hoped that its interaction with scopolamine on memory functions would elucidate the effects of adrenergic stimulation and arousal on antagonizing the actions of anticholinergic drugs. Another aim of the study was to investigate the memory effects of methamphetamine. Search of the literature revealed that in spite of the wide therapeutic use and abuse of amphetamines and related central nervous system stimulant drugs, there is paucity and conflict of data on the effect of these drugs on human learning and memory and their mechanisms of action.

## METHOD

### *Subjects*

The subjects were 35 male and 35 female university students who served as paid volunteers. Their mean age was 22.6 and ranged from 18 to 32. An informed consent for participation in the study was obtained from each subject, although to avoid bias the subjects did not know the specific treatment they would receive. Five male and 5 female subjects served in each of the drug treatments listed below.

### *Treatments*

Each drug was administered intramuscularly in the dose listed: scopolamine (8 μg/kg), physostigmine (32 μg/kg), methamphetamine (0.2 and 0.3 mg/kg) and saline (placebo).

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*Design*

There were seven drug combinations as displayed in Table 1. The subjects were tested in groups of five and were assigned to conditions in an unbiased fashion. All subjects tested during a particular experimental session were given the same treatment. The order of the treatments was determined by block randomization and the tests were administered under a double blind procedure. In order to familiarize the subjects with each experimental task a practice session preceded the actual experiment. Each of the following tests was then administered in the order displayed in Table 2.

*Subjective Rating Questionnaire*

Subjects marked their feelings on 16 scales, each consisting of an adjective pair connected by a 100 mm line. The adjectives represented the extremes of the feelings being rated. The pairs fell into one of four categories of feelings: mental sedation (e.g., alert-drowsy), physical sedation (e.g., strong-weak), tranquilization (e.g., calm-excited) and other feelings (e.g., interested-bored). Subjects marked their feelings by drawing a perpendicular line across the horizontal scale. The position of the vertical line was measured in millimeters and served as the dependent variable [16].

*Immediate Recall of Lists in Set 1*

Subjects listened to a list of 16 words presented once by a tape recorder. Immediately following the presentation of the list subjects were given 1.5 min to write in any order as many of the words as they could recall from that list. Retention of eight lists was tested in this fashion. The lists were presented at a rate of 2 sec per word. The words in each list were all nouns and had a frequency of 10–40 per million according to the Thorndike-Lorge word count [20].

*Delayed Free Recall of Lists in Set 1*

Subjects were asked to recall in any order as many of the words as they could remember from the eight lists learned prior to injection. Recall was written and lasted 20 min.

*Delayed Recognition of Lists in Set 1*

Each subject received a booklet containing 128 pairs of words. Within each pair one word was "old", i.e., it was one of the words from the eight lists learned previously. The other word was "new", i.e., it had not previously been presented in the experiment. The subjects were asked to check the "old" word of each pair. Ten minutes were allowed for completing the task. (Note: Subjects were not informed that any of the lists would be tested following injection and neither the delayed recall nor recognition task was included in the practice sessions.)

*Immediate Recall of Digit Sequences*

Subjects heard a nine-digit sequence presented by a tape recorder at the rate of two digits per sec. Following presentation of the last digit in each sequence a tone was sounded which served as a cue for recall. Subjects were then to write as many digits as they could remember from that sequence on an answer sheet which contained 24 series of nine interconnected boxes. Twelve seconds were allowed for recall of each sequence. Recall of 24 random sequences was tested.

TABLE 1

TREATMENT GROUPS

| First Drug | Second Drug |
|---|---|
| 1. Methamphetamine (small dose) | Placebo |
| 2. Methamphetamine (large dose) | Placebo |
| 3. Placebo | Placebo |
| 4. Scopolamine | Placebo |
| 5. Scopolamine | Methamphetamine (small dose) |
| 6. Scopolamine | Methamphetamine (large dose) |
| 7. Scopolamine | Physostigmine |

TABLE 2

SCHEME OF THE EXPERIMENTAL PROCEDURES

| Elapsed time since first drug administration* | Experimental Procedures |
|---|---|
| | Subjective Questionnaire 1 |
| | Practice session |
| | Presentation and immediate recall of first set of lists |
| | First drug or placebo administered |
| 30 min | Subjective Questionnaire 2 |
| 35 min | Delayed recall test of first set of lists |
| 55 min | Delayed recognition of first set of lists |
| 65 min | Immediate recall of digit sequences |
| 75 min | Second drug or placebo administered |
| 95 min | Presentation and immediate recall of second set of lists |
| 115 min | Subjective Questionnaire 3 |
| 120 min | Delayed recall of second set of lists |
| 140 min | Delayed recognition of second set of lists |

*Minutes from first drug administration to the beginning of each test.

*Immediate, Delayed, and Recognition Tests of Lists in Set 2*

A second set of eight lists similar in construction to those of Set 1 were presented and tested with the same procedures as described above. For the delayed recall test subjects were told to recall only those words from the most recent set of eight lists. None of the words in the lists nor the foils in the recognition test had been presented previously in the experiment.

TABLE 3

MEAN NUMBER OF WORDS RECALLED AND THEIR CORRESPONDING STANDARD ERRORS FOR EACH RETENTION TEST FOR LISTS IN SET 1 AND 2

| Set 1 | | Immediate Recall | Delayed Recall | Recognition |
|---|---|---|---|---|
| Methamphetamine (small dose)* - Placebo | Mean | 66.90 | 31.60 | 109.10 |
| | S.E. | 5.29 | 4.45 | 2.83 |
| Methamphetamine (large dose)† - Placebo | Mean | 65.10 | 34.00 | 110.00 |
| | S.E. | 4.11 | 3.47 | 3.00 |
| Placebo - Placebo | Mean | 67.30 | 30.50 | 112.70 |
| | S.E. | 3.79 | 2.56 | 2.53 |
| Scopolamine - Placebo | Mean | 74.50 | 37.20 | 107.00 |
| | S.E. | 3.29 | 4.40 | 5.12 |
| Scopolamine - Methamphetamine (small dose)* | Mean | 75.50 | 37.70 | 110.70 |
| | S.E. | 6.48 | 7.93 | 3.83 |
| Scopolamine - Methamphetamine (large dose)† | Mean | 73.80 | 36.30 | 109.80 |
| | S.E. | 4.64 | 4.97 | 1.39 |
| Scopolamine - Physostigmine | Mean | 73.80 | 35.00 | 107.50 |
| | S.E. | 5.19 | 5.97 | 3.23 |
| Methamphetamine (small dose)* - Placebo | Mean | 63.00 | 35.90 | 111.40 |
| | S.E. | 3.02 | 1.51 | 2.00 |
| Methamphetamine (large dose)† - Placebo | Mean | 69.00 | 41.00 | 111.70 |
| | S.E. | 4.87 | 3.30 | 2.12 |
| Placebo - Placebo | Mean | 62.40 | 25.90 | 109.10 |
| | S.E. | 3.11 | 3.34 | 3.34 |
| Scopolamine - Placebo | Mean | 34.50 | 6.70 | 95.00 |
| | S.E. | 3.45 | 1.23 | 4.23 |
| Scopolamine - Methamphetamine (small dose)* | Mean | 47.00 | 21.80 | 104.10 |
| | S.E. | 5.88 | 4.49 | 3.26 |
| Scopolamine - Methamphetamine (large dose)† | Mean | 43.70 | 24.80 | 101.10 |
| | S.E. | 2.65 | 3.46 | 3.86 |
| Scopolamine - Physostigmine | Mean | 54.00 | 22.30 | 102.60 |
| | S.E. | 5.24 | 4.39 | 3.67 |

*0.2 mg/kg
†0.3 mg/kg

## RESULTS

The results for each of the memory tests for material learned in Set 1 and Set 2 were analyzed by means of a 2×7 (Sex × Drug) analysis of variance. The means and standard errors for the immediate recall, delayed recall, and recognition tests for these two sets of tests are presented in Table 3.

### *Recall of Lists in Set 1*

In order to determine whether the groups differed in learning ability prior to injection, an analysis was made of the total number of correct responses made during the immediate free recall task. No significant differences were observed among groups ($F<1$). Recall tests administered following the first drug injection, i.e., the delayed recall and recognition tests, also indicated there were no significant differences among the groups ($F<1$ in each case). None of the Sex × Drug interactions were significant either, $p<0.2$ in each case.

### *Recall of Lists in Set 2*

Following the second injection, as is apparent in Table 3, large performance differences were observed in immediate recall $F(6,56)=8.06$, $p<0.001$. Tukey's honest significant difference test indicated that scopolamine impaired performance, as the scopolamine-placebo group recalled significantly less than the placebo alone and either of the methamphetamine-placebo groups. In addition, physostigmine was found to antagonize the effects of scopolamine as the scopolamine-physostigmine group recalled significantly more than the scopolamine-placebo group ($p<0.05$). A similar but nonsignificant trend was observed for the scopolamine-methamphetamine treatments, for while the groups receiving methamphetamine after scopolamine did not perform significantly different from the scopolamine-placebo group, they also did not perform significantly different from the placebo alone group ($p>0.05$).

The delayed recall test for retention of the second set of lists also revealed a strong drug effect, $F(6,56)=10.03$, $p<0.001$. Tukey contrasts indicated that the scopolamine-placebo group recalled significantly less than all the other groups, ($p<0.05$) and the group receiving the large dose of methamphetamine followed by a placebo recalled significantly more than the placebo-placebo group ($p<0.05$).

The main effect for drug treatment was also significant in the recognition test, $F(6,56)=3.10$, $p<0.05$. However, while both the methamphetamine-placebo groups performed better than the scopolamine-placebo group ($p<0.05$), the compari-

son between the scopolamine-placebo and placebo-placebo group only approached significance ($0.1<p<0.05$).

*Intrusion Errors in Set 1 and Set 2*

To further examine performance on the memory tasks a count was made of the number of times subjects made intrusion errors on each of the recall tests, i.e., "recalled" words which were not in the lists. For analysis of Set 1 scores the four scopolamine treatments were combined into one group since they had been treated identically through Set 1. There were no significant differences in intrusion rate in the immediate recall tests for either Set 1 or Set 2. However, a significant drug effect was observed in delayed recall of both Set 1 and Set 2, $F(3,62)=4.53$, $p<0.01$, and $F(6,56)=3.17$, $p<0.01$, respectively. The mean intrusion rate on Set 1 for the small and large dose of methamphetamine was 8.4 and 8.6 words respectively. Both these scores differed significantly from the 3.9 intrusion rate in the placebo groups, $p<0.05$. The scopolamine group mean was 4.0, which of course did not differ from the placebo. For Set 2 the corresponding intrusion rate in the "small" and "large" methamphetamine groups was 15.4 and 24.1 respectively. The mean for the placebo-placebo group was 4.3. The difference for the small dose approached significance, $p<0.1$, while for the large dose the difference was significant, $p<0.01$. In the scopolamine-methamphetamine large dose group the intrusion rate was 15.5, $p<0.1$ when compared to the placebo-placebo group, but the other three scopolamine groups averaged only 6.0 intrusions and did not differ from the placebo.

*Immediate Recall of Digit Series*

The data were scored by both a serial position scoring and a free recall scoring criterion. According to the serial position scoring criterion, an item is counted as correct only if it is recalled in its proper position in the sequence. According to a free recall scoring criterion, a response to a stimulus item is correct if it occurs any place in the response sequence. The first method scores for retention of both item and order information while the latter scores only for retention of item information. The first three sequences and the last sequence were not scored. For the remaining 20 sequences the number correct at each position in the sequence was determined. Scores for each nonoverlapping set of three items were collapsed into one score in order to add stability to the serial position data. These scores were then analyzed in a 3×4 (Serial Position × Drug) analysis of variance. (Note: Because this test was conducted prior to the second injection, the four scopolamine treatments were collapsed into one group for this analysis.) Results for the serial position scoring criterion are displayed in Figure 1. This figure makes apparent the significant serial position effect, $F(2,132)=26.71$, $p<0.001$, resulting from the classic bowed serial-position curve. In addition, there was a significant main effect for drug, $F(3,66)=4.75$, $p<0.01$. Follow-up analyses indicated that subjects who received scopolamine recalled significantly less than subjects in the other conditions, $p<0.01$, while none of the methamphetamine-placebo contrasts were significant. The same pattern of results was observed with free recall scoring.

*Subjective Questionnaire*

Due to the great variability inherent in subjective ratings, the data were analyzed by means of an analysis of covariance. Scores following drug administration were adjusted by the scores on the pre-drug questionnaire. Results for individual adjective pairs were collapsed to reflect the first three categories of feelings described earlier and other pairs were analyzed separately. Except where indicated all comparisons are with the placebo-placebo group.

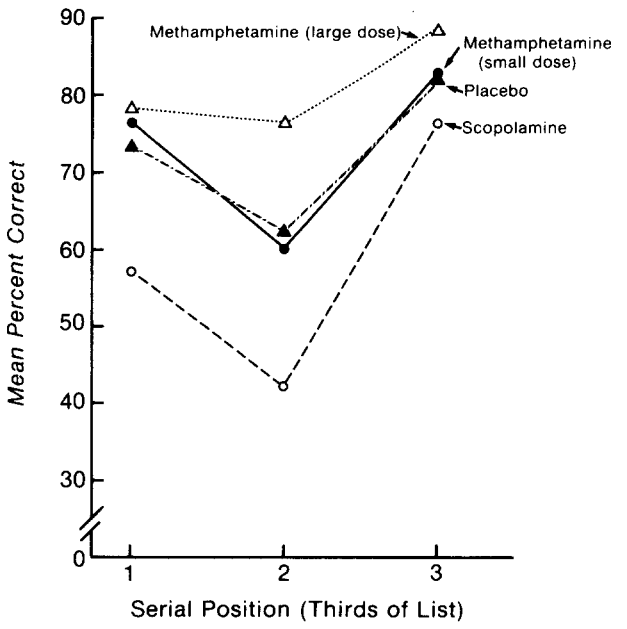


FIG. 1. Mean percent correct for successive thirds of the nine-digit sequences.

The analysis of ratings following first drug administration indicated that scopolamine produced marked feelings of mental and physical sedation, $p<0.001$. On the other hand, both the methamphetamine treatments produced significant feelings of mental and physical arousal when compared to the placebo, $p<0.05$. The methamphetamine treatments also generally increased feelings of happiness and friendliness or extroversion, $p<0.05$.

The ratings following the second injection indicated that subjects who had received scopolamine still felt mentally and physically sedated compared to the placebo group, $p<0.01$. In addition, subjects receiving either physostigmine or methamphetamine after scopolamine felt less sedated than the scopolamine-placebo group, $p<0.01$. However, the scopolamine-physostigmine group still displayed some mental and physical sedation when compared to the placebo-placebo group, $p<0.05$.

## DISCUSSION

According to a popular model of memory, two memory systems are involved when retention is required over intervals greater than one second [2]. The first, called the short-term storage system, can hold a limited amount of information for only a short time, e.g., typically a few seconds to a few minutes. The second, the long-term storage system, can theoretically hold an infinite amount of information permanently. According to the model, information passes through the short-term store in order to reach the long-term store.

We previously suggested that scopolamine does not interfere with the retrieval of information from the memory stores, but does greatly impair the transfer of information from the short-term to the long-term store [10,11]. The present results are consistent with these interpretations. That scopolamine does not impair retrieval processes is indicated by the fact that scopolamine did not affect the postinjection recall of information learned prior to injection, i.e., delayed recall and recognition of Set 1. On the other hand, recall of material presented following drug administration was greatly impaired by scopolamine. Since both types of immediate recall tasks employed here presumably exceed the capacity of the short-term store, the fact that retrieval was not affected implies that the performance deficits following injection resulted from interference with the memory storage or transfer process.

Physostigmine antagonized most of the memory impairment and mood changes produced by scopolamine. Methamphetamine produced similar effects, although antagonism of scopolamine impaired performance on the immediate recall test did not reach statistical significance. The efficacy of methamphetamine in antagonizing the memory impairment produced by scopolamine is contrary to recent results reported by Drachman after finishing our experiment [6]. Drachman found that d-amphetamine had either no effect or slightly increased the impairment on several cognitive tasks produced by scopolamine. There are several possible reasons for the difference between the two sets of results. In addition to employing different protocols and tests, the dosage of drugs used and their route of administration are pertinent. Drachman administered scopolamine (1.0 mg) subcutaneously and d-amphetamine (10 mg) orally. Since he did not report the weight of his subjects, assuming a 70 kg person, this would be a 14 μg/kg dose of scopolamine and a 0.1 mg/kg dose of d-amphetamine. In contrast, we administered intramuscularly scopolamine in a dose of 8 μg/kg and methamphetamine at 0.2 and 0.3 mg/kg. Methamphetamine is a stronger central nervous system stimulant than d-amphetamine. In addition, the latter drug was administered orally by Drachman without reporting the relationship between the time of drug intake and the last meal taken by the subjects. Presence of food in the stomach may delay absorption and attainment of a high blood level of the drug. We think that if Drachman had used a smaller dose of scopolamine (we achieved adequate memory blockade with 8 μg/kg) and a larger dose of amphetamine (our subjects tolerated more than 2 to 3 times the dose he used) his results would have been different.

There are at least two mechanisms by which physostigmine and methamphetamine may antagonize the memory impairment produced by scopolamine. The first is stimulation of specific memory processes in the brain. Both the cholinergic and adrenergic systems seem to be involved in memory processes. Deutsch has presented experiments from which he concludes that the cholinergic system is essential in information storage mechanisms [4]. Mandel and Ebel [15] found a highly significant cholinergic enzyme activity in the temporal lobes of a strain of mice characterized by high levels of avoidance and maze learning as compared to a strain with poor avoidance and maze learning. Scopolamine is an anticholinergic drug that competes with acetycholine at cholinergic receptors. Physostigmine is an anticholinesterase agent that increases acetylcholine at cholinergic synapses. Various evidence also suggest that catecholamines are required for memory storage. Thus, post-trial injection of reserpine impaired memory consolidation of an active avoidance task and this effect was reversed by dihydroxyphenylalanine (dopa) [5]. β-adrenergic blockade in the amygdala of rats disrupted long-term memory formation in a passive avoidance task [8]. Methamphetamine releases catecholamines from presynaptic terminals and inhibits their uptake [12]. It also acts directly on postsynaptic norepinephrine receptors [19]. There are also several effects on dopaminergic pathways, including increased release and inhibition of uptake of dopamine and inhibition of monoamine oxidase [9].

The second mechanism through which these drugs may interact is through a general arousal effect. Amphetamines produce cortical arousal or activation and promote wakefulness, actions which are well known and shown by subjects in the present study. Physostigmine tends to wake subjects from natural sleep [18] and may shorten the duration of postanesthetic somnolence [3]. Both methamphetamine and physostigmine were capable of counteracting the sedation produced by scopolamine. The experimental literature on arousal and memory have been recently reviewed [7]. Arousal tends to improve the consolidation process and subsequently improves delayed tests of recall [22]. Our data do not allow us to determine if the scopolamine, physostigmine and methamphetamine interactions on memory are the result of specific transmitter mechanisms in memory tracts or a general behavioral arousal.

A final purpose for the present experiment was to study the effects of methamphetamine on human memory. Although amphetamines have been widely studied in animals for their effect on learning and memory, the results of human experiments are far from conclusive. Weiss and Laties [23] concluded that amphetamine does not possess properties which improve intellectual functions except occasionally in those instances where normal performance is impaired by fatigue or boredom. However, as mentioned above some research has found that arousal in general has beneficial effects upon performance [22] including studies which employed amphetamines [13] or other stimulants [1]. In the present experiment methamphetamine was found to have no significant influence on retrieval of information learned prior to injection. It also did not affect performance in two types of immediate recall tasks. However, it produced a significant improvement in delayed recall of information which was acquired while the subjects were under the influence of the drug. These results are similar to those of Hurst, Radlow, Chubb, and Bagley [13]. That methamphetamine would have a larger effect in delayed recall than immediate recall is consistent with Walker's theory of arousal [21]. However, Walker also predicts that immediate recall performance should be impaired by high degrees of arousal. This did not occur. Eysenck [7] points out that frequently tests of Walker's theory which have employed a free recall task have failed to support this immediate recall prediction.

One further result of interest in the present study is the effect of methamphetamine on subjects' production of incorrect responses, i.e., intrusions in recall. While methamphetamine produced a small increment in intrusions in the delayed recall of Set 1, the drug produced a huge increase in incorrect responses simultaneously with the improvement in correct performance in Set 2. Subjects who received the large dose of methamphetamine produced almost six times as many intrusions as placebo subjects. This suggests the possibility that at least part of the recall improvement observed after methamphetamine may be an artifact produced

by the subjects' response strategy. Subjects who received methamphetamine may have displayed little inhibition in their recall. They may have "recalled" every word that occurred to them. Normal subjects typically filter their responses better. They may only recall words they are fairly confident are correct. The increase in correctly recalled items by subjects who received methamphetamine then could be items which nondrugged subjects had available but inhibited as responses because of their stricter confidence criterion. Schwartz [17] provides some evidence that high arousal does produce this type of shift in response strategy. However, further studies are needed to elucidate the effects of arousal on subject's recall and response bias in order to test this proposal. In addition, in view of the difference between Set 1 and Set 2 results, future work should investigate the relationship between response bias and recall as a function of drug administration during storage or retrieval processes.

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