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Scopolamine Impairs Human Recognition Memory: Data and Modeling

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Eight subjects studied a set of complex visual images after administration of 0.4 mg scopolamine. Another 8 subjects performed the same task without drug administration. On a subsequent item recognition test, subjects rated, on a 5-point scale, their confidence that the studied pictures and an equal number of unstudied lures were actually presented. Results showed that scopolamine affected responses to studied items, but not unstudied lures, demonstrating an unambiguous effect of scopolamine on recognition memory. To describe the scopolamine-injected subjects' data, the authors constructed a new model of 2-process recognition that includes the A. P. Yonelinas (1994) model as a limiting case. The model analysis suggests that scopolamine affected both familiarity and recollection. In particular, scopolamine did not affect the frequency with which recollection took place, but rather, affected the amount of recollected information.

The neuromodulator acetylcholine plays an important role in memory. Numerous studies in human subjects have demonstrated that drugs that block muscarinic acetylcholine receptors cause impairments in memory for verbal (Ghoneim & Mewaldt, 1975; Peterson, 1977; Crow & Grove-White, 1973) and nonverbal (Flicker, Serby, & Ferris, 1990) stimuli. In monkeys, systemic or local infusions of scopolamine impair encoding of visual stimuli for subsequent recognition (Aigner & Mishkin, 1986; Tang, Mishkin, & Aigner, 1997). In rats, muscarinic blockade impairs the learning of platform location in the Morris water maze (Sutherland, Whishaw, & Regehr, 1982). The memory deficits in Alzheimer's disease may be associated with the loss of cholinergic cortical innervation (Perry, Gibson, Blessed, Perry, & Tomlinson, 1977), and the available clinical treatments for Alzheimer's disease are acetylcholinesterase inhibitors (Sugimoto, Yamanishi, Iimura, & Kawakami, 2000).

The experimental study of memory can largely be divided into recall tasks and recognition tasks. In recall tasks, subjects are required to produce stimuli, usually words, as evidence of their memory for the learning episode. In recognition tasks, subjects are presented with stimuli and must determine whether or not they were presented as part of the learning episode. Previous studies of muscarinic antagonist effects have found striking effects on the free recall of words. It is well known that items studied under the influence of scopolamine are harder to recall after a delay (Crow & Grove-White, 1973; Frith, Richardson, Samuel, Crow, & McKenna, 1984; Ghoneim & Mewaldt, 1975, 1977). Some authors have shown that immediate recall is spared (Crow & Grove-White, 1973; Ghoneim & Mewaldt, 1975; Safer & Allen, 1971), with the recall deficit only appearing after a delay of tens of seconds. Other studies show that scopolamine does not disrupt recall of items learned prior to the administration of scopolamine (Ghoneim & Mewaldt, 1977).

In contrast to the unambiguous evidence for a free-recall deficit with scopolamine, the evidence regarding scopolamine's effect on recognition is much less clear. Recognition impairments have been observed for recognition of visual stimuli in monkeys (Aigner & Mishkin, 1986; Tang et al., 1997). To this point, however, there is equivocal evidence for an effect of scopolamine on recognition memory in humans. Some recent studies (Richardson, Frith, Scott, Crow, & Cunningham-Owens, 1984; Mintzer & Griffiths, 2001) have observed a recognition deficit with scopolamine, but the use of lures that are semantically (Mintzer & Griffiths, 2001; Richardson et al., 1984) or phonologically (Richardson et al., 1984) related to list items makes it possible to interpret these results as a consequence of altered response bias in combination with semantic or perceptual confusion, rather than a purely mnemonic effect. Many previous studies tested recognition memory for items that had been studied and previously recalled under the influence of scopolamine (Beatty, Butters, & Janowsky, 1986; Ghoneim & Mewaldt, 1975, 1977). Subjects in those experiments were initially

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presented with a list of words, then tested for free recall of the list prior to the recognition test. The recognition test, in effect, tested not only on their memory for the original encoding event, but also on their memory for their performance on the recall tests. Because recalled words are reexperienced during these recall tests, later recognition memory should be improved by the act of recalling. Subjects administered scopolamine recall fewer words, so they would be expected to get less of a benefit from the recall test. Thus, the presence of a recall deficit could lead, by itself, to a recognition deficit when sequential testing is used. Despite this confound, several groups failed to observe a significant deficit in item recognition (Beatty et al., 1986; Ghoneim & Mewaldt, 1975), suggesting that scopolamine might have little or no effect on recognition memory (Hasselmo & Wyble, 1997).

Episodic Memory and Recognition

Episodic memory is defined as memory for specific events or experiences. As we experience the world, we attempt to interlink specific items or events to their corresponding spatiotemporal context. This is necessary for successful performance in episodic recall tasks, which are known to be affected by scopolamine. In typical episodic recall tasks (e.g., free recall), the individual items being encoded are not novel, but the experimental context, or situation, in which they were experienced is novel. The task, then, does not simply require memory for the specific items—all of the items are well known—but requires the subject to remember that the items were presented in a specific spatiotemporal context (Howard & Kahana, 1999, 2002).

Tulving (1983) characterized recognition memory as supported by two processes, familiarity and recollection. *Recollection,* or "remembering," is an episodic memory process that entails a conscious retrieval of a prior experience along with contextual information associated with that event. In contrast, *familiarity,* or "knowing" is a semantic process that does not rely on memory for spatial or temporal context. Episodic recall, which has been shown to be reliably affected by scopolamine, is closely related to recollection. Perhaps the reason that an item recognition deficit has been difficult to observe with scopolamine is that familiarity is relatively unaffected by scopolamine, and familiarity is sufficient to support near-normal performance in item recognition.

The idea that two processes support recognition memory has a long history (Atkinson & Juola, 1974; Mandler, 1980). Atkinson and Juola (1974) argued that an initial fast familiarity process can support recognition performance. Sometimes, however, a second, slower process is also engaged. This second process, similar to recall, involves a search through memory in an attempt to retrieve specific details of the event. Similarly, Mandler (1980) argued that prior experience with an item by itself facilitates subsequent perceptual analysis, leading to a general feeling of familiarity. Like Atkinson and Juola (1974), Mandler (1980) also argued that a search process like that involved in recall contributes to recognition performance. He introduced the idea that these two processes operate in parallel rather than in series, and that the medial temporal lobe should be specifically involved in recollection.

The Yonelinas High Threshold Model

Yonelinas (1994, 1999, 2001) has implemented dual process theory in a way that enables it to predict performance in multiple-response recognition. In multiple-response recognition subjects rate their confidence in having previously seen a test item rather than simply saying "yes" or "no" in response to recognition probes. The Yonelinas model assumes that old items (probes that were presented) give rise to a range of confidence ratings as a consequence of their familiarity. New items also give rise to some familiarity, but not as much as items from the prior list, which, by virtue of having been recently presented, are on average more familiar. In addition to the contribution from familiarity, recollection is assumed to take place for a subset of the old items. The qualitative nature of recollection is assumed to enable subjects to respond with certainty. Probes that cause recollection are assumed to exceed all possible response criteria, resulting in a highest confidence "yes" response. For this reason, we will refer to this formulation of dual process theory as the Yonelinas High Threshold model. The Yonelinas High Threshold model has been shown to successfully describe the distribution of confidence ratings under a variety of conditions (for a recent review, see Yonelinas, 2001).

Experiment 1

Previous results have suggested that episodic recall is specifically impaired following administration of scopolamine. There are no clear data, however, showing an effect of scopolamine on recognition. In the current experiment, we used a recognition task with multiple confidence ratings as responses to examine the effects of scopolamine on recollection and familiarity as defined by the Yonelinas High Threshold model. If episodic recall is selectively affected by scopolamine and episodic recall corresponds to recollection, then we predicted that scopolamine would impair recollective processes while producing a minimal effect on familiarity.

Method

Subjects. Eight subjects, 6 women and 2 men, participated in the scopolamine group. Their ages ranged from 19 to 25 ($M = 22.0 \pm 0.6$). These subjects were recruited from the Boston University student community to participate in a cognitive drug study. Their mean level of education was 15.6 ± 0.3 years. Respondents spoke to the study neurologist (Alireza Atri), who discussed with them the potential risks of participation and prescreened them by taking a detailed medical history. Exclusion criteria included a history of neurological or psychiatric conditions, recent physical illness, ongoing or recent use of psychoactive medications, medical contraindications to anticholinergics, or any medical condition that could potentially be exacerbated by administration of anticholinergic drugs. One subject was not enrolled on the basis of the medical exclusion criteria. Drug administration and cognitive testing took place in an exam room in the Neurology Clinic of Massachusetts General Hospital. Subjects administered scopolamine were paid $75 for their participation.

An additional eight subjects, six women and two men, served as behavioral controls. Behavioral controls were also recruited from the Boston University student community. Their ages ranged from 19 to 30 ($M = 22.0 \pm 1.5$). Their mean level of education was 15.1 ± 0.7 years. This did not differ significantly from the level of education of the scopolamine-injected group, $t(14) = 0.68$. Control subjects were excluded if they reported an existing psychological or neurological condition, or if they reported taking psychoactive medications. No control subjects were excluded on the basis of these criteria. Testing of control participants was conducted in a cognitive testing room at Boston University. Control participants were paid $30 for their participation. The study was approved

by institutional review boards at both Massachusetts General Hospital and Boston University.

Materials. The stimuli for the experiment consisted of complex visual scenes similar to those used in previous imaging studies of memory encoding (Kirchhoff, Wagner, Maril, & Stern, 2000; Stern, Sherman, Kirchhoff, & Hasselmo, 2001). The set of 604 stimuli contained equal numbers of pictures showing indoor and outdoor scenes.

Cognitive testing was administered with a Macintosh iBook computer. A four-key button box connected to the USB port of the machine was used to collect behavioral responses during the encoding phase of the experiment. Recognition testing was controlled with PsyScope (Cohen, MacWhinney, Flatt, & Provost, 1993).

Procedure. After providing informed consent, subjects in the scopolamine group underwent a detailed history, and general physical and neurological examinations. Each subjects' blood pressure, heart rate, respiratory rate, pupillary size and weight were recorded. In addition, female participants were administered a urine pregnancy test. Following this initial examination, subjects were administered 0.4 mg scopolamine (scopolamine hydrobromide, 0.4 mg/ml, American Pharmaceutical Partners, Los Angeles, CA) via intramuscular injection in the deltoid. The weights of the injected subjects ranged from 52 to 82 kg ($M = 68.8$). Cognitive testing began 90 min following injection. Prior work has shown that scopolamine has its maximal amnesic effect during this time period (Dundee & Pandit, 1972; Ebert, Siepmann, Oertel, Wesnes, & Kirch, 1998; Pandit & Dundee, 1970; Safer & Allen, 1971). Subjects were continuously monitored over the next 4 hr. They were periodically examined, with particular focus on their mental status, coordination, balance, and gait; and their blood pressures, heart rates, respiratory rates, and pupillary size changes were recorded.

A 300-picture subset of the picture pool was selected for presentation. Half of these pictures were indoor scenes, and the other half were outdoor scenes. Presentation of the pictures was divided into 10 study trials, each lasting 2.5 min. After the first 5 study trials, there was a 15-min break, during which the drug-injected subjects were examined.

All stimuli were presented for 2 s in the center of the computer screen, surrounded by a black background. The pictures occupied an area of 6.8 cm $\times$ 10.23 cm on the computer screen. Subjects sat with their faces approximately 30 cm from the screen.

Presentation of fixation crosses and repeated pictures were intermixed pseudorandomly with presentation of the 300 pictures in order to allow us to implement this design in a future functional magnetic resonance imaging study. Two pictures were repeated 75 times each during the first five trials. Another two pictures were repeated during the last five trials. The responses to these pictures are not analyzed here.

To minimize strategic effects, and to ensure that the drug-injected group was attending to the stimuli, an orienting task was used during the study. During the encoding phase, subjects were required to make an indoor-versus-outdoor discrimination for each picture by pressing one of two buttons on the button box. Subjects were instructed to make the indoor–outdoor discrimination as quickly as possible without sacrificing accuracy. They were also instructed to encode the pictures into memory in preparation for a subsequent memory test. All subjects were monitored during the orienting task, and verbal prompting was used as needed.

Following the last presentation trial there was a 15-min delay prior to the start of the recognition test. During this delay, the drug-injected subjects were reexamined by the study neurologist. During recognition testing, the entire set of 604 pictures was presented. Of these, 300 pictures had been presented once during study. Another 300 pictures were lures that had not been presented during study. The remaining 4 pictures had been presented multiple times during study. Responses to these repeated pictures were not analyzed. Subjects indicated whether each tested item was presented by pressing a number from 1 to 5 on the computer keyboard. A 1 response indicated that the subject was highly confident the test item was presented during the study phase. A 5 response indicated that the subject was highly confident that the test item was not presented during the study phase. Because we were concerned that a scale in which memory decreases with increasing numerical values was counterintuitive, for expository purposes, we will invert this scale for the remainder of this article. That is, high-confidence "yes" responses will be referred to as 5s and high-confidence no responses will be referred to as 1s, despite the fact that this does not correspond to the actual buttons the subjects pressed. Each picture remained on the screen until the subject made a valid response. We encouraged subjects to respond as quickly as possible without sacrificing accuracy. Scopolamine-injected subjects were observed for at least 5 hr postinjection. Following a final formal medical assessment, they were escorted home.

Results and Discussion

Drug side effects. All subjects injected with scopolamine were found to have pupillary dilation, and they reported mild or moderate dryness of the mouth and a perception of mild alteration in their cognitive and/or emotional state (nondysphoric). Five of the 8 participants injected with scopolamine also reported feeling mildly or moderately tired. These findings are expected side effects of scopolamine in this dose range (Safer & Allen, 1971). None of the subjects were found to have abnormal coordination or gait following drug administration.

Attentional effects. To determine whether scopolamine caused gross impairments in arousal, we examined performance on the orienting task. The accuracy of the control subjects was .957 $\pm$ .006. The scopolamine group's accuracy (.94 $\pm$ .01) did not differ from that of the control group, $t(14) = 1.4$, $p \simeq .20$. This argues that the scopolamine group was able to attend to the task and identify the pictures as well as the control group. Any observed memory deficits are therefore unlikely to be a consequence of gross attentional deficits for the subjects in the scopolamine group.

Recognition performance. Figure 1 shows response distributions to old and new items for control subjects and subjects receiving scopolamine. Qualitatively, the new item response distributions appear to be similar across groups. In contrast, the old item distributions appeared to be disrupted by scopolamine. To quantify these observations, we calculated a chi-square with the observed variance for both the old and new distributions. Although the new item distributions were not significantly different from each other, $\chi^2(4) = 0.68$, $p > .20$, the old distributions were significantly different from each other, $\chi^2(4) = 38$, $p < .001$. These data suggest that scopolamine disrupts item recognition.

To illustrate the difference between the effects of scopolamine on the new and old distributions, we performed regressions comparing response proportions of the scopolamine group to those of the control group for new and old items. The results of this regression are summarized in Figure 2. If there was no effect of scopolamine on the response distributions, then all of the points in the figure would lie on the diagonal. Specifically, if there was no difference between the groups, the slope of the regression line would be 1.0 and the intercept would be zero. The actual regression lines are shown in Figure 2. For the new items, the obtained slope of .9 $\pm$ .2 (the .2 here refers to the 95% confidence interval), was not significantly different from one. The intercept for the new items of .014 $\pm$ 0.04 was not different from zero, which is consistent with the null hypothesis. For the old items, the obtained slope of .5 $\pm$ .4 was significantly different from one and the intercept of 0.10 $\pm$ 0.095 was also significantly different from zero.

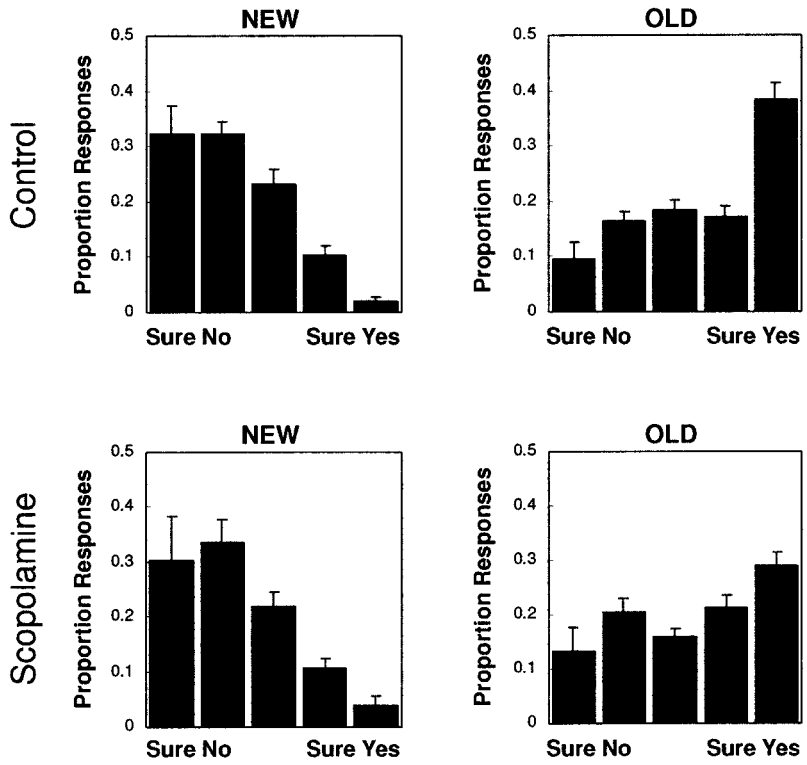

Figure 1. Response distributions. The left column shows the distributions of responses to new items (items not shown during encoding). The right column shows the distributions of responses to old items (items presented during encoding). The difference between the new and old distributions is attributable to memory. The top row shows response distributions for control subjects. The bottom row shows response distributions for subjects administered scopolamine. Error bars reflect *SE.*

Because scopolamine did not affect the new item distributions, this rules out several uninteresting explanations for the changes in recognition performance with scopolamine. For instance, if scopolamine had induced a change in response criteria, that is, a change in the meaning of a 2 response, then we would have expected to see a change in the new item distribution as well as the old item distribution. Similarly, if scopolamine had induced a change in the ability to visually discriminate the pictures, we would also have expected to see an effect on the new item distribution. The fact that we observed no

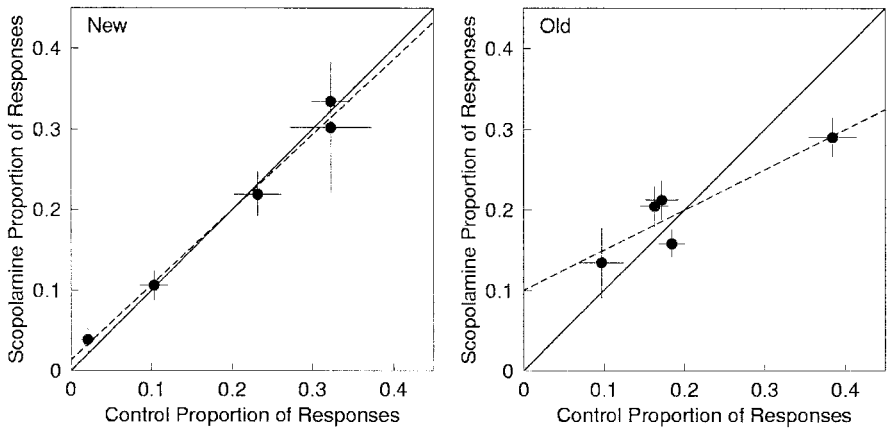

Figure 2. Scopolamine selectively disrupts confidence ratings of old items. This figure plots proportion of responses for the scopolamine group as a function of proportion of responses for the control group for each level of confidence. Error bars are ±1 *SE*. The left panel shows responses to new items; the right panel shows responses to old items. If the null hypothesis were true, all of these points would lie along the diagonal. The dashed lines show the results of the regression.

change in the new item distribution argues against these alternative explanations.

To provide stronger evidence that the results we observed were not a consequence of some change in criteria, we reanalyzed the data as *z*-ROC curves. In multiple-response recognition, the different responses presumably correspond to different response criteria, which should be the same for both new and old items. Plotting hits as a function of false alarms yields a *receiver operating characteristic* (ROC) curve. ROC curves have been extensively studied in signal detection theory (Macmillan & Creelman, 1991). Changes in response criteria alone should change the location of the observed data points, but should not change the shape of the underlying curve. If the hit and false alarm rates are transformed to a *z*-score, the result is a *z*-ROC curve. These functions have a number of well-understood properties. A linear *z*-ROC curve is consistent with normal distributions of strength for old and new items. A high-threshold "yes" process should cause a deviation from linearity as the curve inflects upward at very high criteria (i.e., on the left side of the curve), an effect that has been empirically observed (Yonelinas, 1994, 1997).

Figure 3 shows averaged *z*-ROC curves for control and scopolamine-injected subjects. As can be seen from the figure, scopolamine was associated with changes in *z*-ROC space. The data for scopolamine-injected subjects are shifted down on the *z*(Hits) axis relative to the control subjects' data. This indicates reduced discriminability for the subjects injected with scopolamine.

Qualitative effects of scopolamine. It is clear from the foregoing analyses that scopolamine-injected subjects showed a difference in their response distributions specifically for old items. The old item response distribution from control subjects showed an apparently bimodal distribution, with one peak toward the center of the response continuum and another peak lying entirely on the "sure yes" response.[1] The old item response distribution for the scopolamine-injected subjects also appears bimodal. However, both of the peaks appear altered relative to the control group. The central peak (presumably corresponding to familiarity) is centered lower on the confidence axis than the corresponding peak from control subjects. The high-confidence peak (presumably corresponding to recollection) appears "spread" across multiple responses, rather than being restricted to the highest confidence "yes" response.

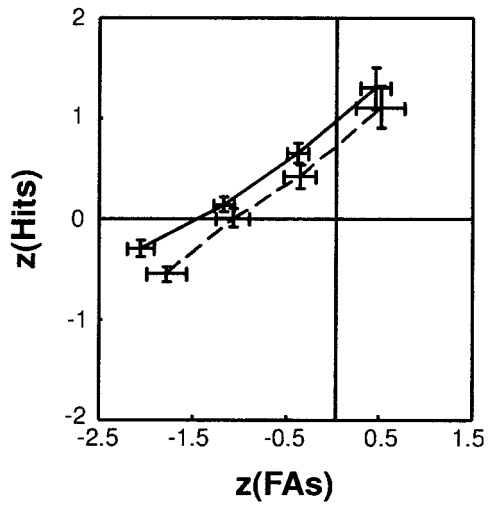

Figure 3. Response distributions replotted as *z*-transformed receiver operating characteristic (*z*-ROC) curves. To construct a *z*-ROC curve from a response distribution, the hit rate and false alarm (FA) rate for each of the four criteria are first calculated. These values are then *z*-transformed and the *z*-score of the hit rate is plotted as a function of the *z*-score of the false alarm rate. The control data are connected by a solid line. The scopolamine data are connected by a dashed line. Error bars are ± 1 *SE*. The scopolamine data are shifted down on the *z*(Hits) axis, indicating that discriminability is affected by scopolamine in a way that is not attributable to response criteria.

Qualitative differences also appear in *z*-ROC space (Figure 3). The control subjects show an upward inflection toward the left side of the curve, which is believed to be a consequence of recollective processing. In contrast, the scopolamine subjects' data show an upward deflection midway through the curve, followed by a downward deflection at the left side of the curve. This upward deflection is perfectly consistent with an increase in discriminability, as would be expected from a recollective process. The subsequent downward deflection is consistent, then, with a recollective process that does not exceed all criteria, but is itself variable.

This interpretation, while intriguing, could change dramatically with changes in just a few of the points in Figures 1 and 3. Therefore, to informally assess the reliability of these qualitative changes with scopolamine, we examined data from individual subjects. Figure 4 shows old item response distributions and *z*-ROC curves from representative control and scopolamine-injected subjects. The pattern of results seen with scopolamine in the averaged response distribution data—a broadened recollective peak and a shifted familiarity-based peak—was evident in individual subjects' data as well as in the averaged data. This suggests that the pattern apparent in Figure 1 is not merely an artifact of averaging, but is a reliable description of the effect of scopolamine on responses to old items. Similarly, the qualitative changes in the *z*-ROC curves seen in the averaged data were also observed at the individual subject level. The potential importance of these qualitative changes will be discussed at length in the modeling section.

Yes–no analysis. In typical item recognition experiments, subjects simply respond "yes" or "no" to probe items. In the present study, subjects provided multiple levels of response. In yes–no recognition, the response criteria—the amount of evidence one has to have to say "yes"—is left to the subject. In contrast, subjects in the present study responded with multiple levels of confidence. To determine whether the discrepancy between the present results and previous failures to observe a disruption of item recognition might be attributable to these methodological differences, we reanalyzed our data as a yes–no experiment with each of four different response criteria. To give a concrete example, we could count all of the 5 responses as a "yes" and all other responses as "no" responses. We can then use this criterion to calculate hit rates and false alarm rates for each subject. Using standard methods, we can transform hits and false alarms into d', as might be done in an experiment using yes–no recognition. Using this criterion, and the

[1] It is not quite correct to say that the two peaks observed in Figure 1 are indicative of a bimodal distribution of strength. Because the "recollective" peak includes all items with a strength that exceeds the highest confidence criterion, the two peaks in the data could be caused by an underlying distribution that decays very slowly as strength increases.

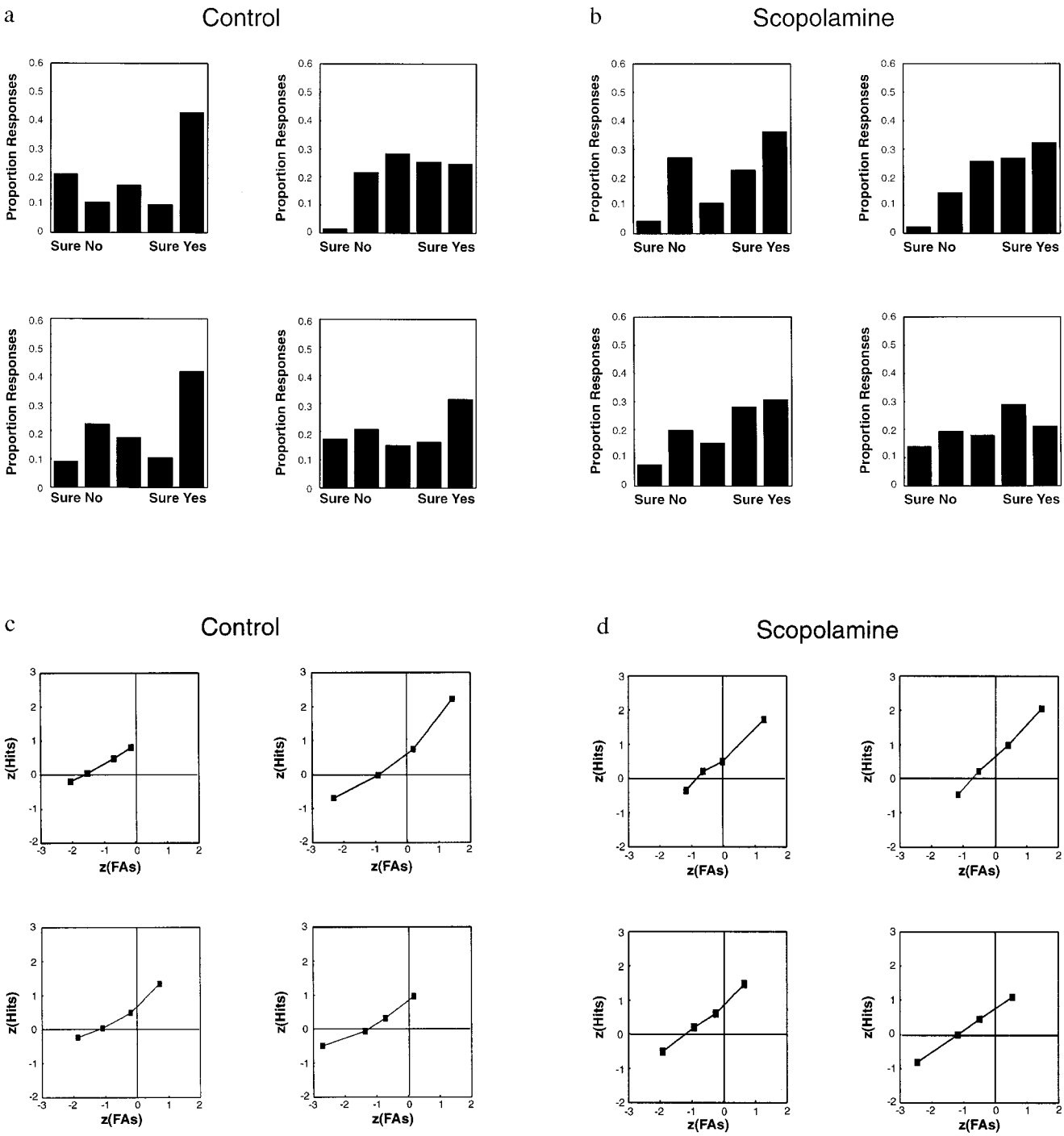

Figure 4. The patterns observed in the averaged data were also observed at the individual subject level. a: Old-item response distributions from representative control subjects. The presence of a putative familiarity-based peak can be inferred in all of the individual panels. The presence of a sharp, putative recollective peak around "sure yes" can be seen in 3 of the 4 subjects. b: Old-item response distributions from scopolamine-injected subjects. All four distributions appear to show a familiarity-based peak. All four distributions appear to show a spread in the putative recollective peak. c: *z*-transformed receiver operating characteristic (*z*-ROC) curves corresponding to the data from control subjects shown in a. The control subjects show a characteristic curvilinear *z*-ROC function. Note that the different panels have different scales. d: *z*-ROC curves corresponding to the data from the scopolamine-injected subjects shown in b. Note that the different panels have different scales. FA = false alarm.

derived values for d', we can then ask whether d' is significantly different for the subjects taking scopolamine than for the control subjects. Instead of treating 5 responses as "yes" responses, we might have used a different criterion, treating both 4 and 5 responses as "yes" responses, and all other response levels as "no" responses. We performed this calculation for all possible response thresholds.

The results of this analysis are shown in Table 1. Despite the clear effect on item recognition performance observed in the response distributions (see Figure 2), we were unable to observe a significant difference between d' calculated from yes–no scoring using any response threshold criterion. Although the disruption of item recognition is dramatic when measured with graded confidence ratings (Figure 2), it became harder to observe when using yes–no scoring. This provides a possible means to reconcile the clear effect of scopolamine on item recognition observed here with prior failures to observe such an effect.

Modeling

We modeled the resulting response distributions using the Yonelinas High Threshold model (Yonelinas, 1994, 1999, 2001). In the Yonelinas model, two processes, recollection and familiarity, contribute to recognition memory performance. The initial goal of this exercise was to determine whether scopolamine differentially affects recollection versus familiarity. However, it became necessary to consider more general models. To this end, we developed the Variable Recollection model, a straightforward extension of the Yonelinas High Threshold model.

Method

We fit both the Yonelinas High Threshold model and the Variable Recollection model to both averaged response distributions and averaged *z*-ROC curves. In deriving results for response distributions, we assumed that the response criteria were evenly spaced. Fitting *z*-ROC curves has the advantage of being completely insensitive to response criteria. The methods used to implement these complementary treatments are described in turn.

The Yonelinas High Threshold model: Response distributions. The Yonelinas model assumes that both old and new items generate some degree of memory "strength." Subjects respond with a given level of confidence if the strength of the item exceeds the threshold associated with that confidence judgment. Strength comes from two sources, recollection and familiarity. Both old and new items generate familiarity, but only old items are assumed to be recollected. New item familiarity is assumed to be chosen from the normal, or Gaussian, distribution with mean μ_N and standard deviation σ_N, where these parameters are to be estimated from the data. Familiarity of old items is also assumed to be a random variable chosen from a normal distribution with mean μ_O and standard deviation σ_O. Here we assume that the strength distributions arising from the familiarity process have the same variance, so that $\sigma_O = \sigma_N$. Because μ_O is typically greater than μ_N, familiarity can support successful recognition performance. In addition to the signal-detection-based familiarity process, Yonelinas also assumes that some old items are recollected with probability R. These items are assumed to exceed all response criteria and are given the highest confidence "yes" response.

So, with probability R, subjects make a highest confidence "yes" response to old items on the basis of recollection. With probability $(1 - R)$, subjects respond to old items on the basis of familiarity. The probability of familiarity resulting in a response that exceeds the highest response threshold is just the integral, from that threshold to infinity, of the familiarity distribution for old items. To find the probability that familiarity results in some other response, we need only take the integral of the old item familiarity distribution over the appropriate interval corresponding to that response. Assuming, then, that subjects respond with the numbers 1–5, with 1 corresponding to confident "no" and 5 being confident "yes," we used the following equations to estimate the proportion of responses at each level of confidence:

$$\begin{aligned} P(\text{`5'}|\text{old}) &= R + (1 - R)\int_4^{\infty} N(\mu_O, \sigma_O, s)ds \\ P(\text{`4'}|\text{old}) &= (1 - R)\int_3^{4} N(\mu_O, \sigma_O, s)ds \\ \vdots &= \vdots \\ P(\text{`1'}|\text{old}) &= (1 - R)\int_{-\infty}^{1} N(\mu_O, \sigma_O, s)ds, \end{aligned} \quad (1)$$

where $N(\mu, \sigma, s)$ is the value of the normal, or Gaussian, distribution with mean μ and standard deviation σ evaluated at point s. The equations determining the response distributions for the new items were analogous to those for old items, with the exception that new values μ_N and σ_N were used, and there is no chance of recollection of items that were not previously seen:

$$\begin{aligned} P(\text{`5'}|\text{new}) &= \int_4^{\infty} N(\mu_N, \sigma_N, s)ds \\ P(\text{`4'}|\text{new}) &= \int_3^{4} N(\mu_N,\sigma_N,s)ds \\ \vdots &= \vdots \\ P(\text{`1'}|\text{new}) &= \int_{-\infty}^{1} N(\mu_N, \sigma_N, s)ds. \end{aligned} \quad (2)$$

We fit the above model of recognition performance to the average old and new response distributions by minimizing chi-square.

The Variable Recollection model: Response distributions. To explain the pattern of results observed under scopolamine, it became necessary to extend the Yonelinas model. An assumption of the Yonelinas High Threshold model is that recollection always results in a high-confidence "yes" response. Perhaps by relaxing this assumption, we can accommodate the broadened recollective peak apparent in the scopolamine subjects' old-item distribution. To describe this effect, we assumed that, rather than being all-or-none, recollection, like familiarity, is variable. We postulate that the distribution of strengths associated with recollection is normal with mean μ_R and standard deviation σ_R (see Figure 5). This straightforward gener-

Table 1
Mean (±SEM) Values of d′ Obtained by Reanalyzing Data From Experiment 1 Using Yes–No Scoring

	Response threshold			
Group	1	2	3	4
Control	0.97 ± 0.18	1.05 ± 0.15	1.34 ± 0.16	1.95 ± 0.20
Scopolamine	0.64 ± 0.11	0.82 ± 0.12	1.17 ± 0.14	1.50 ± 0.20
$t(14)$	1.60	1.20	0.80	1.54

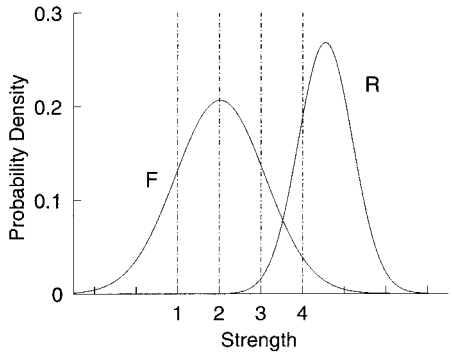

Figure 5. Schematic of the variable recollection extension of the Yonelinas High Threshold model. The Yonelinas High Threshold model assumes that recollective responses always result in a highest confidence "yes" response. In contrast, this model also assumes that familiarity gives rise to a range of strengths (the distribution F). In a simple generalization of the Yonelinas model, we assumed that recollection also gives rise to a distribution of strengths (the distribution R). If the recollective distribution lies sufficiently far above the highest confidence threshold, the Yonelinas High Threshold model is recovered.

alization of the Yonelinas model gives rise to the following equations to generate the response distributions:

$$P(\text{`5'}|\text{old}) = R\int_4^\infty N(\mu_R, \sigma_R, s)ds + (1-R)\int_4^\infty N(\mu_O, \sigma_O, s)ds$$

$$P(\text{`4'}|\text{old}) = R\int_3^4 N(\mu_R, \sigma_R, s)ds + (1-R)\int_3^4 N(\mu_O, \sigma_O, s)ds$$

$$\vdots \quad = \quad \vdots$$

$$P(\text{`1'}|\text{old}) = R\int_{-\infty}^1 N(\mu_R, \sigma_R, s)ds + (1-R)\int_{-\infty}^1 N(\mu_O, \sigma_O, s)ds. \quad (3)$$

This expanded model includes the Yonelinas High Threshold model as a limiting case. If the entire recollective distribution lies above the highest confidence threshold, then the recollective distribution contributes only to highest confidence "yes" responses. Under these circumstances, the Variable Recollection model simplifies to the Yonelinas High Threshold model. This occurs when $\mu_R - 4 \gg \sigma_R$, leading to $\int_4^\infty N(\mu_R, \sigma_R, s)ds \simeq 1$.

Fits to z-ROC curves. The connection between the response distribution equations used above and the equations we used for fitting the *z*-ROC curves is described in some detail in the Appendix. To fit the Yonelinas High Threshold model to the *z*-ROC data, we generated parametric curves in c using

$$P(\text{hit}) = P(\text{fa}) + R + (1-R)\Phi\left(\frac{d'}{2}, c\right) - \Phi\left(-\frac{d'}{2}, c\right), \quad (4)$$

where $\Phi(x, y)$ is just shorthand for the normal integral, $\Phi(x, y) := \int_y^\infty N(x, 1, s)ds$. We varied c from -5.5 to 5.5 in increments of 0.01. We *z*-transformed the resulting hit and false alarm rates. We found the point along the curve that came as close to each observed value of *z*(fa) as possible, and minimized the sum of squared errors between the observed *z*(hit) and the value predicted at that point.

To generate *z*-ROC curves for the Variable Recollection model, we used the equation:

$$P(\text{hit}) = P(\text{fa}) + R\int_c^\infty N(\mu_R, \sigma_R, s)ds + (1-R)\Phi\left(\frac{d'}{2}, c\right) - \Phi\left(-\frac{d'}{2}, c\right). \quad (5)$$

This equation differs from Equation 4 by the inclusion of an additional integral describing the variable recollection process.

A number of factors keep it from being immediately clear how goodness-of-fit statistics should be null-distributed for the fits to *z*-ROC data. For instance, the predicted values should themselves give rise to some variability inherited from the experimental variability in the *x* data. Further, the data points are not independent of each other, being a transform of a cumulative function. For these reasons, formal model evaluation was only done for the response distribution fits.

Results and Discussion

The best-fitting parameters for the fits of each model to the response distributions are shown in Table 2. The best-fitting parameters for the *z*-ROC fits are shown in Table 3.

Figure 6 shows the best-fitting response distribution and *z*-ROC curves generated by the Yonelinas High Threshold model. The model provided a good fit to the control subjects' response distributions, $\chi^2(4) = 4.42$, $p > .3$. Consistent with prior work, the Yonelinas model also did a good job describing the control data in *z*-ROC space. The model comes very close to each point and captures the characteristic inflected shape of the control subjects' curve.

In contrast to the excellent fits of the Yonelinas High Threshold model to the control data, the model failed to provide an adequate description of the data from the scopolamine subjects. Figure 6a reveals systematic discrepancies between the scopolamine subjects' old-item response distributions and the predictions of the model, $\chi^2(4) = 22.03$, $p < .001$. In *z*-ROC space, the Yonelinas model failed to capture the characteristic "hitched" pattern seen in the scopolamine subjects' *z*-ROC data (Figure 4).

The Yonelinas High Threshold model captures the key feature of the new item distribution: a unimodal distribution with a peak toward "sure no." The model also succeeds in describing the shape of the new-item distributions for both control subjects and subjects receiving scopolamine. Consistent with a wealth of prior modeling work, the Yonelinas High Threshold model also does a good job of

Table 2
Best-Fitting Parameter Values for the Fits of the Yonelinas High Threshold (YHT) Model and the Variable Recollection (VR) Model to the Averaged Response Distribution Data From Experiment 1

	YHT		VR	
Parameter	Control	Scopolamine	Control	Scopolamine
μ_O	2.46	2.46	2.46	1.81
μ_N	1.53	1.49	1.53	1.59
σ	1.26	1.52	1.26	1.25
R	0.32	0.17	0.32	0.40
μ_R			4.93	4.08
σ_R			0.07	0.19

Note. Empty cells indicate that those parameters do not apply to the YHT model.

Table 3
Best-Fitting Parameter Values for Fits of the Yonelinas High Threshold (YHT) Model and the Variable Recollection (VR) Model to the Averaged z-ROC Data From Experiment 1

	YHT		VR	
Parameter	Control	Scopolamine	Control	Scopolamine
d'	0.62	0.52	0.60	0.33
R	0.35	0.22	0.36	0.35
μ_R			2.50	1.80
σ_R			0.50	0.39

Note. Empty cells indicate that those parameters do not apply to the YHT model. z-ROC = z-transformed receiver operating characteristic.

describing control subjects' distribution of responses to the old items as well as their z-ROC curves. The model captures the broad central peak in the control subjects' old-item response distribution attributable to familiarity-based recognition. The model also captures the high-confidence peak, attributable within the model to a recollective contribution to recognition performance. In contrast to its success in describing the control subjects' old-item response distribution, the Yonelinas High Threshold model fails to capture the basic features of the scopolamine group's old-item response distribution. The model places the central peak too far to the right on the strength axis. This is apparently in an attempt to compensate for the model's inability to describe the breadth of the putative recollection-based peak.

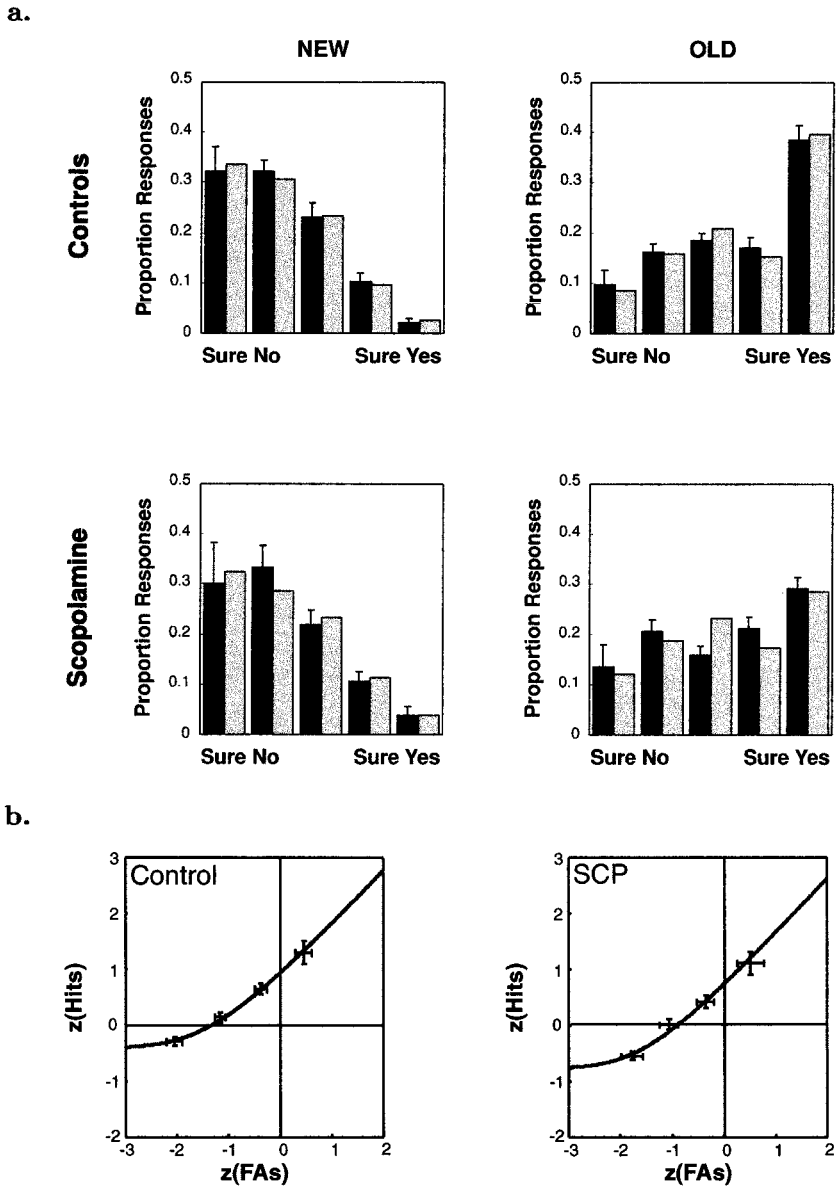

Figure 6. Fits of the Yonelinas High Threshold model to the data from the current experiment. a: Fits to response distributions. Empirical data are in black; model predictions are in gray. b: Fits to the z-transformed receiver operating characteristic data. Although the Yonelinas model fits the control data very well, it does not capture the characteristic shape of the scopolamine data. Error bars are ±1 *SE*. FA = false alarm.

Figure 7 shows the best-fitting response distribution and *z*-ROC curves generated by the Variable Recollection model. Like the Yonelinas model, the Variable Recollection model described the response distribution data from the control subjects well, $\chi^2(2) = 4.42$, $p > .10$. This is consistent with the best-fitting parameters, which placed the recollective peak at $\mu_R = 4.93$. The model also set the standard deviation of the recollective peak at $\sigma_R = 0.07$. The mean of the recollective distribution was thus in excess of 10 standard deviations from the highest confidence threshold (at 4.0). Under these circumstances, the predictions of the Variable Recollection model are essentially the same as those of the Yonelinas High Threshold model. The Variable Recollection model also provided a good fit to the control subjects' *z*-ROC data. Over the range of criteria that contain the observed data, the model captures the characteristic upward inflection.

In contrast to the Yonelinas High Threshold model, the Variable Recollection model provided an adequate fit to the response distributions from the scopolamine-injected subjects, $\chi^2(2) = 2.77$, $p > .25$, as well. This constitutes a significant improvement over the fit from the Yonelinas High Threshold model, $\chi^2(2) = 19.30$, $p < .001$. The Variable Recollection model also provided a good description of the characteristic

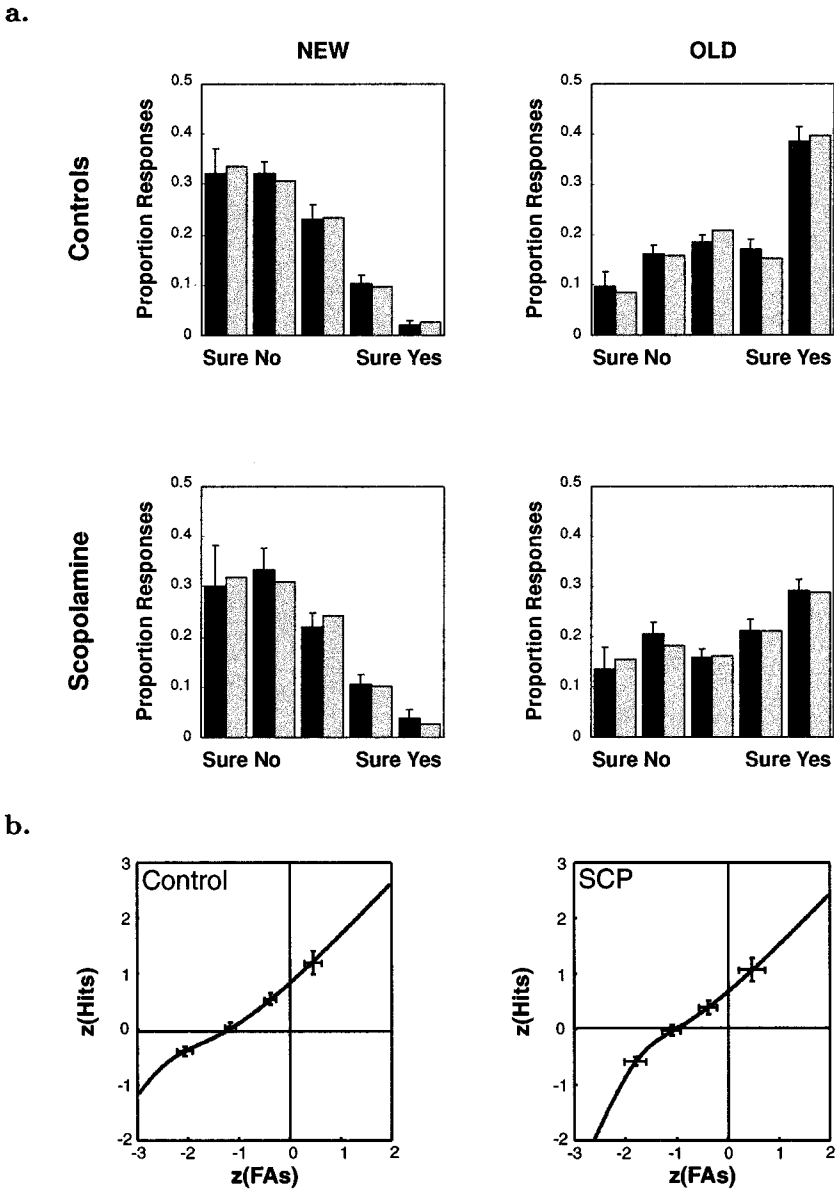

Figure 7. The Variable Recollection model describes the deficit associated with scopolamine. a: Fits to response distributions. Empirical predictions are in black; model predictions are in gray. b: Fits to the *z*-transformed receiver operating characteristic (z-ROC) curves. The Variable Recollection model assumes that recollection is not all-or-none, but can be described by a normal distribution. The model describes the qualitative pattern of results across conditions. In particular, the model describes the broadened recollective peak and multiply inflected *z*-ROC curves seen under scopolamine. FA = false alarm.

pattern of results in *z*-ROC space, showing a downward trend toward the left side of the curve.

In addition to providing a qualitative fit to the data from the scopolamine-injected subjects, the Variable Recollection model provides some insight into the source of the deficit within the context of dual-process theory. An inspection of the best-fitting parameters for the Variable Recollection model (Tables 2 and 3) shows that scopolamine was associated with a change in the discriminability due to familiarity. In the fits to the response distributions, this can be seen by a relatively large decrease in μ_O, whereas the other parameters governing the familiarity process were minimally affected. Similarly, the fits to the *z*-ROC data resulted in a large decrease in d' associated with scopolamine.

Of particular interest is the nature of the recollective deficit associated with scopolamine. Although scopolamine had a relatively small effect on the frequency with which recollection was engaged, it had a large effect on the efficacy of recollection. For the fits to the response distributions, the model predicted that there was actually a small *increase* in the frequency of recollection for the scopolamine-injected subjects. Similarly, in fitting the *z*-ROC data, the Variable Recollection model predicts that R was essentially unchanged by the administration of scopolamine. However, whereas the model placed the recollective peak over 10 standard deviations from the highest confidence response threshold for the control subjects in fitting the response distributions, the peak was less than one half of a standard deviation away for the scopolamine-injected subjects.

General Discussion

Using a recognition task with multiple confidence ratings as responses, we tested the effect of scopolamine on the ability to differentiate previously studied (old) items from previously unstudied (new) items. Scopolamine disrupted memory for studied items, while leaving the distribution of responses to unstudied items unchanged. This is, to our knowledge, the first report of an unequivocal demonstration of a deficit in item recognition associated with scopolamine. In an attempt to reconcile this finding with prior results, we reanalyzed our data by scoring responses as binary responses with a variety of criteria, simulating a "yes–no" experiment. We did not find a significant difference for any of the criteria used. Confidence judgments collect a more sensitive measurement of subjects' memory for items than do yes–no responses. Further, confidence judgments provide a more detailed picture of the processes underlying recognition performance. In particular, had the present study used yes–no responses, or forced-choice recognition, the qualitative changes in the shape of the old-item response distributions and *z*-ROC curves with scopolamine would not have been observed.

Two-process theory (Atkinson & Juola, 1974; Mandler, 1980; Norman & O'Reilly, in press) postulates that recognition performance is supported by two dissociable processes, recollection and familiarity. We anticipated that recollection would be more sensitive to scopolamine than familiarity. In an attempt to observe this dissociation, we modeled our data using the Yonelinas High Threshold model, a concrete implementation of dual-process theory. The Yonelinas model, however, did not fit the old-item distribution generated by the scopolamine group. In order to fit the scopolamine-injected subjects' old-item distributions, it was necessary to relax some of the Yonelinas High Threshold model's assumptions. The breadth of the peak in the old-item distribution of the scopolamine-injected subjects suggests that recollection is not an all-or-none process with low doses of scopolamine. One possibility, then, is to simply assume that rather than generating a "sure yes" response, recollection generates a strength from a normal distribution with some mean and standard deviation. In particular, the breadth of the peak could result from a decrease in the mean of the recollective distribution and/or an increase in the variability associated with it.

By assuming that recollection is variable, rather than all-or-none, we extended the Yonelinas High Threshold model. Using this Variable Recollection assumption, we were able to accurately describe both control subjects' and scopolamine-injected subjects' performance on the task. Analyses with this model argued that scopolamine affected both familiarity and recollection. The nature of the recollection deficit was of some interest. Although we did not observe a big change in the probability of recollecting items with low-dose scopolamine injection (i.e., R was comparable across groups), there was a large effect on the amount of information resulting from successful recollection. This was wholly unexpected, and provides a new and important clue into the nature of recollective encoding and recognition more broadly.

The observation that scopolamine affects both recollection and familiarity does not necessarily demonstrate that these cognitive processes are less separable than previously thought. It is possible that scopolamine affects each process, but independently. Acetylcholine has many distinct physiological effects. It is also possible that scopolamine affects the transformation of memory strength into a response, or a processing stage prior to both recollection and familiarity. For instance, scopolamine might affect the representation of complex visual scenes. However, if the representation of all items is distorted, then both recollection and familiarity should be affected. Recollection, which presumably relies on associative processes that bind together all elements of an episode, should be ineffective if item information is corrupted and thus does not allow for extraction of commonalities within a specific event. Familiarity, which relies on a presented item's inherent memory strength relative to the strength of other similar but nonpresented items, should also be impaired if item representations are distorted by scopolamine.

Another possibility is that recollection and familiarity, though functionally separable under some circumstances, rely on a common physiological mechanism that depends on the activity of acetylcholine at muscarinic receptors. Physiological evidence indicates a role for muscarinic cholinergic modulation in regions believed to be important for episodic memory (e.g. Klink & Alonso, 1997a, 1997b; Fransén, Alonso, & Hasselmo, 2002). Further, lesions of regions giving rise to cortical cholinergic innervation cause impairments in memory tasks (see review in Hagan & Morris, 1989; Numan & Quaranta, 1990). Recent work shows that selective cholinergic lesions alone do not cause strong impairments but suggests that sparing in those cases results from the involvement of GABAergic projections from basal forebrain nuclei, as combined cholinergic and GABAergic lesions do cause impairments (Pang, Nocera, Secor, & Yoder, 2001). Drugs that influence cholinergic receptors (scopolamine) and drugs that influence GABA receptors (e.g., the benzodiazepines) both have strong, and nearly indistinguishable (Ghoneim & Mewaldt, 1975, 1977; Mintzer & Griffiths, 2001; Sperling et al., 2002), effects on explicit memory in humans.

Theta (4–8 Hz) oscillations are a plausible common physiological target of both cholinergic and GABAergic modulation. Theta is known to play a prominent role in hippocampal physiology (Buzsáki, Leung, & Vanderwolf, 1983; Bland, 1986; Kocsis, Bragin, & Buzsáki, 1999). Further, both GABA and acetylcholine are essential components of the septal input to the hippocampus that is necessary for theta (Wu, Shanabrough, Leranth, & Alreja, 2000). Given the importance of the hippocampus in episodic memory (Eichenbaum, 2000; Squire & Zola, 1996), the fact that scopolamine disrupts non-movement-related theta (or Type 2 theta as defined by Vanderwolf, 1969) in animals (Teitelbaum, Lee, & Johannessen, 1975) provides a possible mechanism for the effect of scopolamine on recollection. Physiological evidence suggests that theta oscillations are not limited to hippocampal regions but are also observed in entorhinal cortex (e.g., Alonso & Garcia-Austt, 1987), anterior cingulate (Borst, Leung, & MacFabe, 1987) and frontal regions (Ishii et al., 1999). In addition, recent work using intracranial recording from humans has demonstrated that large-amplitude theta oscillations can be observed in a wide variety of locations in human cortex (Caplan, Kahana, Sekuler, Kirschen, & Madsen, 2000; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Raghavachari et al., 2001). It is quite possible, then, that theta is important in the function of regions that support familiarity, even if those regions prove to be separate from the medial temporal lobe regions presumed to be involved in recollection.

From a conceptual view, it makes sense that recollection and familiarity should be closely interrelated. When presented with a test item, subjects must initially rely on some kind of stimulus identification process, like that believed to support familiarity. This stimulus identification process may or may not lead to an episodic retrieval experience. Presumably, the better the stimulus is identified, the better the chances are that it will lead to retrieval. In this way familiarity decisions could support successful recollection. Indeed, Atkinson and Juola (1974) originally argued that recollection and familiarity operated in serial stages. If initial familiarity strength did not signal whether the item was new or old, a more elaborative recollective process was engaged.

Our use of the Variable Recollection assumption should be seen as an incremental advance within the context of the Yonelinas High Threshold framework. Although we rejected the High Threshold assumption as a quantitative description of the data from the scopolamine group, the present study provides some of the strongest evidence to date for the most basic assumptions underlying the Yonelinas model. A great deal of evidence has led to unanimity among the memory modeling community that the distribution of memory strengths associated with old items is effectively more variable than the distribution of strengths associated with new items (Glanzer, Adams, Iverson, & Kim, 1993; McClelland & Chappell, 1998; Ratcliff, McKoon, & Tindall, 1994; Ratcliff, Sheu, & Gronlund, 1992; Shiffrin & Steyvers, 1997).[2] Yonelinas' original arguments for the High Threshold model hinged on a very specific property of the response distributions. This property[3] could simply be a consequence of a single-process strength distribution that falls off very gradually. However, the old-item distribution we observed with administration of scopolamine clearly shows two distinct peaks. Assuming that the response criteria are evenly spaced, this pattern cannot be explained by a unimodal distribution, no matter how skewed it might be. A two-process model provides the most parsimonious explanation for a bimodal distribution like the one we observed with scopolamine-injected subjects. We would argue that it is also more parsimonious to assume that the scopolamine data reveal properties of the control data that are not typically observable, rather than assuming that scopolamine gives rise to a completely novel memory process that results in high-confidence "yes" judgments. The Variable Recollection assumption can, in principle at least, be distinguished from the High Threshold assumption in controls by examining recollective responses at sufficiently high response criteria. The High Threshold assumption predicts that no matter how high the criterion is, recollective responses will always exceed it.

We studied recognition memory for complex visual pictures in subjects administered scopolamine and control subjects. Subjects responded with one of five confidence ratings. Although the distribution of responses to new items was the same for each group, there was a clear difference between the response distributions to old items, indicating an effect of scopolamine on item recognition memory. Although the old item response distributions from the scopolamine-injected subjects could not be fit by the Yonelinas High Threshold model (Yonelinas, 1994, 1999), they were well fit by a simple extension of this model that assumes that recollection is variable. The bimodal response distributions obtained for scopolamine-injected subjects constitute strong evidence that two processes underlie item recognition, supporting the central thesis of the Yonelinas High Threshold model. Rather than finding a dissociation between recollection and familiarity, as we expected a priori, we found that scopolamine affected both recollection and familiarity.

[2] This statement is true only insofar it is actually possible to establish unanimity among the memory modeling community.

[3] Curvilinear *z*-ROC curves.

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Appendix

Response Distributions and *z*-ROC Curves for the Yonelinas High Threshold Model

In this appendix, we describe the connection between the treatment of response distributions and *z*-ROC curves for the Yonelinas High Threshold model. The connection between response distributions and *z*-ROC curves follows a similar development for the Variable Recollection model.

In his own writings, Yonelinas (1994, 1996, 1997) has fit *z*-ROC curves with the High Threshold model. The strategy is to describe the hit rate as a function of the false alarm rate for possible values of the criterion. Given a response criterion c, the probability of saying yes given that the item is old is just

$$P(\text{`yes'}|\text{old}) = R + (1 - R)\int_c^\infty N(\mu_O, \sigma_O, s)ds, \qquad \text{(A1)}$$

whereas the probability of saying yes to an item that was not presented is just

$$P(\text{`yes'}|\text{new}) = \int_c^\infty N(\mu_N, \sigma_N, s)ds. \qquad \text{(A2)}$$

The connection between these equations and Equations 1 and 2 in the text should be immediately clear. As c varies from $-\infty$ to ∞, this becomes a parametric equation in c determining a curve in R^2, where the two dimensions are P (hit) and P (fa). Because all values of c are used, this parametric curve is unaffected by translations of c, $c \rightarrow c + A$. We can therefore translate c such that

$$P(\text{hit}) = P(\text{fa}) + R + (1 - R)\int_c^\infty N(\mu_{\text{rel}}/2, \sigma_O, s)ds - \int_c^\infty N(-\mu_{\text{rel}}/2, \sigma_N, s)ds, \qquad \text{(A3)}$$

where $\mu_{\text{rel}} := \mu_O - \mu_N$, without changing the resulting curve. Let us now assume that $\sigma_O = \sigma_N$, as we did in fitting the response distribution data, and refer to this common value as σ. Noting the definition of N, it is clear that we can "undo" any change in μ_{rel} by manipulating σ appropriately. For instance, if we took $\mu_{\text{rel}} \rightarrow A\mu_{\text{rel}}$, we could recover the original curve by rescaling $\sigma \rightarrow A\sigma$. The parameters μ_{rel} and σ are therefore not identifiable. We can rescale the means by defining

$$d' := \frac{\mu_O - \mu_N}{\sigma}$$

to obtain Equation 5:

$$P(\text{hit}) = P(\text{fa}) + R + (1 - R)\Phi\left(\frac{d'}{2}, c\right) - \Phi\left(-\frac{d'}{2}, c\right), \qquad \text{(A4)}$$

where $\Phi(x, y) := \int_y^\infty N(x, 1, s)ds$. This equation defines a ROC curve with two free parameters, d' and R.

In fitting the Yonelinas High Threshold model to response distributions (Equations 1 and 2, main text), there are four free parameters, whereas only two were used to fit to the model to *z*-ROC curves. This apparent discrepancy is a consequence of the parametricity of the *z*-ROC curves. Because a translation of the criterion c has no effect, the absolute values of the parameters governing the means are meaningless. It is necessary only to define the difference between the means in units of the standard deviation σ. The decrease in the number of free parameters has not come without any cost, however. Fitting *z*-ROC curves requires no assumptions about the location or spacing of the response criteria. Sweeping through all possible values of the criteria and choosing the point closest to the data essentially allows the values of each of those criteria to function as free parameters. The response distribution treatment (Equations 1 and 2, main text) is limited in that it assumes that the spacing between the criteria is constant. This assumption could clearly be violated if, for instance, subjects responded by only using a subset of the possible responses.

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