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Scopolamine impairs auditory delayed matching-to-sample performance in monkeys

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ABSTRACT

Information concerning the major neurotransmitters critical for auditory memory is sparse. One possibility is the cholinergic system, important for performance in some tasks requiring visual short-term memory and attention [T.G. Aigner, M. Mishkin, The effects of physostigmine and scopolamine on recognition memory in monkeys, Behav. Neural. Biol. 45 (1986) 81–87; N. Hironaka, K. Ando, Effects of cholinergic drugs on scopolamine-induced memory impairment in rhesus monkeys, Jpn. J. Psychopharmacol. 16 (1996) 103–108; T.M. Myers, G. Galbicka, M.L. Sipos, S. Varadi, J.L. Oubre, M.G. Clark, Effects of anticholinergics on serial-probe recognition accuracy of rhesus macaques (*Macaca mulatta*), Pharmacol. Biochem. Behav. 73 (2002) 829–834; H. Ogura, T.G. Aigner, MK-801 Impairs recognition memory in rhesus monkeys: comparison with cholinergic drugs, J. Pharmacol. Exp. Ther. 266 (1993) 60–64; D.M. Penetar, J.H. McDonough Jr., Effects of cholinergic drugs on delayed match-to-sample performance of rhesus monkeys, Pharmacol. Biochem. Behav. 19 (1983) 963–967; M.A. Taffe, M.R. Weed, L.H. Gold, Scopolamine alters rhesus monkey performance on a novel neuropsychological test battery, Cogn. Brain Res. 8 (1999) 203–212]. Five rhesus monkeys were trained to perform an auditory go/no-go delayed matching-to-sample (DMTS) task wherein two acoustic stimuli (500 ms), separated by variable memory delays (500 ms, 2500 ms, or 5000 ms), were either identical sound presentations, i.e., match trials, or two different sound presentations, i.e., nonmatch trials. Sound stimuli were chosen semi-randomly from a large set sound set (~900). After reaching a criterion of 80% correct on the behavioral task, monkeys were injected with saline or doses of scopolamine hydrochloride mixed in saline (3 μg, 5 μg, and 10 μg per 1 kg of weight), 30 min before training. Scopolamine impaired performance accuracy on match trials in a dose-dependent manner. Blocking muscarinic receptors with scopolamine did not significantly impair motor responses, food motivation, or responses to rewarded sound. These findings support the hypothesis that the cholinergic system is important for auditory short-term memory.

Short-term memory judgments of stimulus recency (working memory) or stimulus familiarity (recognition memory) are critical for a multitude of basic tasks during daily life. While several studies elucidate the brain areas involved with working and recognition memory using visual cues [5,14,21], only a few have assessed multimodal auditory plus visual cues or auditory cues only [13,15,20,35,38]. One behavioral task that assesses short-term memory utilizing working and recognition memory is delayed matching-to-sample (DMTS). DMTS studies typically use visual cues wherein a sample visual object presentation is followed by a delay memory period, after which the sample object and a novel choice object are presented. The animal is rewarded for choosing the previously presented sample stimulus. While identification of the possible brain areas involved with short-term auditory memory has started [7,13], the neurotransmitters critical for auditory memory have not been examined.

Several studies have shown that blocking muscarinic receptors impairs visual memory performance on a variety of tasks including DMTS, delayed nonmatching-to-sample (DNMTS), self-ordered spatial search, and serial-probe recognition [1,16,23,24,26,36]. Other acetylcholine receptor antagonists, such as atropine, impair short-term memory [26]. These findings have generally been interpreted as a visual working memory deficit; however others have concluded that these types of deficits may be due to a lack of visual attention, especially when the tasks involve visual cues in classical and operant conditioning, or spatial tasks [32,33].

The cholinergic system is important for tasks requiring visual short-term memory, and it may also be important for auditory memory. Auditory cortex demonstrates plasticity in perceptual training and associative learning of auditory cues [18,27]; and

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cholinergic input into that system may be important for auditory memory [39]. One example of the cholinergic system modulating learning and memory is during fear conditioning. Various experiments have shown that administration of scopolamine via systemic injections in rats impairs the auditory cue fear memory [3,31]. Although the fear memory trace differs from working memory it does illustrate how the cholinergic system may be imperative for auditory memory processes.

Acetylcholine for memory and attentional processing may be conserved across species as blocking it impairs memory performance in rats, pigeons, monkeys and humans [11,12,17,28,34]. Based on evidence that the cholinergic system is utilized for visual DMTS, we hypothesize that blocking the cholinergic system with scopolamine hydrochloride (ScHCl), a muscarinic cholinergic receptor antagonist, will impair performance of the auditory DMTS task. Monkeys were tested on an auditory DMTS task with variable delay times after systemic injections of ScHCl or saline vehicle.

Five rhesus monkeys (*Macaca mulatta*), three females and two males (11–12 years old; 5–10 kg), were born and raised in captivity, and housed in Spence Laboratories at the University of Iowa (12-h light/dark cycle). Monkeys were fed standard monkey chow (Harlan Teklad Global Diet, Madison, WI, USA), fresh fruit, and vegetables. The majority of food was given after training each day. Water was provided ad libitum in the home cage with all animals given environmental enrichment. Each animal's weight was maintained above 85% of starting weight and adjusted upwards based on age. The Institutional Animal Care and Use Committee at the University of Iowa approved all procedures.

Sound stimuli (~900), tones, music, human voices (speech and non-speech sounds), monkey calls, bird calls, other animal calls, and man made sounds (e.g., cars, train whistles or airplanes), were eventually repeated throughout training so none are unfamiliar. However, because they are pseudo-randomly presented in a trial unique fashion prediction based on familiarity is not possible. Sound stimulus duration was truncated at 500 ms, and all sounds played from a single speaker positioned just above the response button.

Monkeys sat comfortably in restraint chairs placed inside a sound attenuation chamber. There was a response button in front (height 18 in.; 5 in. from monkey's chest), a speaker (height 22 in.), and a copper tube connected to a dish (1 in. from monkey's fingertips) from which to collect reward. A house light provided illumination throughout the training session. A stimulus light remained on during the intertrial interval (ITI). LabView software (National Instruments, Austin, TX) controlled lights, sound stimuli, and treat dispenser. To the upper left of the monkey a small video camera allowed observation by the experimenter.

The DMTS task used approximately 75 stimulus set sounds/day. Training sessions were held 5 days a week, 50 trials/session. The task was designed as a go/no-go task. For match trials the monkey was to respond by pressing the response button releasing a small chocolate candy reward. For nonmatch trials the monkey was not to respond. If the monkey pressed the button after a nonmatch trial they received a 500 ms air puff reminder not to respond. This mild air puff is applied semi-randomly during normal training after nonmatch errors to discourage incorrect responding. During sessions with saline or drug injections, animals only received air puff after the first incorrect nonmatch trial.

Match and nonmatch trials consisted of a 500-ms sound followed by a pseudo-randomly selected inter-stimulus interval (ISI) of 500 ms, 2500 ms, or 5000 ms. Then a second 500 ms sound was played, and the response button lit up for 1000 ms. This happened on both match and nonmatch trials as a cue that signaled the possible response time, and did not in anyway signal which were match versus nonmatch trials. If the animal did not respond during this time interval, it lost the chance for a reward on that trial, and the ITI of 12,000 ms began.

Monkeys trained to a criterion of 80% or better on this variable ISI schedule before the saline and drug doses were administered. The three time delays were chosen because they were well within the auditory short-term memory capacity for all five monkeys. With the standard training at 5000 ms, they could perform the task at shorter delays. We wanted to ascertain performance with these relatively short delays, which a larger number of our trained monkeys can consistently perform. Other work has shown that when delays are lengthened past 37.5 s on a similar auditory task performance starts to drop below 70% correct [13].

All monkeys served as within subject controls. After meeting behavioral criterion, they were injected with saline, 3 μg, 5 μg, and 10 μg of scopolamine hydrochloride (salt) (Sigma–Aldrich, St. Louis), per 1 kg of weight. Drug doses were selected based on similar ranges in other scopolamine studies with rhesus macaques [1,24]. All animals received two sessions with each drug dose, and five sessions with saline. All means reported are the average of those sessions. Drug or saline was administered 30 min before the behavioral session. Drug dose sessions were assigned in a semi-random order and counter balanced so that some monkeys received 3 μg, 5 μg, then 10 μg, while others received 10 μg, 3 μg, 5 μg, etc. Saline was always administered on the first weekday of training, followed by a drug dose day, then a training day. For example: Monday = saline; Tuesday = 3 μg ScHCl; Wednesday = training alone; Thursday = 10 μg ScHCl; Friday = training alone.

To examine the effects of scopolamine on the animals' response to food rewards, i.e., motivation, without a memory demand, we compared sessions with saline and a 5-μg/kg dose of scopolamine per 1 kg of weight during a food test. During the regular DMTS training the session lasts about 20 min and animals work to receive 20–25 rewards. In these food reward test sessions, monkeys were placed in the sound booth (20 min after injection) and given one small treat through the pellet dispenser as during regular DMTS, per minute for 20 min. The pellet dispenser emits the sound of the solenoid turning on and off to drive the delivery device. There is also the sound of the pellet falling through the copper delivery tube. Monkeys only had to reach for the reward upon hearing the pellet dispenser release the treat. The control saline injection session with food reward test occurred the day before the scopolamine injection session.

To investigate whether the monkeys could pay attention to a simple task that did not require memory within a trial we designed a task that presented sound trials with a repeated white noise stimulus (25) and no sound trials (25). On every sound and no sound trial the lighted response button was briefly lit just as in the variable memory delay DMTS task. Button presses on the sound trials resulted in food reward and button presses during the no sound trials were scored as errors. For sound trials the delay was set at 500 ms but the same white noise sample was used for every stimulus on every trial. Variable ITIs (8000 ms, 10,000 ms, and 12,000 ms) prevented animals from predicting when each trial would start. We compared sessions with saline and a 5-μg/kg dose of scopolamine per 1 kg of weight (30 min wait time).

To investigate whether the monkeys were attending to the cues and performing the basic task we shortened the ISI delay to 50 ms. This is an extremely short ISI but still allows for the detection of two separate sounds. Both match ($n = 25$) and nonmatch ($n = 25$) trials were presented with the short ISI. The very short delay was so slight virtually no memory demand is present. This concept is similar to some visual paradigms, which present the sample and then leave the sample up while presenting the choice stimulus [29,36]. The trial unique sound stimulus set and ITIs were the same

as those used in the variable DMTS task. We compared sessions with saline and a 5-μg/kg dose of scopolamine per 1 kg of weight (30 min wait time). This design reduces the memory component but still tests whether the monkeys are attending and able to process sound quality beyond the white noise presented in the same sound DMTS.

Performance of the animals, measured by percent error (the number of incorrect trials/by the total number of trials; per session), was analyzed. The variable DMTS task was analyzed with a repeated measures analysis of variance (ANOVA) using SPSS 13 software (SPSS, Chicago, IL, USA), one within factor was dosage (saline, or 3 μg, 5 μg, and 10 μg of scopolamine) and the other within factor was ISI delay (500 ms, 2500 ms, and 5000 ms). Two separate ANOVAs were used for match and nonmatch trials as response requirements differed. In order to balance the statistical design, we selected two of the saline sessions that were closest to the mean across all saline sessions. The match latency to respond was also analyzed with repeated measures ANOVAs using the same within factors as above. The p-value was set at 0.05. The food reward test, same sound DMTS task, and low memory DMTS task were analyzed with planned independent t-statistics with the p-value set at 0.05.

For the nonmatch latency data we used the Bonferroni procedure, with Keppel's modification, to correct for the "family wise" error rate among comparisons of t-statistics [19]. Under each delay, the latency to respond under the four drug conditions was examined. Thus, 18 pairwise comparisons were conducted to reveal differences between saline and scopolamine conditions. The four drug conditions were then entered as the experimental treatment, the number of degrees of freedom for the treatment source of variance ($4 - 1 = 3$) was multiplied by the standard critical probability level (0.05), and the product was divided by the number of t-test comparisons (i.e., 18), yielding the corrected, critical probability level of 0.008.

Animals met a criterion of 80% or better on average for match and nonmatch trials before beginning drug sessions. Performance for match and nonmatch trials was calculated using the number of incorrect responses divided by the total number of responses of that type and converted to percent error.

For performance on match trials, there was a significant effect of dose ($F_{3,27} = 16.03$, $p < 0.05$; Fig. 1) showing an increase in percent error at all three delays. For performance on match trials, there was no significant effect of delay and no significant interaction.

For performance on nonmatch trials, there were no significant main effects of dose or delay and no significant interaction effect.

In addition to overall behavioral performance, we also examined the latency to respond. On match trials responding is a correct response, however on nonmatch trials responding is an incorrect response and considered an error. On the highest dose (10 μg dose) animals rarely responded to nonmatch trials. For this reason, some animals were missing latencies for response errors on nonmatch and an ANOVA was not viable. Instead we used t-tests, with a corrected p-value (0.008) for multiple comparisons to examine differences between dosages at each delay. There were no significant response latency differences for match or nonmatch trials.

During saline sessions for the food reward test monkeys reached for and obtained all 20 treats. During the scopolamine sessions all but one of the monkeys reached for and obtained all 20 treats made obtainable throughout the food reward test. There was no significant difference between the number of rewards taken on saline versus scopolamine during the food reward test (t-test: $p = 0.35$).

Animals performed well on the same sound DMTS task during both saline and scopolamine conditions. There were no significant differences in performance between the saline and scopolamine session for sound match trials (t-test: $p = 0.90$) nor on the light only trials (t-test: $p = 0.37$).

There were no significant differences on low memory demand DMTS task performance for match or nonmatch trials between saline and scopolamine sessions (t-test: match trials, $p = 0.51$; nonmatch trials, $p = 0.18$).

Blocking muscarinic transmission with scopolamine impairs performance of auditory DMTS. The two higher dosages of ScHCl impaired performance on the auditory variable DMTS at all three delays. Additional tests indicate that this deficit is more likely due to a deficit in auditory memory than in attention as the intermediate dose of ScHCl did not impair performance with very short delays of 50 ms.

A decrease in responding could be interpreted as a general lack of motivation and/or a motor deficit caused by impaired muscarinic transmission. However, in this study neither of those explanations can account for the decrement in responding on match trials. Performance on nonmatch trials during which a motor response should be withheld for a correct response was not impaired, i.e., no significant changes in over- or under-responding. If the basic deficit on match trials was a decrement in overall responsiveness we would expect to see a significant decrease in errors made on the nonmatch trials as well. Response latency on match and nonmatch trials was not affected either. This does not support the argument that decreases in performance are due to motor impairment. Results of the food reward test demonstrate that even while under the influence of the same dose of scopolamine that led to deficits on the memory task, the animals were still motivated to reach for and consume treats. The simple food reward task in which

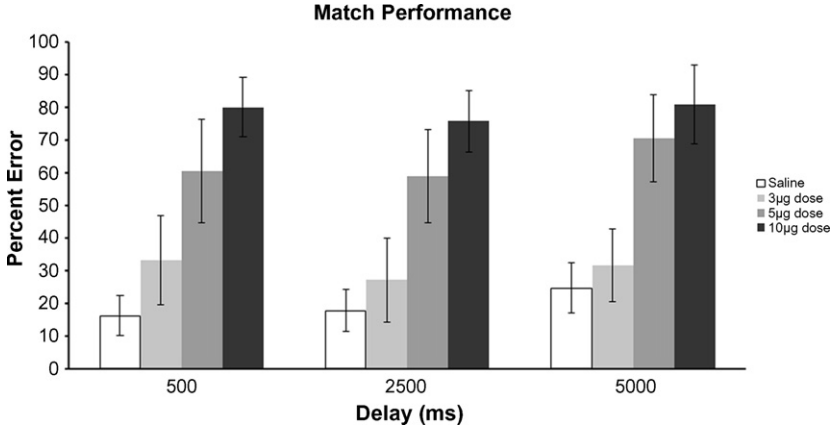

Fig. 1. Match performance as measured by percent error, there was a significant effect of dose. Performance on 5 μg and 10 μg doses was significantly impaired compared to saline ($p < 0.05$). Performance on 5 μg and 10 μg doses was also significantly impaired compared to the 3 μg dose ($p \leq 0.05$).

monkeys routinely responded under the influence of scopolamine to retrieve and eat food rewards, and the decrease in responding on match trials indicates a DMTS specific problem that is not attributable to a lack of motivation or motor impairment.

Given that the animals were impaired at all three original delays of 500 ms, 2500 ms, and 5000 ms one could argue that it was attentional processing that was affected. Acetylcholine is important for cue detection, which is affiliated with attentional control [25]. In opposition to this finding, however, the food reward test demonstrates that the animals are attending in some capacity in that they hear the sound of the pellet dispenser, orient, and obtain the food reward while under the influence of scopolamine. Furthermore, while on the intermediate dose of scopolamine, the monkeys performed well on the same sound DMTS task but with a very simple, repeated, white noise stimulus thus with a lower memory demand at a delay of 500 ms. The monkeys responded well to the sound presentations and ignored the light only trials confirming their ability to detect sound. Although the monkeys were impaired at the shortest 500 ms delay during variable DMTS with scopolamine, performance at the briefest delay of 50 ms was not impaired in the low memory DMTS suggesting that encoding of auditory stimuli was intact.

Good performance on the control conditions demonstrates that the monkeys were attending and responding to sound, food, and matching sound stimuli. Thus the observed deficit induced by scopolamine in the variable DMTS task cannot be due primarily to problems with attention, motivation, or motor performance. The performance decrement is more likely due to a deficit in memory processing, particularly short-term memory, e.g., working memory, due to the time frame of 5000 ms or less. The lack of a delay effect in addition to the overall deficit observed across memory delays may be related to the much smaller memory capacity of the non-human primate auditory system. A half second delay may seem incredibly short in a visual task, but in an auditory task this may be a substantial memory load as auditory memory performance starts to fall below 70% at only 37.5 s as compared to the visual system that may have a capacity measured in minutes to hours [13]. After ruling out attentional, motivational, or motor impairments, an overall decrement in short-term memory performance appears to be the main impairment.

Our current findings, showing impaired auditory memory task performance when the cholinergic system is temporarily disabled with a receptor antagonist, are similar to work done in the visual field where short-term recognition memory was examined by Aigner and Mishkin using a DNMTS wherein the delay between sample and test object was 15 s (1986). Several other non-human primate and lower animal studies [16,23,24,26,36], as well as a human study [29], suggest a role for acetylcholine in visual short-term memory. Although task requirements differed across the experiments all tested some form of short-term memory and consistently found across multiple species that blocking acetylcholine impaired visual memory performance. Taken together with our current results concerning the important role of acetylcholine in auditory memory, we suggest that a similar mechanism utilizing the cholinergic system may be conserved for short-term memory across multiple modalities.

Visual short-term memory relies on several brain areas including areas of the frontal lobe, rhinal cortex, parietal lobe, and other visual cortical areas [8,13,16,37,41]. Auditory short-term memory relies on areas within the medial temporal lobe such as the superior temporal gyrus [13], but other areas such as the prefrontal cortex may also be involved [7]. Working memory is thought to rely heavily on the prefrontal cortex and its involvement has been demonstrated in neurophysiological and imaging work [4,10,22]. The prefrontal cortex receives cholinergic input and blocking cholinergic input directly via prefrontal infusions of scopolamine has been shown to impair visual working memory [9]. A possible link between visual and auditory memory could be the neurotransmitter system involved, as well as shared brain areas like the prefrontal cortex [20,38,30].

Future studies could address if cholinergic agonists improve auditory memory as some have shown using visual cues [1,6,24,26], determine the exact process that is impaired, e.g., encoding of stimuli, storage, or retrieval [2,29,40], or determine if acetylcholine is important across all modalities for other similar types of tasks. The current findings lend support to the idea that the cholinergic system plays a role in short-term memory performance regardless of the modality of the given cues and suggests that diseases and medications affecting the cholinergic system may generally influence short-term memory performance in at least two modalities.

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