

**Article abstract**—The administration of scopolamine, an anticholinergic drug, reduced the ability to recall and recognize stimuli presented previously—abilities thought to require declarative memory. In contrast, measures of procedural memory were unaffected by scopolamine: performance on a serial reaction time task incorporating a repeating stimulus and response sequence showed no difference in acquisition and retention of the sequence after scopolamine or saline. These results suggest that the cholinergic system is required for declarative but not procedural memory.

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## Neurochemical dissociation of memory systems

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The administration of scopolamine, a drug that blocks the action of acetylcholine centrally and peripherally, is known to affect memory. Recall of items from memory is reliably and substantially reduced in subjects who have been given scopolamine<sup>1-9</sup>; recognition is also affected.<sup>3</sup> Although scopolamine can reduce the level of alertness, its effects on memory are independent of its effect on alertness. Scopolamine-induced memory impairments are largely reversed by physostigmine, an anticholinesterase drug, but not by D-amphetamine, even though the latter increases alertness.<sup>4</sup> These findings and others support the hypothesis that cholinergic neurotransmitter systems play a central role in learning and memory.

It is thought that scopolamine affects primarily the storage of new information in long-term memory rather than the retrieval of previously learned information.<sup>3,5,6</sup> What is not clear from previous research is whether long-term memory storage is affected uniformly or selectively. Recent theories of human memory, motivated in part by findings from patients with amnesia, assert that long-term memory is not unitary, but instead includes multiple memory systems that are distinct both anatomically and functionally.<sup>10-13</sup> According to one framework,<sup>10,11</sup> declarative memory supports the learning and retention of facts and the conscious, explicit recollection of prior events. A separate system, procedural memory, supports the learning and retention of skills; it has been characterized as comprising learned connections between stimuli and responses.<sup>13</sup> Declarative memory is indexed by memory tests such as recall and recognition that require explicit memory of a study episode. In contrast, procedural memory is indexed by tasks in which memory is expressed implicitly by facilitation of performance as a result of prior experience.<sup>14</sup> In patients with amnesia, this facilitation can

occur in the absence of the ability to remember the episodes in which learning occurred.<sup>15-18</sup>

Previous studies of the effect of scopolamine on human memory have been concerned exclusively with declarative memory function. We sought to determine whether scopolamine affects declarative memory alone, or whether procedural memory functions are also compromised. An answer to this question would indicate whether procedural and declarative memory systems differ neurochemically, or whether they both require cholinergic pathways.

**Methods. Subjects.** A group of 24 healthy individuals whose native language was English and who ranged in age from 19 to 35 years were recruited from the University of Minnesota community. All subjects received a medical examination in order to identify and exclude anyone with physical, ocular, urologic, cardiac, neurologic, or psychiatric contraindications for the administration of scopolamine. Subjects were assigned to the scopolamine or the saline group according to a predetermined, random-assignment sequence. A double-blind procedure was followed. Subjects in the scopolamine group received 0.43 mg scopolamine subcutaneously; those in the saline group received 0.5 cc normal saline solution subcutaneously. (It may be noted that a peripherally acting anticholinergic drug, methscopolamine, is no longer available in the United States for parenteral use. With the low dosage of scopolamine that was used, the only peripheral effect reported by subjects who received scopolamine was dryness of the mouth.)

The scopolamine group included seven women and five men with a mean age of 24.8 years. The saline group included nine women and three men with a mean age of 24.3 years. One subject in each group was left-handed.

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All subjects provided informed consent and received \$25 for their participation.

**Tests.** A series of tests of memory and cognition were administered to each subject individually. Several tests required the explicit recall of declarative information learned before or during the experiment. In the *Generation of City Names* test, subjects were allowed 2 minutes to list in alphabetical order as many names of cities as they could. In the *Generation of Surnames* test, subjects were given a list of 40 first names (eg, Katherine) and were instructed to write the first surname that came to mind for each one (eg, Hepburn). The number of items completed in 2 minutes was recorded. A shortened version of the *Boston Naming Test*,<sup>19</sup> in which subjects named 30 line drawings of objects, was administered. *Digit Span* was assessed. A *Verbal Free Recall* test employed the paradigm described by Drachman and Leavitt.<sup>2</sup> On each of three successive study-test trials, subjects heard the same set of 35 words and were asked to recall them in any order.

**Serial reaction time.** On each trial of the serial reaction time task,<sup>20</sup> which was intended to assess the learning and retention of procedural information, an asterisk appeared on a video monitor at one of four locations arranged horizontally and separated by 3.8 cm. Below the monitor was a four-button response board. Subjects were instructed to press the button that was directly below the location in which the stimulus appeared. Reaction time (RT) to each stimulus was measured to the nearest millisecond. The stimulus remained present until the correct button was pressed, at which time it was extinguished, and another one appeared following a 500-msec delay.

All subjects completed eight blocks of 100 trials each. During Blocks 1 to 4, the location of the stimulus followed a particular 10-trial sequence. Each of these blocks of trials comprised 10 repetitions of the 10-trial sequence, but the end of one repetition and the beginning of the next was not marked in any way. The existence of the repeating sequence was not mentioned to subjects; their task was simply to respond to each light as quickly as possible without making errors. In Block 5, the location of the stimulus on each trial was determined randomly, the only constraint being that the same position could not be used on successive trials.

To the extent that subjects learned the repeating 10-trial sequence, their response latency should decrease during the first four blocks and increase in Block 5, when they were transferred to the random sequence. In order to assess retention of the sequence, subjects were given three additional blocks of trials (Blocks 6 to 8) following a delay of 30 minutes. The same repeating sequence used in Blocks 1 to 4 was presented in these blocks. If subjects retained the sequence, RT in Block 6 should be as fast as RT in Block 4.

**Generate task.** Subjects' explicit knowledge of the repeating sequence was assessed by asking them to generate it in a cued recall procedure. The generate task immediately followed Block 8 of the serial reaction time task and was similar to it, except that instead of pressing the button directly below the stimulus that appeared, subjects were instructed to press the button

corresponding to where they thought the *next* stimulus would appear. As before, the stimulus remained present until the correct button was pressed. Instructions emphasized accuracy rather than speed of response. Subjects performed two blocks of 100 trials each.

**Repetition priming and recognition memory.** The repetition priming effect refers to the finding that people are better able to complete a word fragment, identify a briefly presented word, or read a mirror-reversed word if the word was presented previously in the experiment than if it was not.<sup>13-16,21,22</sup> A word-fragment completion test was used in this experiment to assess the repetition priming effect; subjects' explicit memory for the same set of words was also determined with a recognition memory test.

Subjects were shown 50 low-frequency words at a rate of 3 seconds per word on a video monitor and were instructed to try to remember the words. Stimulus materials were taken from those used by Tulving et al.<sup>23</sup> Following a delay of 60 minutes, subjects were given a recognition memory test in which 10 of the studied words and 10 foils were listed. The instructions were to circle the studied words. Then subjects were given a list of 90 fragments of words (eg, A \_ \_ A \_ \_ IN), and they were asked to try to complete each fragment with the first word that came to mind, working quickly and going on to the next item if they could not think of a completion.

Of the 90 fragments, 10 were items that had been studied initially and appeared on the recognition test as targets (studied and tested); 10 had been studied, but had not appeared on the recognition test (studied only); 10 had not been studied, but had appeared on the recognition test as foils (tested only); and 10 had not appeared before in the experiment (new). The remaining 50 fragments were filler items of somewhat lower difficulty.

Assignment of particular stimuli to the four critical conditions of the fragment completion test (studied and tested, studied only, tested only, and new) and to the two conditions of the recognition test (target and foil) was counterbalanced across subjects. For example, for one-fourth of the scopolamine group and one-fourth of the saline group, one set of 10 words appeared in the study phase and as targets on the recognition test (studied and tested), whereas for another one-fourth of the subjects in each group, those same 10 words appeared in the study phase but not on the recognition test (studied only), and so on.

**Procedures.** The tests of memory and cognition began 45 minutes following injection and took 90 minutes. Tests were administered in the following order: generation of city names, generation of surnames, visual presentation of words for the fragment completion test, serial reaction time (Blocks 1 to 5), digit span, Boston Naming Test, verbal free recall, reaction time (Blocks 6 to 8), generate task, recognition of words for fragment completion test, and fragment completion test.

**Results.** Scopolamine produced dramatic effects on the performance of some tasks, but left others unaffected. Some of the results are summarized in table 1. Scopolamine did not affect performance on three tests of the ability to retrieve from memory previously ac-

**Table 1. Results from scopolamine and saline groups on tests of memory and cognition**

Test	Group	
	Scopolamine	Saline
Generation of city names (no. produced in 2 min)	13.2 ± 1.5	12.8 ± 1.2
Generation of surnames (no. produced in 2 min)	25.3 ± 2.0	27.9 ± 1.4
Boston Naming Test (no. correct of 30)	27.7 ± 0.6	28.2 ± 0.4
Digit span	6.7 ± 0.3*	7.7 ± 0.3
Free recall (no. recalled of 35)		
Trial 1	6.1 ± 1.0*	12.7 ± 1.3
Trial 2	10.6 ± 0.9*	22.0 ± 1.6
Trial 3	14.1 ± 1.3*	26.9 ± 1.3
Generate task (percent correct)		
Block 1	69.6 ± 6.6*	83.4 ± 4.3
Block 2	71.9 ± 6.4*	91.3 ± 2.8
Recognition (d')	1.4 ± 0.3*	2.2 ± 0.2

Values are means plus or minus one standard error.

\* Mean of scopolamine group significantly less than mean of saline group, by *t* test,  $p < 0.05$  or less.

**Table 2. Percent of word fragments completed by scopolamine and saline groups**

Type of item*	Group	
	Scopolamine	Saline
Tested only	37.5 ± 5.5	51.7 ± 7.2
Studied and tested	44.2 ± 6.3	52.5 ± 7.1
Studied only	20.8 ± 4.7	35.8 ± 7.9
New	16.7 ± 2.8	17.5 ± 2.8

Values are means plus or minus one standard error.

\* Tested only words appeared 5 minutes before the fragment completion test, studied and tested words appeared both 5 and 60 minutes before the test, and studied only words appeared 60 minutes before the test. New items had not been presented previously.

quired declarative knowledge: scopolamine and saline groups did not differ significantly in the number of city names produced ( $t[22] = 0.21$ ), the number of surnames produced ( $t[22] = 1.06$ ), or the number of correct responses on the Boston Naming Test ( $t[22] = 0.68$ ). Mean digit span was modestly but significantly reduced in the scopolamine group ( $t[22] = 2.63$ ,  $p < 0.005$ ). In other studies,<sup>2,9</sup> mean digit span was found to be lower in scopolamine groups than in saline groups, but not significantly so, suggesting that the effect of scopolamine on digit span is small and unreliable across studies.

As expected, scopolamine caused an impairment in the ability to recall a list of words. On each of the three successive trials, the scopolamine group recalled approximately half as many words as the control group; on the third trial, all scopolamine subjects performed worse than all saline subjects. Although both groups improved across trials, the improvement was greater in

**Table 3. Repetition priming effect shown by scopolamine and saline groups**

Type of item*	Group	
	Scopolamine	Saline
Tested only	21%	34%
Studied and tested	27%	35%
Studied only	4%	18%

Values correspond to the probability of completing fragments of each type of repeated word minus the probability of completing fragments of new words.

\* Tested only words appeared 5 minutes before the fragment completion test, studied and tested words appeared both 5 and 60 minutes before the test, and studied only words appeared 60 minutes before the test. New items had not been presented previously.

the saline group than the scopolamine group. A two-way analysis of variance of the number of words recalled, with group and trial as factors, indicated significant main effects of group ( $F[1,22] = 39.42$ ,  $p < 0.001$ ) and trial ( $F[2,44] = 176.03$ ,  $p < 0.001$ ) and a significant interaction between group and trial ( $F[2,44] = 14.98$ ,  $p < 0.001$ ).

In contrast to the deficit in recall, there was no effect of scopolamine on learning or retention as assessed by the facilitation of responses on the serial RT task. Group means of the median RT in each block, shown in the figure, indicated the following: first, the scopolamine group responded more slowly than the saline group. Second, RT decreased from Block 1 to Block 4 and then increased in Block 5. Third, RT in Block 6 was as fast as that in Block 4. Fourth, the pattern of performance over Blocks 1 through 8 was the same for the two groups of subjects. These impressions were confirmed by a two-way analysis of variance, with group and block as factors, which indicated main effects of group ( $F[1,22] = 5.10$ ,  $p < 0.05$ ) and block ( $F[7,154] = 50.30$ ,  $p < 0.001$ ), but no interaction between group and block ( $F[7,154] = 0.82$ ). The scopolamine group tended to respond less accurately (92.8% correct responses) than the saline group (96.7% correct responses), and accuracy dropped in Block 5. An analysis of variance of accuracy data resulted in main effects of group ( $F[1,22] = 15.04$ ,  $p < 0.001$ ) and block ( $F[7,154] = 10.92$ ,  $p < 0.001$ ), but no interaction ( $F[7,154] = 1.68$ ).

The generate task provided an explicit measure of subjects' knowledge of the repeating sequence. In both blocks of this task, the saline group responded more accurately than the scopolamine group (table 1). A two-way analysis of variance, with group and block as factors, indicated significant main effects of group ( $F[1,22] = 5.01$ ,  $p < 0.05$ ) and block ( $F[1,22] = 6.44$ ,  $p < 0.025$ ). Although saline subjects tended to improve more in the second block than scopolamine subjects, the interaction of group and block was not significant ( $F[1,22] = 1.91$ ).

Results from the fragment completion test appear in tables 2 and 3. Table 2 shows the percent of word fragments completed by each group of subjects in each of the four item types. Repetition priming effects derived from these results are shown in table 3. These

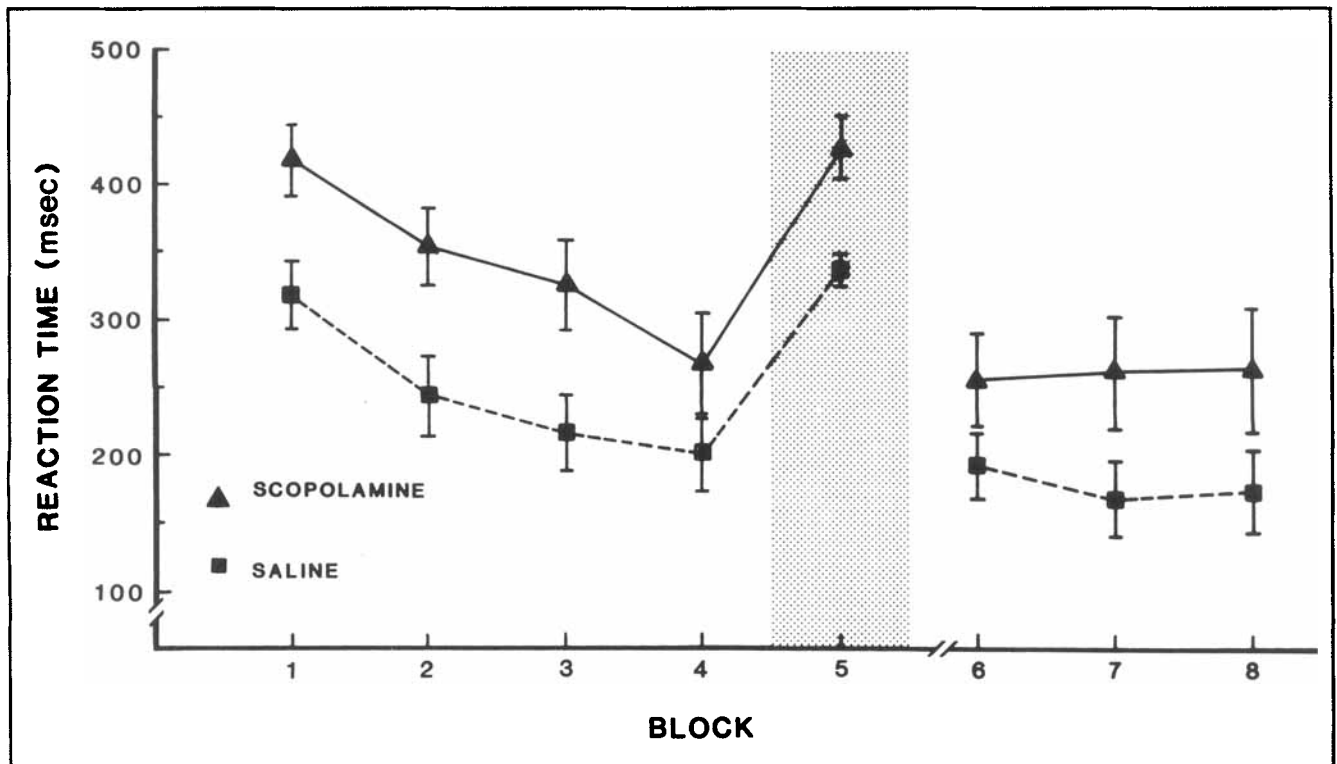


Figure. Learning and retention of a repeating stimulus-response sequence by individuals injected with scopolamine or saline solution. Reaction time was measured in blocks of trials employing a repeating sequence (Blocks 1 to 4 and 6 to 8) and in a block employing a random sequence (Block 5, shaded). An interval of 30 minutes separated Blocks 5 and 6. Points indicate mean of median reaction time; bars indicate one standard error above and below the mean.

values correspond to the probability of completing a fragment of a word that appeared previously minus the probability of completing a fragment of a word that was not presented before. The results allow the assessment of repetition priming effects at two retention intervals. If there is priming over relatively short intervals, then subjects should complete more fragments of words that appeared approximately 5 minutes earlier on the recognition test than new items. Both groups of subjects showed an advantage for tested only as compared with new items:  $t(22) = 3.35, p < 0.005$  and  $t(22) = 4.45, p < 0.005$ , for scopolamine and saline groups, respectively. Similarly, studied and tested items, which also appeared on the recognition test, were completed more often than new items by both groups ( $t[22] = 4.00, p < 0.005$  for scopolamine subjects and  $t[22] = 4.61, p < 0.005$  for saline subjects). Although it appears that saline subjects may have derived greater benefit from repetition at these relatively short intervals (table 3), the differences between groups in the size of these two priming effects were not significant ( $t[22] = 1.22$  and  $t[22] = 0.82$ ). If there is a longer-lasting priming effect, then subjects should complete more fragments of words that appeared approximately 60 minutes earlier during the study phase (but not subsequently) than fragments of new words. The saline group demonstrated this advantage for studied only items as compared with new items ( $t[22] = 2.17, p < 0.025$ ), but the scopolamine group did not ( $t[22] = 0.75$ ). Scopolamine subjects were less able than saline subjects to recognize words pre-

sented during the study phase. Recognition  $d'$ , a measure that reflects both the correct recognition of target words and the correct rejection of foils, was significantly lower in the scopolamine group ( $t[22] = 2.25, p < 0.025$ ) (table 1).

**Discussion.** The results of this study indicate that the effect of scopolamine is specific to declarative memory. Scopolamine caused a substantial impairment in declarative memory as assessed by recall, recognition, and cued recall tests. Results from the serial RT task, however, indicated that the learning and retention of procedural knowledge is not affected by central cholinergic blockade.

We consider the reduction of response latency on the repeating sequence of the RT task to reflect procedural learning for several reasons. First, it clearly indicates the development of skilled performance. Second, it demonstrates the learning of specific stimulus-response sequences, which Tulving<sup>13</sup> has suggested is a characteristic of procedural learning. Finally, this is a task in which learning is expressed implicitly, without the requirement for explicit remembering of what occurred before. Indeed, patients with memory disorders resulting from Korsakoff's syndrome<sup>20</sup> and some patients with probable Alzheimer's disease<sup>24</sup> also show by their performance that they learn the repeating sequence: their response times decreased with practice on the repeating sequence and then increased when a random sequence was introduced. This pattern of results oc-

curred despite the fact that these patients were not aware of the existence of a repeating sequence. Furthermore, Korsakoff patients and control subjects showed perfect retention of the sequence across a delay of 1 week. When tested in two sessions separated by a week, response times to the repeating sequence were as fast at the beginning of the second session as at the end of the first session.<sup>25</sup>

The fact that the scopolamine group responded more slowly than the saline group in all blocks of trials was expected; others have also reported that scopolamine increases RT.<sup>8</sup> The critical finding of interest is that the two groups did not differ in our measures of learning and retention in this task. The reduction in RT in Blocks 1 through 4 and the increase in Block 5, which together indicate acquisition of the sequence, were equivalent for the two groups. Furthermore, both groups responded as fast in Block 6 as in Block 4, indicating that scopolamine did not affect 30-minute retention of the sequence. It is clear that these results indicate learning and retention of the specific sequence that was used and not solely the learning of more general task characteristics; otherwise, there should be no slowing in responses upon transfer to the random sequence in Block 5.

It is not the case that the learning that facilitates performance on the serial RT task is necessarily easier or more automatic than other forms of learning. Normal subjects who are given this task show virtually no learning of the sequence if they are prevented from attending fully to the task by the requirement to discriminate and count auditory tones during training.<sup>20</sup> It is also important to note that the present study included both implicit (RT) and explicit (cued recall) measures of the extent to which subjects learned the sequence. These two measures were formally parallel, involving the same stimuli and responses. Nevertheless, the explicit measure, presumably reflecting declarative knowledge, was significantly affected by scopolamine, whereas the implicit measure, presumably reflecting procedural knowledge, was not.

Like measures of procedural learning, the repetition priming effect provides a way to assess the effect of prior experience implicitly rather than explicitly. Patients with memory disorders of various etiologies demonstrate repetition priming effects despite poor ability to explicitly recall or recognize the words they saw earlier.<sup>13-16,21,22</sup> It is thought that the prior presentation of the repeated word allows its representation in memory to be activated and made more accessible.<sup>26,27</sup>

The results of this study showed that scopolamine tended to reduce the advantage derived from the prior presentation of stimulus words. The fact that scopolamine and saline groups were equally likely to complete fragments of words that had not been presented previously in the experiment indicates that scopolamine did not affect the ability to generate completions per se. Rather, it was the repetition priming effect itself—the advantage for repeated words—that was affected.

There are alternative interpretations of the findings from the fragment completion task. The interpretation

we favor is that some of the processes that subserve explicit declarative memory may also contribute to fragment completion performance.<sup>28,29</sup> According to this view, repetition priming occurs largely because the presentation of a word increases the activation of the representation of that word in memory. This is an implicit effect. In addition, the ability to explicitly remember the words that were presented previously may in some circumstances enhance even further the probability that fragments of those words will be completed. On this account, scopolamine leaves the activation process unaffected. The saline group showed a somewhat larger repetition priming effect because of their superior explicit declarative memory for the set of words. This interpretation is consistent with findings from other investigators that repetition priming is not always fully intact in amnesic patients.<sup>28,29</sup>

Central cholinergic blockade presumably results in disruption of function in the cholinergic projection system to the neocortex and hippocampus.<sup>30,31</sup> It causes a striking reduction in the acquisition of declarative knowledge, but it leaves the acquisition and retention of procedural knowledge unaffected. Some patients with Alzheimer's disease,<sup>24</sup> Korsakoff's syndrome,<sup>15,20</sup> bilateral medial temporal lobectomy,<sup>16-18</sup> and lesion of the dorsomedial nucleus of the thalamus<sup>15</sup> exhibit a similar dissociation between procedural and declarative memory systems. In contrast, lesions in the basal ganglia in animals and humans may have substantial effects on procedural learning.<sup>32,33</sup> We conclude that the neurochemical and anatomic substrates for the two memory systems may be distinct.

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