

Cholinergic Influences on Feature Binding

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The binding problem refers to the fundamental challenge of the central nervous system to integrate sensory information registered by multiple brain regions to form a unified neural representation of a stimulus. Human behavioral, neuropsychological, and functional neuroimaging evidence suggests a fundamental role for attention in feature binding; however, its neurochemical basis is currently unknown. This study examined whether acetylcholine (ACh), a neuromodulator that has been implicated in attentional processes, plays a critical role in feature binding. Using a within-subjects pharmacological design and the cholinergic muscarinic antagonist scopolamine, the present experiments demonstrate, in a rat model, a critical role for the cortical muscarinic cholinergic system in feature binding. Specifically, ACh and the attentional resources that it supports are essential for the initial feature binding process but are not required to maintain neural representations of bound stimuli.

Keywords: attention, feature binding, acetylcholine, muscarinic, basal forebrain

The mammalian brain is organized in a modular fashion such that spatially distinct regions are primarily responsible for detecting and processing the different features of a stimulus. The unknown mechanism by which a unified neural representation of a stimulus is formed is referred to as the binding problem (Robertson, 2003; Treisman & Gelade, 1980). Feature Integration Theory (Treisman & Gelade, 1980) suggests that attention is necessary for binding stimulus features into unified objects. Evidence for the attention-dependent nature of feature binding has come from two main sources: behavioral and neuroimaging studies, with neurologically intact humans demonstrating the need for attentional allocation during feature binding, as well as neuropsychological studies demonstrating the impaired feature binding performance of spatial neglect and Balint's syndrome patients (Bernstein & Robertson, 1998; Cohen & Rafal, 1991; Corbetta, Shulman, Miezin, & Petersen, 1995; Friedman-Hill, Robertson, & Treisman, 1995; Luck & Ford, 1998; Reynolds & Desimone, 1999; Treisman, 1998; Treisman & Gelade, 1980).

In humans, visual search has frequently been used to examine the attentional requirements of feature binding (Treisman, 1998;

Treisman & Gelade, 1980). In a feature-singleton search, the demand on attention is negligible as targets appear to “pop out” from the background of distractors (e.g., “find a green *X* within an array of red *X*s”). This has been argued to reflect that processing of single features (e.g., color) is accomplished intracortically without the need for feature binding and thus with little need for focal attention. By contrast, a feature-conjunction search (e.g., “find a green *X* within an array of red *X*s and green and red *O*s”) requires feature binding and intercortical sensory integration. As such, it results in an attentionally demanding serial search for the target, as demonstrated by a linear increase in detection time with increasing numbers of conjunction distractors (Treisman, 1991).

Although the attention-dependent nature of feature binding has been well documented in the human literature (Bernstein & Robertson, 1998; Cohen & Rafal, 1991; Corbetta et al., 1995; Friedman-Hill et al., 1995; Luck & Ford, 1998; Reynolds & Desimone, 1999; Treisman, 1998; Treisman & Gelade, 1980), its neurochemical basis is currently unknown. The neurochemical acetylcholine (ACh) is a worthy candidate. The cholinergic basal forebrain (BF) is an ascending neuromodulatory system that provides ACh to the entire neocortex; thus, ACh is poised to play an important role in information processing. In nonhuman animals, cholinergic input that acts at muscarinic receptors in cortical regions of the brain has been implicated in a variety of attentional processes, including selective, sustained, and cross-modal divided attention (Bushnell, 1998; Butt, Noble, Rogers, & Rea, 2002; Chiba, Bucci, Holland, & Gallagher, 1995; Himmelheber, Sarter, & Bruno, 2000; McGaughy, Dalley, Morrison, Everitt, & Robbins, 2002; Mirza & Stolerman, 2000; Turchi & Sarter, 1997). There is reason to suspect cholinergic involvement in feature binding, as patients with Alzheimer's disease, a neurodegenerative disorder characterized by attentional impairment and deterioration of cortically projecting BF neurons, show deficits in feature-conjunction, but not feature-singleton visual search tasks (Foster, Behrmann, & Stuss, 1999; Tales et al., 2002).

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An animal model would allow for a more direct investigation of the neuroanatomical and neurochemical basis of feature binding. As a first step, we designed a cross-modal feature-binding task for use in rats to determine whether one role of ACh in attention is to facilitate feature binding. We designed a digging task to allow us to measure cross-modal feature binding. On every trial, rats were simultaneously presented with two digging bowls: a cross-modal odor–texture bowl covered with a texture and scented with an odor and a blank bowl with no odor or texture component. We used these two digging bowls to create a forced-choice paradigm with two trial types: target and distractor. Target odor–texture bowls were presented on target trials and were defined by a specific combination of odor and texture (e.g. ylang ylang–sandpaper and lavender–foam). On target trials, the reward was always found in the odor–texture bowl, not the blank bowl. Distractor odor–texture bowls were presented on distractor trials and contained the same component odors and textures as target bowls, but they were presented in different combinations (e.g. ylang ylang–foam and lavender–sandpaper). On distractor trials, the reward was always found in the blank bowl, not in the odor–texture bowl (Figure 1A). The use of distractor bowls ensured that rats could not use odor or texture alone to find the reward, as cross-modal binding of odor and texture was required to determine the reward location. This feature-conjunction (FC) task thus required rats to cross-modally bind features to know where to dig for a reward. Additionally, we designed a feature-singleton (FS) task that required the same number of odor–texture discriminations as did the FC task but without the requirement of feature binding, as each odor–texture

stimulus bowl was characterized by a distinct odor and texture feature. Therefore, in the FS task, rats could use odor, texture, or the combination to determine where to dig for a reward.

Using a within-subject pharmacological design, we tested rats' ability to acquire (Experiment 1) and retrieve (Experiment 2) the FC task as well as to acquire the FS task (Experiment 3) under the muscarinic cholinergic antagonist scopolamine relative to two control drug conditions, methylscopolamine and physiological saline. We predicted that any scopolamine-induced impairment would be specific to feature binding as a result of its attention-dependent nature, impairing the ability of rats to acquire the FC, but not the FS, task. Past research has implicated the muscarinic cholinergic system in the encoding of new information but not in its subsequent retrieval (Bartus & Johnson, 1976; Everitt & Robbins, 1997; Hasselmo & McGaughy, 2004; Kirk, White, & McNaughton, 1988; Orsetti, Casamenti, & Pepeu, 1996; Parkes & White, 2000; Safer & Allen, 1971; White & Ruske, 2002). Thus, we further hypothesized that scopolamine would have no impact on the retrieval of previously bound FC stimuli, sparing retrieval of the FC task.

Experiment 1: Feature-Conjunction Acquisition

Rats were first given drug-free training with baseline stimuli to learn target and distractor trial response classification without the need for feature binding (Figure 2). The target baseline bowl was defined by a specific combination of odor and texture (patchouli–masking tape) and was presented on target trials in which the

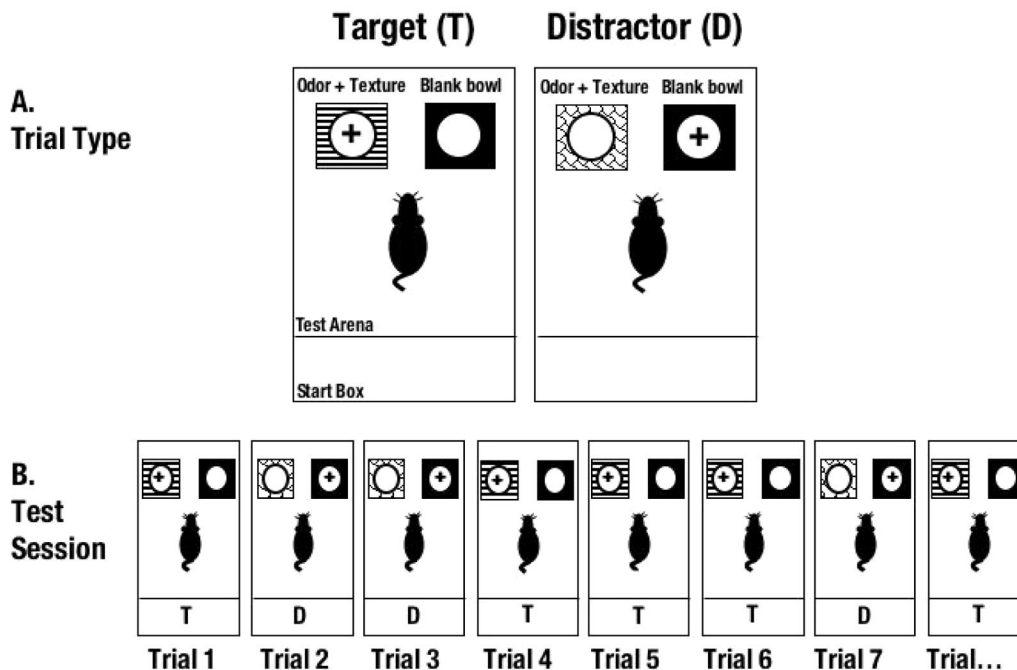


Figure 1. (A) Illustration of the two different trial types, target (T) and distractor (D), used in all three experiments. On target trials, the reward (+) was buried in the odor–texture bowl while on distractor trials, the reward (+) was buried in the blank bowl. (B) Illustration of a typical session. On every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. Half of the trials were target trials, and the remaining half were distractor trials presented in a pseudorandom order. Rats had to use the odor–texture features of the presented stimulus bowl to determine where the reward could be found.

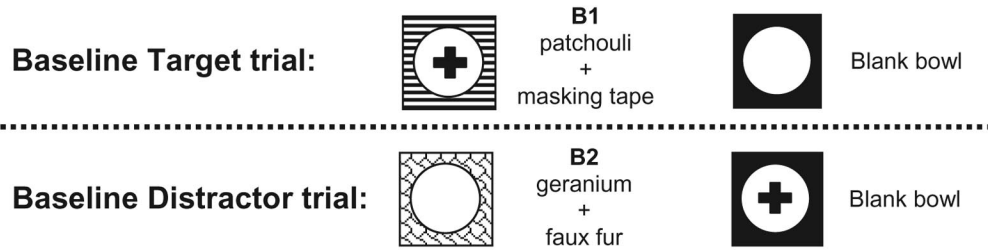


Figure 2. Baseline stimuli, which were used in all three experiments. On every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. On baseline target (B1) trials, the reward (+) was buried in the odor–texture bowl, and on baseline distractor (B2) trials, the reward (+) was buried in the blank bowl. These baseline stimuli were initially used to train rats on the digging responses needed for the forced-choice paradigm of our tasks. Next, baseline stimuli were presented at the beginning of each subsequent feature-conjunction (FC) and feature-singleton (FS) session to measure the effect of drug on general stimulus discrimination and digging performance.

reward was found in the odor–texture bowl, not in the blank bowl. The distractor baseline bowl was defined by a distinct combination of odor and texture (geranium–faux fur) and was presented on distractor trials in which the reward was found in the blank bowl, not in the odor–texture bowl. Rats could thus use odor, texture, or the combination to discriminate the baseline stimuli, as each was characterized by a distinct odor and texture. Once the rats acquired the response mapping of digging in the odor–texture bowl on target trials and digging in the blank bowl on distractor trials, they were given drug-free training on the FC task with FC Stimulus Set 1 (Figure 3) so that they could acquire the concept of feature binding using this “learning-to-learn” stimulus set. Rats’ ability to acquire the FC task using three novel FC stimulus sets was then tested under cortical muscarinic blockade using a within-subject design such that each rat was tested under each drug condition.

Method

Table 1 outlines the temporal structure of all three experiments.

Subjects

Eight experimentally naïve male Long–Evans rats (Charles River Canada) that weighed 216–240 g at the start of the experiment were used throughout all of the experiments. Rats were housed individually in 45 cm long × 25 cm wide plastic tub cages and maintained on a reversed 12-hr light–dark cycle (lights off at 8 a.m.), with testing occurring during the dark phase (between 10 a.m. and 4 p.m.). Rats were maintained at 90% of ad libitum free-feeding weight for the duration of the experiment.

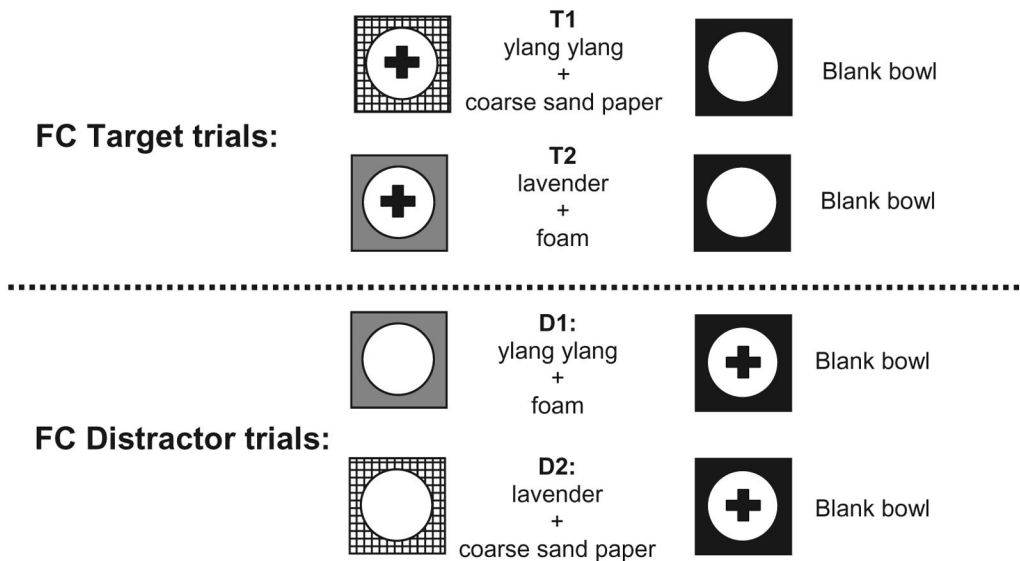


Figure 3. Feature-conjunction (FC) Stimulus Set 1 used in Experiments 1 and 2. On every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. On FC target (T1, T2) trials, the reward (+) was buried in the odor–texture bowl, and on FC distractor (D1, D2) trials, the reward (+) was buried in the blank bowl. The same reward contingencies were used for all FC stimulus sets.

Table 1
Temporal Structure of Experiments

Forced-choice digging tasks with equal no. of target and distractor trials		
Experiment	Task	No. trials per session
1	Baseline acquisition	14
	Feature-conjunction acquisition	16 (4 baseline + 12 feature conjunction)
	Feature-conjunction acquisition under drug	16 (4 baseline + 12 feature conjunction)
2	Feature-conjunction retrieval under drug	16 (4 baseline + 12 feature conjunction)
3	Feature-singleton acquisition under drug	16 (4 baseline + 12 feature conjunction)

Apparatus

The training environment was a black Plexiglas chamber 30.5 cm high \times 76.2 cm long \times 45.7 cm wide. A black slide-in-door of the same material separated the chamber into two compartments. The door was positioned 25.4 cm from the back wall of the chamber creating a "start box" (25.4 cm long \times 45.7 cm wide) and a "testing arena" (50.8 cm long \times 45.7 cm wide). The experimental room was illuminated by a single 60-W lightbulb. The digging apparatus was positioned on a table next to a computer equipped with speakers that emitted white noise and ambient voices to mask any extraneous noises.

Pharmacology

A within-subject blinded pharmacological design was used such that the same rats were used throughout all three experiments and each rat participated in each of three drug conditions: scopolamine hydrobromide (0.2 mg/kg dissolved in normal 0.9% physiological saline, pH 7.4), scopolamine methylbromide/methylscopolamine (peripheral nervous system control, 0.2 mg/kg), and physiological saline (injection control). Thus, any change in behavior under the influence of scopolamine implicated central cholinergic processes at muscarinic receptors. This dosage of scopolamine was chosen to reveal cognitive impairments with limited changes to motor function and motivation (Dawson & Iversen, 1993; De Rosa & Hasselmo, 2000; Doty, Bagla, Misra, Mueller, & Kerr, 2003; Dunnett, 1985). Rats were given intraperitoneal (IP) injections of the appropriate solution 15 min prior to testing; the experimenter was unaware of which drug was being given. We used a within-subject experimental design; thus, the same rats were tested in all three drug conditions and in all three experiments. To illustrate the strength of our within-subject design, we have included both the effect size (measured by η^2) and power associated with the effect of scopolamine on feature binding.

Odor–Texture Stimulus Bowls

Thirteen copper bowls painted matte black, 4 cm deep and 8 cm in diameter, were used. Each bowl was attached to a heavy 10-cm², 4-mm-thick black metal base. The outside surface, rim, and metal base of 12 bowls were covered by a textured cloth with silicon glue, which allowed for the easy removal of the textures. To minimize the tendency for rats to use visual cues to discriminate the textures, all textures were various shades of brown. Cotton gauze was placed inside 12 metal caps, 3.8 cm in diameter and 1.1 cm high. Each cap contained 32 small holes, 3 mm in diameter. A

cap was glued with silicon to the inside bottom of the 12 textured bowls. At the beginning of each training day and after the first 4 rats completed their sessions, the gauze was injected with 0.1 ml of the appropriate scented mineral oil (Aveda, Blain, MN; The Body Shop, Wake Forest, NC). Before bowls were reused, they were thoroughly soaked in rubbing alcohol for three days to remove any lingering odor.

Bowls were filled approximately three quarters of the way full of the granular commercial bedding Bed-o’cobs (The Andersons, Maumee, OH) mixed with finely ground pieces of Froot Loops (Kellogg’s) sweetened cereal to mask the location of a Froot Loop reward. The rewarded bowl contained a half Froot Loop buried approximately two thirds of the way down into the bowl.

Baseline Stimuli

On every trial, rats were simultaneously presented with two digging bowls: a cross-modal odor–texture bowl covered with a texture and scented with an odor and a blank bowl with no odor or texture component. We used these two digging bowls to create a forced-choice paradigm with two trial types: target and distractor. The baseline stimuli served as an introduction to the different responses needed for these two trial types without the need for feature binding. That is, rats should dig for a reward in the odor–texture bowl on target trials and dig for a reward in the blank bowl on distractor trials. Once the rats acquired the correct response mapping for target and distractor trials, the baseline stimuli were presented on the first 4 trials of all subsequent FC and FS sessions to measure the effect of the drug on general stimulus discrimination and digging performance. Figure 2 illustrates the two baseline odor–texture stimulus bowls (B1 and B2; see description below) used throughout all three experiments. Rats could use odor, texture, or the combination to discriminate the baseline stimuli as each was characterized by a distinct odor and texture. One of the baseline stimulus bowls (B1) was designated a target and was presented on target trials in which the reward was buried in the odor–texture bowl while the blank bowl was unrewarded. The remaining baseline stimulus bowl (B2) was designated a distractor and was presented on distractor trials in which the reward was buried in the blank bowl while the odor–texture bowl was unrewarded.

Feature-Conjunction Stimuli

Each FC stimulus set contained four conjunction odor–texture stimulus bowls. Two of the four stimulus bowls were designated

targets (T1 and T2) and were presented on target trials in which the reward was buried in the odor–texture bowl while the blank bowl was unrewarded. The remaining two odor–texture stimulus bowls were designated distractors (D1 and D2) and were presented on distractor trials in which the reward was buried in the blank bowl while the odor–texture bowl was unrewarded. Figure 3 illustrates FC Stimulus Set 1, the learning-to-learn set, which rats acquired drug-free for the purpose of acquiring the concept of feature binding. The binding of odor and texture cues was required to discriminate the FC stimuli because each was characterized by overlapping odor–texture features such that each odor and texture element was associated with two different digging responses (dig in odor–texture bowl or dig in blank bowl) equally often. Rats acquired three novel FC stimulus sets (Sets 2–4) under the three different drug conditions. FC Stimulus Sets 2–4 used the following odors and textures: Set 2 included chamomile, cinnamon, silk, and plastic netting; Set 3 included frankincense, peppermint, low-pile carpet, and rubber; Set 4 included tea tree, tangerine, terry cloth, and packing tape.

Training Procedures

Habituation. The testing arena portion of the digging apparatus was baited with two whole Froot Loops, and rats were allowed to explore the apparatus until they consumed at least one of the treats.

Pretraining. For 2 days, rats were trained to dig for single whole Froot Loops buried at the bottom of an aluminum metal food bowl in their home cages. Sessions lasted approximately 1 hr. The bowls used in their home cages were different from those used during subsequent experimental training in the testing arena and measured 4 cm deep and 8 cm in diameter.

Forced-choice training procedures. On every trial, rats were simultaneously presented with two digging bowls in the testing arena: an odor–texture bowl and the blank bowl. The odor–texture bowl was rewarded half of the time (target trials), and the blank bowl was rewarded half of the time (distractor trials). Rats had to use the odor–texture features of the presented stimulus bowl to determine where the reward would be found. Figure 1A illustrates the two different trial types, target and distractor, and Figure 1B illustrates a typical session.

At the start of a session, rats were placed in the start box of the apparatus with the sliding door closed. During this time, the appropriate bowl was baited with a single half Froot Loop and placed beside the unrewarded bowl in the testing arena of the apparatus. Given the initial strategy of rats to dig in the blank bowl, odor–texture bowls were always placed directly in front and flush against the blank bowl to aid acquisition of target trials. The blank bowl was always positioned in the back left corner of the chamber. This configuration was used throughout all three experiments. The sliding door was then lifted, and the rat was allowed to make a bowl choice, after which it was gently pushed into the start box and allowed to eat the Froot Loop (if obtained) with the door closed. A choice was defined as a dig if one or both paws displaced the bedding of the chosen bowl, or if a rat put its nose halfway down into the bedding. Rats remained in the start box between trials while the bowls were re-baited and replaced, which took, on average, 30 s. The first few sessions were always discovery sessions, during which rats were allowed to make as many

choices as necessary to find the buried reward, but only the first bowl choice counted toward accuracy. During all remaining sessions, rats were only allowed to make a single bowl choice. If rats did not make a choice within 2–3 min, then the Froot Loop was removed and placed on top of the bedding of the rewarded bowl for the rat to find and consume in the start box. In between sessions, any bedding that accumulated in the apparatus was vacuumed up, and the walls and floor of the apparatus were wiped down with rubbing alcohol.

Acquisition of baseline stimuli. On every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. On target baseline trials, rats were trained to dig in target baseline bowl B1 when it was presented along with the blank bowl, whereas on distractor baseline trials, rats were trained to dig in the blank bowl when presented along with distractor baseline bowl B2 (Figure 2). Rats could use odor, texture, or the combination to discriminate the baseline stimuli. The first three sessions of training were discovery sessions, during which rats were allowed to make as many choices as necessary to find the buried reward, but only the first bowl choice counted toward accuracy. During all remaining sessions, rats were only allowed to make a single bowl choice. Rats received one session per day. Baseline sessions consisted of 14 trials, half of which were target trials and the remaining half of which were distractor trials, presented in a pseudorandom order such that no more than 3 consecutive trials of the same type occurred in a session. Baseline training continued until the last rat reached a criterion of at least 6 out of 7 correct target responses and 6 out of 7 correct distractor responses for two 14-trial sessions.

Acquisition of the feature-conjunction stimuli. After the final baseline training session, in the subsequent session rats began feature binding training on the FC task with FC Stimulus Set 1, the “learning-to-learn” stimulus set (Figure 3). Again, on every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. On FC target trials, rats were trained to dig in two target bowls (T1 and T2) when either of the two was presented along with the blank bowl, whereas on FC distractor trials, rats were trained to dig in the blank bowl when presented along with either of two distractor bowls (D1 and D2). Rats received one session per day. An FC session consisted of 16 trials, the first 4 of which were baseline trials (2 target and 2 distractor trials) identical to those described above. The remaining 12 trials of a session were 6 FC target trials (3 T1, 3 T2) and 6 FC distractor trials (3 D1, 3 D2) presented in a pseudorandom order, such that no more than 3 consecutive trials of the same type (target or distractor) occurred in a session. The first six sessions were discovery sessions, during which rats were allowed to make as many choices as necessary to find the buried reward, but only the first bowl choice counted toward accuracy. During all remaining sessions, rats were allowed to make only a single bowl choice. Only during training on this initial learning-to-learn stimulus set did rats receive correction trials in which an incorrect response was always followed by the same trial until a correct choice was made. Correction trials did not count toward accuracy. FC training continued until the last rat reached a criterion of at least 5 out of 6 correct FC target responses and 5 out of 6 correct FC distractor responses for two 16-trial sessions.

Acquisition of the feature-conjunction stimuli under drug. After the final FC Stimulus Set 1 training session, in the subse-

quent session, rats began training on the FC task under drug using three novel FC stimulus sets (FC Stimulus Sets 2–4). Because this was a within-subject design, each rat received each drug (saline, methylscopolamine, or scopolamine). The sequence of drug conditions was counterbalanced across rats and across stimulus sets such that all three drug conditions were represented within each stimulus set. Under each drug condition, rats received nine acquisition sessions identical to the FC training sessions described above, and no correction trials were given. Rats received one session per day. The first three sessions were discovery sessions, during which rats were allowed to make as many choices as necessary to find the buried reward, but only the first bowl choice counted toward accuracy. During all remaining sessions, rats were allowed to make only a single bowl choice. Additionally, to ensure that no performance deficits were carried across drug conditions, rats were given two drug-free FC retraining sessions prior to switching drug conditions. Thus, there was a 2-day delay between drug conditions.

Statistical Analysis

For all of our experiments, task accuracy was assessed with proportion of correct responses. Accuracy was submitted to a three-way repeated measures analysis of variance (ANOVA) that contained three within-subject variables: trial type (target or distractor), session, and drug condition (physiological saline, methylscopolamine, or scopolamine). Separate ANOVAs were conducted on the behavioral data for (a) acquisition of the baseline stimuli, (b) acquisition of the FC stimuli, (c) acquisition of the FC stimuli under drug, (d) retrieval of the FC stimuli under drug, and (e) acquisition of the FS stimuli under drug. All statistical analyses were completed with SPSS, with an alpha level of .05.

Results

Initial Drug-Free Training

Rats required 11 sessions to reach criterion performance on the baseline task and 18 sessions to reach criterion performance on the FC task using the learning-to-learn FC Stimulus Set 1.

Acquisition of the Feature-Conjunction Stimuli Under Drug

Figure 4 depicts the acquisition of FC Stimulus Sets 2–4 under each drug condition, with accuracy separated into target and distractor trials. Acquisition data were binned into three blocks of three sessions, with accuracy averaged across rats. The dotted line corresponds to chance-level (50%) performance. As can be seen from the left-hand portion of Figure 4, the target-trial acquisition of rats was impaired under scopolamine. Only under methylscopolamine and saline did rats reach criterion performance on the FC task by the final block of training. This was confirmed by a three-way repeated-measures ANOVA with trial type (FC target or FC distractor), drug condition, and block as within-subject variables. The ANOVA revealed significant within-subject main effects of drug condition, $F(2, 14) = 32.92, p < .001$, block, $F(1.23, 8.63) = 148.66, p < .001$, and trial type $F(1, 7) = 86.52, p < .001$. A significant Trial Type \times Drug Condition interaction, $F(2, 14) = 10.27, p < .01$, as well as a significant Trial Type \times Block interaction, $F(2, 14) = 18.91, p < .001$, were also found. Notably, both the power and eta squared (estimate of effect size) values associated with the main effect of drug condition were very high, 0.961 and 0.825, respectively. The high power value revealed that we had designed a task that had a 96% probability of finding a scopolamine-induced impairment on feature binding, if such an effect existed. The effect size demonstrated that the strength of the

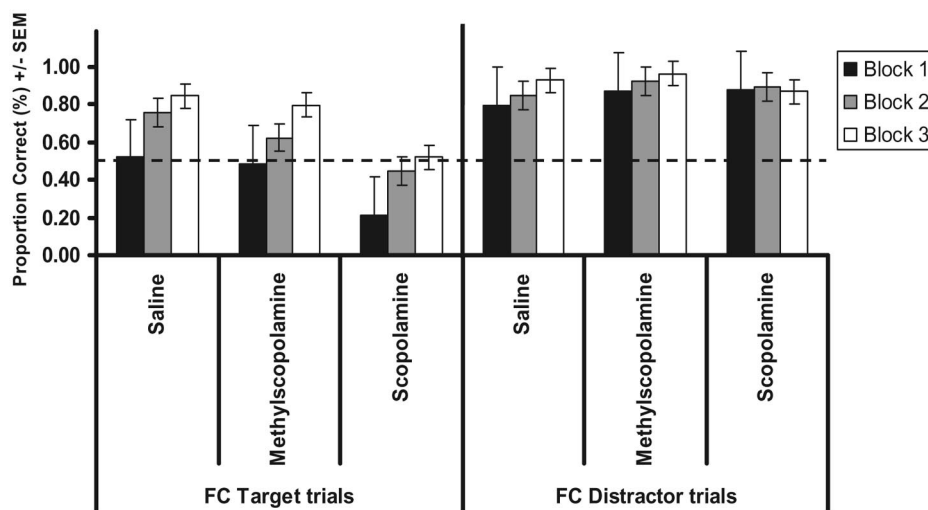


Figure 4. Feature-conjunction (FC) stimulus sets 2–4 acquisition under drug in Experiment 1. Accuracy was separated into target and distractor trials for each drug condition and binned into blocks of three sessions. Accuracy was averaged across rats, with standard error illustrated. The dotted line corresponds to chance-level (50%) performance. SEM = standard error of the mean.

relationship between scopolamine and the reduced ability to feature bind was 83% for this particular sample.

Two separate two-way repeated measures ANOVAs were conducted on FC target-trial and FC distractor-trial acquisition, with drug condition and block as within-subject variables. The distractor-trial ANOVA only revealed a significant within-subject main effect of block, $F(2, 14) = 4.55, p < .05$. The target-trial ANOVA revealed significant within-subject main effects of drug condition, $F(2, 14) = 25.60, p < .001$, and block, $F(2, 14) = 92.57, p < .001$, indicating that irrespective of drug condition, all rats improved on target trials across training. Notably, under scopolamine, the target-trial acquisition of rats was significantly impaired. This was confirmed with within-subject simple contrasts, which revealed significant differences between the target-trial accuracy of rats under saline versus scopolamine ($p < .01$) and under methylscopolamine versus scopolamine ($p < .01$), but no significant difference between target-trial accuracy of rats under saline versus methylscopolamine during the final block of acquisition.

A one-way repeated measures ANOVA on baseline performance revealed nonsignificant within-subject main effects of drug condition and block.

Drug-Free Retraining

All rats reached criterion performance on the FC task (Stimulus Sets 2–4) during the two drug-free retraining sessions that immediately followed each drug condition. A three-way repeated measures ANOVA, with trial type (FC target or FC distractor), previous drug condition, and session as within-subject variables, revealed a significant within-subject main effect of trial type, $F(1, 7) = 13.13, p < .01$, but no significant main effects of previous drug condition or session and no significant interactions. The average target-trial accuracy collapsed across the two retraining sessions was 86%, 86%, and 83%, and the average distractor-trial accuracy collapsed across the two retraining sessions was 99%, 95%, and 95% for rats previously trained under saline, methylscopolamine, and scopolamine, respectively.

Discussion

It is generally accepted by the human cognitive literature that feature binding requires the allocation of attentional resources (Treisman, 1998). Experiment 1 suggests that the cortical muscarinic cholinergic system may play a critical role in feature binding, as evidenced by rats' significantly impaired performance when acquiring the FC task under the influence of scopolamine. By the final block of FC training (Stimulus Sets 2–4), only under saline and methylscopolamine did rats become proficient at FC target trials. As is discussed in greater detail in the General Discussion, we contend that scopolamine caused an attentional impairment that decreased the efficiency of sensory information processing needed for proficient feature binding. Indicative of a scopolamine-induced attentional impairment, removal of drug during retraining resulted in a full rebound in FC performance in rats previously trained under scopolamine. If scopolamine's influence was mnemonic in nature, rats should have required a greater number of drug-free retraining sessions following acquisition under scopolamine to acquire the task. However, this was not the case, as almost all rats

reached criterion performance immediately on the FC task during drug-free retraining.

Observational data revealed that while rats under the influence of scopolamine were acquiring the FC task, they would repeatedly (5–10 times) sample (smell and whisk their vibrissae) the odor–texture and blank bowls during each trial until finally resorting to a dig in the blank bowl. This resulted in their initial below-chance performance on FC target trials. Rats under methylscopolamine and saline did not demonstrate such repeated-sampling behavior, further suggesting that only under scopolamine did rats have difficulty binding the multiple features of the FC stimuli.

Overall, the results of Experiment 1 suggest a role for the cortical muscarinic cholinergic system in feature binding. However, whether cortical muscarinic neurotransmission is critical for the acquisition of feature binding cannot be concluded until its effect on the acquisition of a single feature is determined. Experiment 3 will investigate the influence of the cortical muscarinic system on the encoding of single features.

Experiment 2: Feature-Conjunction Retrieval

A series of human studies have been conducted suggesting that while encoding is a highly controlled process requiring substantial attentional resources, retrieval may occur relatively automatically with minimal attentional requirements (Craik, Govoni, Naveh-Benjamin, & Anderson, 1996; Iidaka, Anderson, Kapur, Cabeza, & Craik, 2000; Naveh-Benjamin, Craik, Perretta, & Tonev, 2000). Experiment 2 set out to further investigate the role ACh plays in feature binding by distinguishing between the encoding and retrieval stages. During encoding, ACh enhances attention to incoming sensory signals by increasing the signal-to-noise ratio (Everitt & Robbins, 1997; Sarter, Hasselmo, Bruno, & Givens, 2005). Nonhuman animal studies have demonstrated that high cortical ACh levels facilitate the encoding of new information but not the retrieval of previously learned information (Everitt & Robbins, 1997; Hasselmo & McGaughy, 2004; White & Ruske, 2002). Mirroring the importance of attention and ACh for encoding, but not retrieval, we hypothesized that scopolamine should have no impact on the retrieval of the learning-to-learn FC stimulus set acquired during Experiment 1 because the odor–texture features had been previously bound.

Method

Subjects, Apparatus, Feature-Conjunction Stimuli, and Pharmacology

The subjects, apparatus, feature-conjunction stimuli, and pharmacology are identical to those of Experiment 1.

Retrieval of the Feature-Conjunction Stimuli Under Drug

After the completion of Experiment 1, we assessed the ability of rats to retrieve under drug the learning-to-learn FC Stimulus Set 1 (Figure 3) acquired during Experiment 1. Rats received two FC retrieval sessions under each drug condition. Retrieval sessions were identical to the FC training sessions described in Experiment 1, and no correction trials were given. Rats received one session per day. The first 4 trials of a retrieval session were baseline trials, consisting of 2 target and 2 distractor baseline trials. The remain-

ing 12 trials of a session were 6 FC target (3 T1, 3 T2) trials and 6 FC distractor (3 D1, 3 D2) trials, presented in a pseudorandom order, such that no more than 3 consecutive trials of the same type (target or distractor) occurred in a session. Unlike Experiment 1, peak performance was demonstrated by rats under all three drug conditions during retrieval of the FC task in Experiment 2. Thus, rats required only a single drug-free FC Stimulus Set 1 retraining session prior to switching drug conditions. Thus, there was a 1-day delay between drug conditions.

Results

Retrieval of the Feature-Conjunction Stimuli Under Drug

Figure 5 depicts FC Stimulus Set 1 (Figure 3) retrieval under each drug condition, with accuracy separated into target and distractor trials. The two retrieval sessions have been binned into a single retrieval block, with accuracy averaged across rats. As can be seen from Figure 5, rats maintained criterion performance on the FC task under all three drug conditions. This was confirmed by a three-way repeated measures ANOVA, with trial type (FC target or FC distractor), drug condition (saline, methylscopolamine, or scopolamine), and session as within-subject variables, which revealed nonsignificant within-subject main effects of drug condition and session. A significant within-subject main effect of trial type, $F(1, 7) = 81.89, p < .001$, was found. A one-way repeated measures ANOVA on baseline performance revealed nonsignificant within-subject main effects of drug condition and block.

Drug-Free Retraining

All rats maintained criterion performance on the FC task (Stimulus Set 1) during the single drug-free retraining session that followed each drug condition. A two-way repeated measures ANOVA, with trial type (FC target or FC distractor) and previous drug condition as within-subject variables, revealed no significant main effects or interactions. During retraining, the average target

trial accuracy was 92%, 98%, and 94%, and the average distractor-trial accuracy was 96%, 94%, and 98% for rats previously tested under saline, methylscopolamine, and scopolamine, respectively.

Discussion

Rats were fully capable of retrieving the FC task under all three drug conditions, indicating that blockade of the cortical cholinergic muscarinic system does not impair the ability of rats to retrieve previously bound FC stimuli. This suggests that following successful binding of a conjunction stimulus, a unified neural representation is formed, thereby eliminating the need for an online and attention-dependent feature binding process during retrieval.

Experiment 3: Feature-Singleton Acquisition

Human behavioral, neuroimaging, and neuropsychological evidence suggests that nonconjunction tasks requiring the encoding of single features do not require attention (Corbetta et al., 1995; Foster et al., 1999; Luck & Ford, 1998; Tales et al., 2002; Treisman, 1998; Treisman & Gelade, 1980). We thus hypothesized that ACh would not be necessary for the acquisition of a feature-singleton task. Our FC task required four odor–texture associations; thus, we took care to give rats four odor–texture associations in our FS task, but without the requirement of feature binding. The FS task was comparable to the feature-encoding tasks used in the human literature, in that rats could use just one feature for discrimination, as each FS stimulus bowl was characterized by a distinct odor and texture (Figure 6). If scopolamine does not impair the ability of rats to encode single features in the FS task, this would provide the critical evidence needed to conclude that the scopolamine-induced FC acquisition impairment found in Experiment 1 was due to the detrimental impact of cortical muscarinic blockade on feature binding.

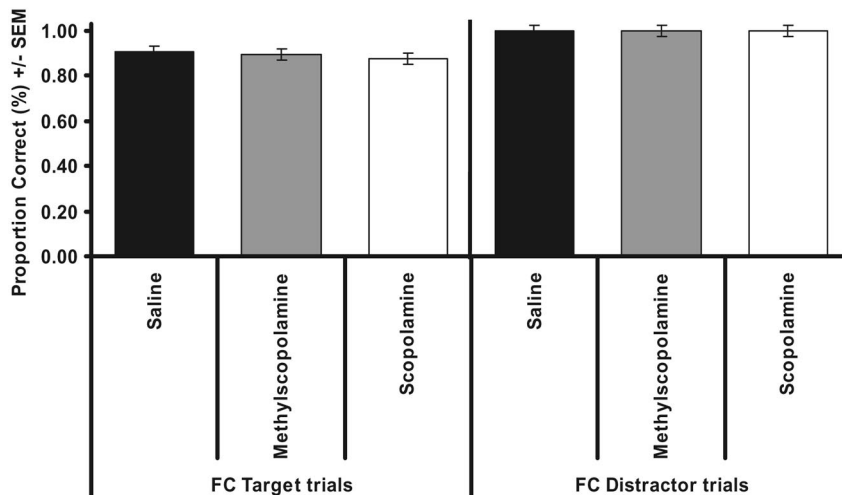


Figure 5. Feature-conjunction (FC) Stimulus Set 1 retrieval under drug in Experiment 2. Accuracy was separated into target and distractor trials for each drug condition collapsed across session. Accuracy was averaged across rats with standard error illustrated. SEM = standard error of the mean.

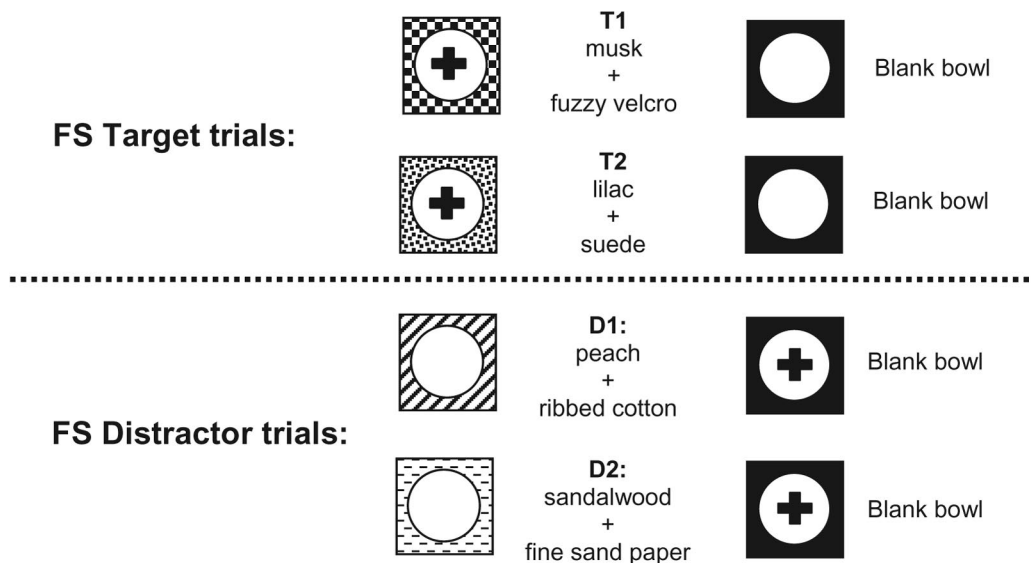


Figure 6. Feature-singleton (FS) Stimulus Set 1 used in Experiment 3. On every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. On FS target (T1, T2) trials, the reward (+) was buried in the odor–texture bowl and on FS distractor (D1, D2) trials, the reward (+) was buried in the blank bowl. The same reward contingencies were used for all FS stimulus sets.

Method

Subjects, Apparatus, and Pharmacology

The subjects, apparatus, and pharmacology are identical to those of Experiments 1 and 2.

Feature-Singleton Stimuli

Figure 6 illustrates the first of three FS stimulus sets. Each set contained four nonconjunction odor–texture stimulus bowls. As was the case in the FC task, on every trial, rats were simultaneously presented with two digging bowls: an odor–texture bowl and the blank bowl. Two of the four stimulus bowls were designated targets (T1 and T2) and were presented on target trials in which the reward was buried in the odor–texture bowl while the blank bowl was unrewarded. The remaining two nonconjunction odor–texture stimulus bowls were designated distractors (D1 and D2) and were presented on distractor trials in which the reward was buried in the blank bowl while the odor–texture bowl was unrewarded. Rats had to use the odor–texture features of the presented stimulus bowl to determine where the reward would be found. Each FS target and distractor bowl was characterized by a distinct odor and texture so that rats could use odor, texture, or the combination for discrimination. FS Stimulus Sets 2 and 3 used the following odors and textures: Set 2 included rose, jasmine, eucalyptus, tobacco flower, rippled chiffon, velvet, duct tape, and rough Velcro; Set 3 included strawberry, vanilla, bergamot, passion fruit, textured chiffon, ribbed cardboard, fine mesh, and smooth cotton.

Acquisition of the Feature-Singleton Stimuli Under Drug

Following the completion of Experiment 2, rats began training on the FS task under drug across three FS stimulus sets. Rats

received one session per day. Using within-subject pharmacological counterbalancing identical to Experiment 1, we administered six acquisition sessions to rats under each drug condition, with the first three sessions being discovery sessions. Discovery sessions allowed rats to make as many choices as necessary to find the buried reward, but only the first bowl choice counted toward accuracy. During all remaining sessions, rats were allowed to make only a single bowl choice, and no correction trials were given. An FS session consisted of 16 trials, the first 4 of which were baseline trials (2 target and 2 distractor trials) using the same baseline stimuli (B1 and B2) used in Experiments 1 and 2. The remaining 12 trials of a session were 6 FS target trials (3 T1, 3 T2) and 6 FS distractor trials (3 D1, 3 D2) presented in a pseudorandom order, such that no more than 3 consecutive trials of the same type (target or distractor) occurred in a session. All rats were given two drug-free FS retraining sessions prior to switching drug conditions using the appropriate stimulus set. Thus, there was a 2-day delay between drug conditions.

Results

Acquisition of the Feature-Singleton Stimuli Under Drug

Figure 7 depicts the acquisition of three FS stimulus sets under each drug condition, with accuracy separated into target and distractor trials. Acquisition data have been binned into two blocks of three sessions, with accuracy averaged across rats. The dotted line corresponds to chance-level (50%) performance. As can be seen from Figure 7, rats met criterion on the FS task under all three drug conditions by the final block of training. This was confirmed by a three-way repeated measures ANOVA, with trial type (FS target or FS distractor), drug condition (saline, methylscopolamine, or scopolamine), and block as within-subject variables, which revealed a nonsignificant within-subject main effect of drug condition. Sig-

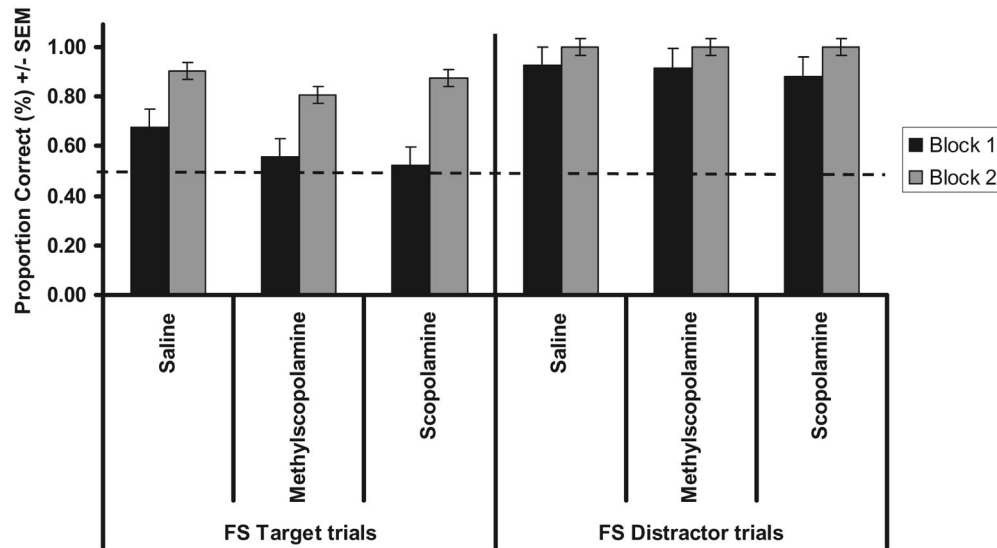


Figure 7. Feature-singleton (FS) Stimulus Sets 1–3 acquisition under drug in Experiment 3. Accuracy was separated into target and distractor trials for each drug condition and binned into blocks of three sessions. Accuracy was averaged across rats, with standard error illustrated. The dotted line corresponds to chance-level (50%) performance. SEM = standard error of the mean.

nificant within-subject main effects of block, $F(1, 7) = 235.37$, $p < .001$, and trial type, $F(1, 7) = 177.67$, $p < .001$, as well as a significant within-subject Trial Type \times Block interaction, $F(1, 7) = 34.16$, $p < .01$, were found. A one-way repeated measures ANOVA on baseline performance revealed nonsignificant within-subject main effects of drug condition and block.

Drug-Free Retraining

All rats maintained criterion performance on the FS task (Stimulus Sets 1–3) during the two drug-free retraining sessions that immediately followed each drug condition. A three-way repeated-measures ANOVA, with trial type (FS target or FS distractor), previous drug condition, and session as within-subject variables, revealed a significant within-subject main effect of trial type, $F(1, 7) = 28.46$, $p < .01$, but no significant main effects of previous drug condition or session and no significant interactions. The average target-trial accuracy collapsed across the two retraining sessions was 95%, 89%, and 92% for rats previously trained under saline, methylscopolamine, and scopolamine, respectively. The average distractor-trial accuracy collapsed across the two retraining sessions was 100% for rats previously trained under all three drug conditions.

Discussion

Rats were fully capable of acquiring the FS task under all three drug conditions, indicating that cortical cholinergic muscarinic blockade does not impair the ability of rats to encode single features. This is consistent with human evidence suggesting that tasks solely dependent on the encoding of single features are not attention dependent (Corbetta et al., 1995; Foster et al., 1999; Friedman-Hill et al., 1995; Luck & Ford, 1998; Tales et al., 2002; Treisman, 1991, 1998; Treisman & Gelade, 1980). Experiment 3

thus provides the critical evidence needed to conclude that cortical muscarinic neurotransmission is essential for feature binding during encoding (Experiment 1) but is not required for the encoding of single features.

General Discussion

Whereas rats were selectively impaired at acquiring the feature binding FC task under the influence of scopolamine (Experiment 1), they were fully capable of retrieving the FC stimuli (Experiment 2) and encoding single features in the FS task (Experiment 3) under all three drug conditions. These latter two findings demonstrate that scopolamine did not impair the ability of rats to discriminate odors and textures. Our within-subject pharmacological design has allowed us to factor out the influence of subject variability across drug conditions, and the use of methylscopolamine as a control substance has allowed us to rule out the influence of any scopolamine-induced peripheral effects on task performance. Thus, this scopolamine-induced impairment in feature binding was due to blockade of cortical muscarinic cholinergic receptors. To our knowledge, this study is the first to implicate a selective role for the muscarinic cholinergic system in the cognitive process of cross-modal feature binding.

We have demonstrated the importance of ACh to the initial feature-binding process and have dissociated it from its role in the retrieval of previously bound conjunction stimuli. Such a finding is consistent with the considerable body of memory research suggesting that blockade of the cortical muscarinic cholinergic system selectively impairs the encoding of new information while sparing the retrieval of previously learned information (Aigner, Walker, & Mishkin, 1991; Anagnostaras, Maren, & Fanselow, 1995; Bartus & Johnson, 1976; Conner, Culbertson, Packowski, Chiba, & Tuszynski, 2003; Everitt & Robbins, 1997; Ghoneim & Mewaldt,

1977; Hasselmo & McGaughy, 2004; Kirk et al., 1988; Orsetti et al., 1996; Parkes & White, 2000; Rogers & Kesner, 2003; Safer & Allen, 1971; Schon et al., 2005; White & Ruske, 2002).

In a recent review article, a model was proposed of how an active cholinergic system is conducive to the encoding of new information, whereas a hypoactive cholinergic system is conducive to the consolidation and retrieval of previously learned information (Hasselmo & McGaughy, 2004). When there are high levels of cholinergic activity in the cortex, afferent input from external sensory stimuli is enhanced while intrinsic processing within cortices is reduced. Intrinsic processing is associated with the reactivation of neural connections representing previously learned information, and a reduction in such processing would prevent the recall of previously learned information from interfering with the encoding of new information, thereby enhancing the signal-to-noise ratio (SNR). This has been demonstrated by studies showing that scopolamine increased proactive interference from previously learned odor- and word-pair associations during the encoding of novel associations in nonhuman and human animals, respectively (Atri et al., 2004; De Rosa & Hasselmo, 2000).

ACh enhances attention by increasing the SNR of incoming sensory information (Everitt & Robbins, 1997; Hasselmo & McGaughy, 2004; Sarter & Bruno, 1997), and we propose that it is through an attentional mechanism that ACh facilitates feature binding at encoding. In Experiment 1, it was evident that scopolamine's influence was on attention, because following impaired FC acquisition under scopolamine, removal of the drug during retraining resulted in an immediate rebound in FC performance, as is seen when attentional demands are removed in human cognitive tasks (Craik et al., 1996). We contend that a scopolamine-induced attentional impairment decreased the efficiency of sensory information processing and in turn challenged rats' ability to encode and bind multiple features during acquisition of the FC task. In other words, scopolamine dampened the critical modulatory influence of ACh on feature binding.

There is a growing body of evidence that ACh is critical for various aspects of attention (Butt et al., 2002; Chiba et al., 1995; Chiba, Bushnell, Oshiro, & Gallagher, 1999; McGaughy, Kaiser, & Sarter, 1996; Mirza & Stolerman, 2000; Turchi & Sarter, 1997), and the hypoactive cortical muscarinic state indicative of Alzheimer's disease results in severe attentional impairments (Mesulam, 2004). Consistent with our finding of a crucial role for ACh in feature binding, Alzheimer's patients are impaired at feature-conjunction, but not feature-singleton detection and discrimination tasks (Foster et al., 1999; Tales et al., 2002). Furthermore, recent studies with healthy human participants have shown that indirectly boosting the muscarinic cholinergic system with caffeine improves visual feature binding (Colzato, Fagioli, Erasmus, & Hommel, 2005) while indirect suppression of the system with alcohol impairs such binding (Colzato, Erasmus, & Hommel, 2004).

Whereas the results of Experiment 1 demonstrate the vulnerability of the feature-binding encoding process to a scopolamine-induced attentional challenge, Experiment 2 demonstrates the immunity of the retrieval of previously bound conjunction stimuli to such a manipulation. This is consistent with previous research demonstrating that whereas disruption of attention with a concurrent continuous reaction time task performed at the time of encoding significantly reduced subsequent paired-associate memory performance in healthy human adults, the same divided-attention task

performed at the time of retrieval had no significant effect on memory performance (Craik et al., 1996; Iidaka et al., 2000; Naveh-Benjamin et al., 2000). Our findings suggest that once a conjunction stimulus has been successfully bound during acquisition, it becomes permanently bound in memory, eliminating the need for an online and attention-dependent feature-binding process during retrieval.

A scopolamine-induced attentional challenge did not impair acquisition of our FS task, as rats were fully capable of encoding single features during central muscarinic cholinergic receptor blockade. This is consistent with the human cognitive literature demonstrating that feature-conjunction encoding tasks are much more attentionally demanding than are feature-singleton encoding tasks (Bernstein & Robertson, 1998; Cohen & Rafal, 1991; Corbetta et al., 1995; Friedman-Hill et al., 1995; Luck & Ford, 1998; Reynolds & Desimone, 1999; Treisman, 1998; Treisman & Gelade, 1980). Healthy human participants are able to detect a visual target much more quickly when it differs from surrounding distractors by a single feature than when the target differs from distractors by multiple features (Treisman & Gelade, 1980). Consistent with such a finding, rats were able to acquire the FS task in fewer sessions than the FC task, irrespective of drug condition, which is reminiscent of the quicker reaction times demonstrated by human participants when performing feature-singleton versus feature-conjunction visual search tasks (Corbetta et al., 1995; Treisman & Gelade, 1980). Research conducted with functional imaging and event-related potentials has found attention-related cortical activity in parieto-occipital regions to be necessary for feature-conjunction visual discrimination but not feature-singleton detection (Corbetta et al., 1995; Luck & Ford, 1998). Furthermore, individuals with attentional deficits are selectively impaired at encoding feature conjunctions while their ability to encode single features remains intact (Bernstein & Robertson, 1998; Cinel, Humphreys, & Poli, 2002; Cohen & Rafal, 1991; Foster et al., 1999; Friedman-Hill et al., 1995; Treisman, 1998).

Such findings from the human cognitive literature suggest that feature binding does not require attention because it is more difficult but, rather, that it is more difficult because it requires attention. Treisman (1991) has shown that even after controlling for target-distractor similarity, which makes both feature-singleton and feature-conjunction visual search tasks more attentionally demanding (Carter, 1982; Duncan & Humphreys, 1989; Foldi et al., 2005; von Grunau, Dube, & Galera, 1980), feature binding in itself requires additional attentional resources over and above those needed for making fine discriminations.

It has been reasoned that the spatial proximity between to-be-bound neurons in the cortex determines whether modulation of the cortical muscarinic cholinergic system will have an effect on feature binding (Colzato et al., 2004, 2005). According to this hypothesis, when a conjunction stimulus is perceived, the neural discharges of the activated neurons are synchronized as the represented features are bound together (Engel & Singer, 2001). Although the spatial-proximity neural synchronization hypothesis predicts that ACh will exclusively modulate intramodal feature binding, our results reveal significant cholinergic contributions to cross-modal feature binding. It should be noted that in their original study, Colzato et al. (2004) only tested cross-modal binding between a sensory and a motor domain (vision and action), rather than binding between two different sensory modalities, as was

done in the present study. Furthermore, inconsistent with Colzato et al. (2004), Roelfsema, Engel, Konig, and Singer (1997) found the strength of neural synchronization between cortical areas to be more related to function than to spatial proximity.

Nonetheless, our results do not preclude a role for ACh in the modulation of feature binding via an enhancement of neural synchronization in the cortex. Selective spatial attention has been shown to enhance gamma-band synchronization in the human cortex during visual feature binding (Muller, Gruber, & Keil, 2000; Tiitinen et al., 1993). Furthermore, Rodriguez, Kallenbach, Singer, and Munk (2004) have shown that modulation of the cortical muscarinic cholinergic system affects gamma-band neural synchronization in the cat visual cortex (Engel, Kreiter, Konig, & Singer, 1991; Friedman-Hill et al., 2000; Gray & Singer, 1989). Thus, the attention and neural synchronization hypotheses of feature binding do not appear to be mutually exclusive, and further research is needed to understand their relationship to each other and to feature binding.

This systemic pharmacological study was an essential first step in establishing the contribution of ACh to the fundamental and attention-dependent cognitive process of feature binding. Furthermore, our data demonstrate that ACh is not required to maintain neural representations of bound stimuli but is essential for the initial feature-binding process. Future research must focus on uncovering the neural underpinnings of the involvement of ACh in feature binding. Use of this animal model will allow for the undertaking of lesion studies to determine which target brain structures cholinergic input must reach for successful feature binding to occur.

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