Neuropsychology
2003, Vol. 17, No. 3, 469–481

0894-4105/03/$12.00 DOI: 10.1037/0894-4105.17.3.469

Enhanced Release From Proactive Interference in Nonamnesic Alcoholic Individuals: Implications for Impaired Associative Binding

Eve De Rosa and Edith V. Sullivan
Stanford University School of Medicine

Proactive interference (PI) occurs when previously learned information reduces the ability to acquire new, related information. Given that PI is modulated by the cholinergic system in rats (E. De Rosa & M. E. Hasselmo, 2000) and that chronic alcohol dependence disrupts cholinergic function in rats and humans, associative properties of PI in patients with alcoholism were examined. It was hypothesized that normal PI contingencies would be disrupted in alcoholic participants. When tested with a paired-associate simultaneous discrimination paradigm, analogous to that used in the rat model, alcoholic participants showed significantly less PI than controls yet performed comparably on a control response reversal task. The absence of PI in alcoholic participants may reflect impaired configural binding of paired-associate stimuli while sparing the elemental ability to process each stimulus component.

A considerable body of research has implicated the neurotransmitter acetylcholine (ACh) in learning and memory. The basal forebrain projection system (Rye, Wainer, Mesulam, Mufson, & Saper, 1984) is a major source of cholinergic innervation to the entire neocortex, hippocampus, amygdala, and olfactory system and therefore has the ability to exert widespread influences on information processing throughout the brain. Research in animal models has demonstrated that the physiological consequences of ACh act specifically to potentiate the effects produced by other excitatory inputs; therefore, cholinergic afferents from the basal forebrain have been hypothesized to increase the signal-to-noise ratio when processing information. The functional relevance of these cholinergic interactions may be to modulate the salience of pertinent stimuli and the behavioral responsiveness to those stimuli, affording enhanced flexibility to make the appropriate choices in their presence (Baxter & Chiba, 1999; De Rosa & Baxter, 2002; Everitt & Robbins, 1997; Sarter & Bruno, 1997). Although it has been long recognized that ACh is critical to memory formation, this specific neuromodulatory contribution of the basal forebrain to memory is largely uninvestigated in humans. The aim of the present study was to explore the concept taken from animal research that ACh is critical for the acquisition of flexible associative relations by examining associative proactive interference (PI) in nonamnesic patients with presumed cholinergic dysfunction.

Eve De Rosa, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine; Edith V. Sullivan, Department of Psychiatry and Behavioral Sciences and Neuroscience Program, Stanford University School of Medicine.

This research was supported by National Institutes of Health Grants AA 10723 and AA 05965 and a minority postdoctoral fellowship to Eve De Rosa from the same institution.

We thank Adam K. Anderson and Adolf Pfefferbaum for their thoughtful discussion on this work, Anjali Deshmukh and Anne O'Reilly for their careful diagnoses of the participants, and Debra Huang and Donna Murray for their assistance in collecting the data.

Correspondence concerning this article should be addressed to Eve De Rosa, who is now at the Department of Psychology, University of Toronto, 100 Saint George Street, Toronto, Ontario M5S 3G3, Canada. E-mail: derosa@psych.utoronto.ca

Effects of Ethanol on the Cholinergic Basal Forebrain

In vivo neuroimaging studies of chronic alcoholism have typically revealed widespread cortical gray matter and white matter volumetric deficits and a complementary increase in cerebrospinal fluid (Jernigan et al., 1991; Pfefferbaum et al., 1992; Sullivan, Mathalon, Lim, Marsh, & Pfefferbaum, 1998), but it is also accompanied by selective neurotoxic actions on cholinergic neurotransmission in the central nervous system. Chronic ethanol consumption exerts neurotoxic effects on the muscarinic cholinergic basal forebrain and its target structures in both humans and rats (Arendt, 1994; Arendt et al., 1989; Casamenti, Scali, Vannucchi, Bartolini, & Pepeu, 1993; Floyd et al., 1997; Freund & Ballinger, 1989; Little, 1999; Nordberg, Larsson, Perdahl, & Winblad, 1982; Nordberg & Wahlstrom, 1992; Rothberg, Yasuda, Satkus, Wolfe, & Hunter, 1993).

In humans, chronic alcoholism has been associated with decreased number and function of muscarinic receptors in the target structures of the basal forebrain (Freund & Ballinger, 1989; Nordberg et al., 1982). In rats, chronic alcohol consumption has been also associated with a reduction in markers of cholinergic function, including ACh content, release, synthesis, choline acetyltransferase (the enzyme that produces ACh) activity, and basal forebrain muscarinic receptor function (Arendt et al., 1989; Casamenti et al., 1993; Floyd et al., 1997; Little, 1999; Nordberg & Wahlstrom, 1992; Rothberg, Yasuda, Satkus, Wolfe, & Hunter, 1993). The extent of the dysfunction of muscarinic receptors is dependent on the length of ethanol dependence; indeed,

cholinergic dysfunction is only temporarily reduced by short-term physical dependence. To induce permanent alterations of the muscarinic receptors in the basal forebrain nuclei and their target structures, there must be repeated or prolonged periods of ethanol exposure resulting in signs of physical dependence (Arendt et al., 1989; Frye, Taylor, Grover, Fincher, & Griffith, 1995; Nordberg & Wahlstrom, 1992). These changes are more pronounced in the basal forebrain nuclei than in their target structures (Arendt et al., 1989).

These observations suggest that ethanol-induced degeneration of the cholinergic basal forebrain projection system from chronic alcohol consumption may be a suitable human model to investigate the changes in cognition that are consistent with cholinergic dysfunction. This possibility is further strengthened by the fact that chronic consumption of ethanol has been used to induce widespread lesions of the cholinergic basal forebrain in rodents that have resulted in selective mnemonic deficits, such as in working memory and passive avoidance tasks (Arendt et al., 1989; Casamenti et al., 1993; Melis, Stancampiano, Imperato, Carta, & Fadda, 1996).

Cholinergic Modulation of Associative PI in Rats

The physiological consequences of ACh allow neurons receiving afferent input to fire in a more sustained manner and increase long-term potentiation; this mechanism has been proposed to strengthen associative connections between paired-associate stimuli and enhance the rate of learning in rats. ACh serves to increase further the signal-to-noise ratio of afferent information to the cortex by exerting a stronger suppression of previously strengthened intrinsic connections between pyramidal cells than afferent connections to pyramidal cells (Hasselmo & Bower, 1993). ACh's ability to suppress selectively the influence of previously stored memories during learning has been investigated in rats, as described below.

A standard method for studying PI is paired-associate learning, in which two different responses are associated with the same stimulus. Using a paired-associate simultaneous discrimination paradigm, De Rosa and Hasselmo (2000) trained rats on a baseline odor pair (A+B−), where a nose poke at Odor A but not Odor B was rewarded. The rats were then required to learn two novel experimental odor pairs simultaneously: (a) an odor pair (A−C+) with the overlapping component of Odor A and (b) an odor pair (D+E−) with no overlapping component. Systemic pharmacological manipulation with scopolamine, a muscarinic cholinergic antagonist, resulted in a selective increase in the magnitude of associative PI, whereas the learning of completely new odor-pair associations was left intact. De Rosa, Hasselmo, and Baxter (2001) then confirmed, with intraparenchymal administration of the cholinergic immunotoxin 192 IgG-saporin, that a specific role of ACh in memory formation is to minimize interference from past learning experiences, thereby allowing the more efficient interleaving of new and old memory traces.

Potential for Disruption of Associative Learning in Nonamnesic Chronic Alcoholic Individuals

In the present study, we modified the simultaneous discrimination paired-associate PI paradigm used in the rat model by replacing olfactory stimuli with color stimuli to test whether the effects of ACh on associative learning could generalize to similar learning conditions in humans. The contributions of paired-associate learning to memory have been delineated by a number of theorists, including Kausler (1974) from a human learning perspective and Mackintosh (1983) from an animal learning perspective. Although alcoholic Korsakoff amnesics have demonstrated pathology in the basal forebrain nuclei (Oscar-Berman & Ellis, 1987; Salmon & Butters, 1987), we studied detoxified, nonamnesic alcoholic individuals to measure the potential effects of cholinergic dysfunction on associative learning. Such nonamnesic alcoholic individuals show selective mild cognitive deficits, including impairments in selective attention and memory (Butters & Cermak, 1980; Nixon, Tivis, Jenkins, & Parsons, 1998; Oscar-Berman, 2000; Oscar-Berman & Ellis, 1987; Parsons & Nixon, 1993; Salmon & Butters, 1987; Sullivan, Fama, Rosenbloom, & Pfefferbaum, 2002; Sullivan, Rosenbloom, & Pfefferbaum, 2000), in contrast to the potentially confounding declarative memory deficits exhibited in Korsakoff patients.

Associative PI is a reflection of past learning and may serve as an index of mnemonic binding of paired-associate stimuli. We speculated that one potential consequence of cholinergic dysfunction during learning would be to decrease associative binding between paired-associate stimuli. The PI task had a more complex association (Stimulus A was paired with two different contexts—B and C) than the response reversal task, which had a simple association of one context with one target stimulus (Stimulus A was only paired with Context B). We therefore hypothesized that detoxified, nonamnesic alcoholic individuals would demonstrate a degraded ability to use context and might be limited to simple associations when carrying out the associative PI task. The predicted degraded ability of associative binding of the target stimulus to its appropriate context could manifest itself as accelerated forgetting in alcoholic individuals. With presumed cholinergic dysfunction, the decreased ability of associative binding of the paired associates might be revealed in an inappropriate release from PI.

Method

The present study used two versions of the simultaneous discrimination paired-associate paradigm: an associative interference task and a response reversal task. These two tasks were designed to produce similar demands on the individual in terms of the response set and differed only in the context in which the new response was required. The associative PI task required the participants to respond to Color A in the context of Color B and then to respond to Color C in the context of Color A. The response reversal task required the participants to respond to Color A in the context of Color B and then to perform only a response reversal—respond to Color B instead of Color A. The response reversal task served as a control task for the response selection and response

reversal components of the associative PI task. Thus differential performances on the associative PI task, and not the response reversal task, would suggest that this difference was not a simple issue of response selection.

Participants

All control participants ($n = 18$ men) were recruited as volunteers from the local community, and the alcoholic participants ($n = 16$ men) were recruited as volunteers from local rehabilitation facilities. Because we examined only men, these results cannot be generalized to alcoholic women. To establish eligibility for the study, all participants underwent medical and psychiatric screening that included a structured alcohol history (Pfefferbaum, Rosenbloom, Crusan, & Jernigan, 1988) and a structured clinical interview (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; *DSM–IV;* American Psychatric Association, 1994). All alcoholic participants met *DSM–IV* criteria for alcohol dependence. The detoxified chronic alcoholic participants were tested only after any acute physiological withdrawal had subsided. In addition to alcohol dependence, 5 of the 16 alcoholic men met the *DSM–IV* criteria for alcohol-induced depression. Only 1 of those men had a current diagnosis of alcohol-induced depression; the other 4 men were in remission at the time of testing. Also, another alcoholic man had a single acute episode of posttraumatic stress disorder 16 years before testing and presented no symptoms at the time of testing. The control participants were screened and excluded for evidence of any *DSM–IV* Axis I disorder and substance abuse or dependence.

On arrival to the laboratory, all participants underwent a breathalyzer test and scored 0.0. All were also administered a brief battery of neuropsychological tests to characterize cognitive status and to screen out amnesia and dementia. No participant from either group presented a profile of clinically or operationally defined amnesia or dementia. When we measured the difference between National Adult Reading Test IQ (NART IQ; Nelson, 1982) and the Wechsler Memory Scale—Revised General Memory Index (GMI; Wechsler, 1987), we found that none of the participants had an IQ–GMI discrepancy greater than 1.5 standard deviations (cf. Oscar-Berman, Clancy, & Weber, 1993). We did have 3 alcoholic men whose IQ–GMI scores equaled or were greater than 20 (i.e., 20, 21, and 23). This discrepancy is suggestive of a mild memory impairment; nonetheless, all of the alcoholic participants achieved Dementia Rating Scale (Mattis, 1988) scores well within normal range. All participants provided written informed consent and were given a modest stipend for their participation. In their lifetime, the alcoholic men had consumed almost eight times more alcohol than the control men, and at the time of testing, the alcoholic men had been sober for a median of 56.5 days. Clinical and demographic data and the alcohol history of the participants are summarized in Table 1.

Measures

Test for color blindness. At the beginning of the session, the participants were assessed for color blindness with the concise 14-plate edition of the Ishihara (2000) color blindness exam. The first 6 plates were used to test for congenital red–green deficiencies.

Color identification. Ten colors (black, blue, brown, green, gray, orange, pink, purple, red, and yellow) were used to create the eight color pairs required for this experiment. During the color identification portion of the experiment, the participants were presented with a computer screen in which half of the screen was filled with a color swatch and the other half contained a list of the 10 color labels. The participants were required to type the number associated with the color swatch, verbally report the label of each color swatch, and received auditory feedback (correct or incorrect tone) from the computer for each response. The color swatch remained on the screen until one of the numerical labels was typed. Each of the 10 colors was presented two times in a pseudorandom order, resulting in 20 trials.

Basic simultaneous discrimination paired-associate paradigm. The entire experiment was created and implemented with PsyScope 1.2.5 (Cohen, MacWhinney, Flatt, & Provost, 1993; see also http://psyscope.psy.cmu.edu). This simultaneous discrimination paired-associate paradigm was designed to investigate the influence of past learning on the acquisition of a simple color discrimination without the need for maintaining information online in working memory. The paired-associate paradigm allows partici-

Table 1
Participant Characteristics

Variable	Alcoholic		Control		Comparison	
	M	*SD*	*M*	*SD*	*t*(32)	*p*
Age (years)	50.3	11.0	59.6	9.6	2.6	.01
Education (years)	15.4	2.3	17.6	2.3	2.7	.01
NART	109.7	8.1	114.7	6.2	2.1	.05
General Memory Index	106.9	14.4	120.6	10.2	3.2	.003
Delayed Memory Index	109.1	15.2	123.6	11.8	3.1	.004
Dementia Rating Scale	140.0	2.6	140.1	3.1	0.4	.91

	Participant alcohol history			
	Alcoholic		Control	
	M	*SD*	*M*	*SD*
Median length of sobriety (days)	56.5			
Total lifetime alcohol consumption (kg)	1,250.6	1,156.8	160.9	174.6

Note. $n = 16$ for alcoholic participants; $n = 18$ for control participants. For median length of sobriety, range = 11–742 days. General Memory Index and Delayed Memory Index measured by Wechsler Memory Scale—Revised (Wechsler, 1987). NART = premorbid estimation of IQ measured by National Adult Reading Test (Nelson, 1982).

pants to learn new responses in similar stimulus settings. For each paired-associate discrimination, two different color stimuli were presented simultaneously, each on half of the computer screen. These two distinct colors created a paired-associate stimulus, a color pair, that filled the entire computer screen. The experiment comprised four blocks each with 64 trials. There were two baseline conditions, one for the PI task and one for the response reversal task, and two experimental conditions. For each block, the participants were required to discriminate a new color component of a color pair that comprised two perceptually distinct colors. The proportion of correct responses and median response time of correct responses, for each block, were the dependent measures.

Using one of two specified keys on the keyboard, the participant reported the side on which one of the target colors appeared. The following general description of the basic discrimination paradigm uses contingencies coupled with two letters to represent the two colors in a color pair: A + signified the target color of the color pair, and a − signified its paired associate. When Color Pair A+B− was presented on the computer screen, the participant responded with the left-hand key to report that Target Color A was on the left side of the screen. When Color Pair B−A+ was presented on the computer screen, the participant responded with the right-hand key to report that Target Color A was on the right side of the screen.

The side on which each stimulus was presented was balanced across trials. Also balanced were the order of the two tasks of the experiment (see Table 2), the target colors for the PI stimuli (see Table 3), and the target colors for the reversal stimuli (see Table 4). A single participant would receive one of the two orders, so that within participants, the exposure to the stimulus and/or response was controlled outside of the paired associate; that is, A+ was only seen in the context of B−, and B− was seen only in the context of A+. It was only across participants that the color context for the target color was balanced. To have the participants presented with the same number of new target colors for each block of the test (PI baseline, response reversal baseline, PI test, and response reversal test), it was essential to have twice the number color pairs in the response reversal conditions relative to the PI conditions. The response reversal required double the number because the same color stimuli were presented again in the test condition, unlike the PI test. These considerations were combined to create four different versions of the test that were balanced across the groups.

Procedure

Practice. On the computer screen, the word "Target" was presented, along with the names of the two target colors. The participant was instructed that one of these two target colors would appear on every trial and to press one of two specified keys on the keyboard that corresponded to the side of the screen displaying the target color. A fixation point appeared in the middle of the computer screen between every trial. The participants were instructed to respond as quickly and as accurately as possible while the colors were still on the computer screen. Two target colors were presented for every block of the paired-associate simultaneous discrimination task (see Tables 3 and 4).

Table 2
Task Order Balance

Version 1	Version 2
Reversal baseline	Proactive interference baseline
Proactive interference baseline	Reversal baseline
Reversal test	Proactive interference test
Proactive interference test	Reversal test

Table 3
Proactive Interference Target-Color Balance

Version	Proactive interference baseline (A+B−)	Proactive interference test (C+A−)
1	Pink:orange	Brown:pink
	Purple:green	Gray:purple
2	Brown:pink	Pink:orange
	Gray:purple	Purple:green

We presented the participants with the target colors because alcoholic individuals have been shown to be inefficient in discovering a rule (e.g., Nixon & Parsons, 1991; Sullivan et al., 1993). We sought to reduce the need for problem solving and to emphasize memory testing in the alcoholic participants. Any potential inefficient problem-solving capability in alcoholic participants would be a confound for any differences we observed in the PI condition. By having control and alcoholic groups respond to the target colors, we were able to equate the groups on the baseline task.

At the beginning of the session, the participants received 16 practice trials that were participant paced; that is, the computer paused until one of the two specified keys were typed. Then the participants were presented with two new target colors and 16 speeded practice trials (700 ms) that were experimenter paced; that is, the computer did not wait for a response to proceed to the next color pair. The timing of the trials necessitated that the participants respond while the colors were on the screen, that is, within 700 ms. The participants received auditory feedback (correct or incorrect tone) from the computer on every trial for the entire experiment, for both practice and the test itself. Each of the four blocks of the actual test was preceded by a 5-s countdown presented in the middle of the computer screen (e.g., "5, 4, 3, 2, 1"), then the instructions for the two target colors remained on the screen for 5 s and were followed by 64 speeded trials. There was no intertrial interval during the 64 trials. The entire test, excluding practice, comprised 256 trials.

Associative PI testing. Figure 1A depicts the baseline and PI tasks of the simultaneous discrimination paired-associate paradigm. In the baseline condition, when Colors A and B were simultaneously presented, the participants were instructed to report on what side of the computer screen A was being presented

Table 4
Response Reversal Target-Color Balance

Response reversal baseline (A+B−)	Response reversal test (B+A−)
Version 1	
Black:red	Red:black
Black:yellow	Yellow:black
Blue:red	Red:blue
Blue:yellow	Yellow:blue
Version 2	
Red:black	Black:red
Yellow:black	Black:yellow
Red:blue	Blue:red
Yellow:blue	Blue:yellow

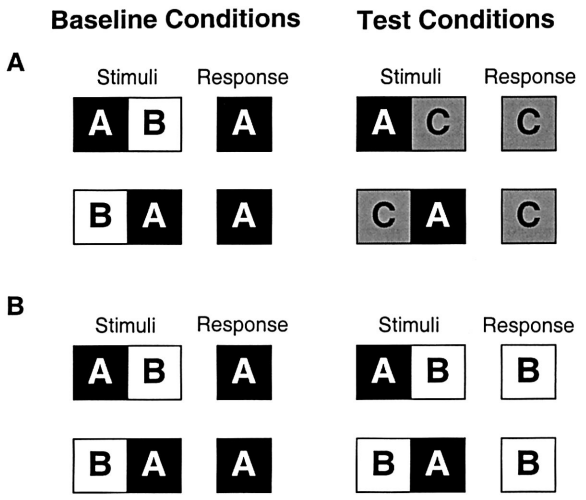


Figure 1. The simultaneous discrimination paired-associate paradigm. Panel A: The associative proactive interference task. Panel B: The response reversal task.

(A+B−). In the test condition, when Colors A and C were simultaneously presented, the participants were instructed to report on what side of the computer screen C was being presented (A−C+).

Response reversal testing. Figure 1B depicts the baseline and response reversal tasks of the paired-associate simultaneous discrimination paradigm. Four color pairs, with only two target colors, were presented for every block of the response reversal task (see Table 4). In the baseline condition, when Colors A and B were simultaneously presented, the participants were instructed to report on which side of the computer screen A was being presented (A+B−). In the test condition, when Colors A and B were simultaneously presented, the participants were instructed to report on which side of the computer screen B was being presented (A−B+). This constituted a simple response reversal.

Statistical Analysis

The participants were presented with a 64-trial baseline acquisition session and then a 64-trial PI acquisition session. Statistical analyses were performed on the trials where PI or the response reversal was expected to be maximal (i.e., the last eight trials of the baseline and the first eight trials of the experimental task). These particular trials were chosen as the "point of transfer." The last eight trials of the baseline were chosen to reflect the point of maximum strength of the association to produce baseline learning. The first eight trials of the experimental task were chosen to reflect the initial transfer of the acquired response to a new learning situation.

The proportion of correct responses or the median response time for correct responses was calculated and submitted to repeated measures 2 × 2 mixed analysis of variance (ANOVA) that contained one within-group factor (task condition) and one between-groups factor (alcohol status). An ANOVA was conducted on the behavioral data for four dependent measures: (a) PI accuracy, (b) PI response time, (c) response reversal accuracy, and (d) response reversal response time. Analyses of covariance (ANCOVA) were used to test whether selected participant characteristics, including age, education, NART IQ, and GMI, would account for group differences yielded from the single ANOVAs.

Results

Color Identification and Color Blindness

The two groups did not differ in color identification, $t(32) = 0.49$. One control participant was identified as colorblind to one color pair. Therefore, the color misperceived by this participant was substituted with another color readily discerned.

Effect of Balancing Target Colors and Task Order

Balancing the target color and task order produced four different versions of the experiment. The target color plus task order was included in the analysis to determine whether balancing the target colors would alter the difficulty of acquiring either the PI or response reversal task. Then the task order alone was included in the analysis to determine whether receiving either the PI baseline first or the response reversal baseline first influenced the outcome. Each of the four mixed ANOVAs included one within-group factor (task condition) and two between-groups factors: a 2 × 2 × 4 mixed ANOVA with one within-group factor (task condition) and two between-groups factors (alcohol status and target color) or a 2 × 2 × 2 mixed ANOVA with one within-group factor (task condition) and two between-groups factors (alcohol status and task order).

None of the ANOVAs yielded significant main effects of target color or task order or significant interactions. Therefore, neither the color context in which the participants received the target color nor the order in which the participants received the two tasks affected the acquisition of either task. Thus, target color was collapsed and not considered as a factor, and then task order was collapsed and not considered as a factor for the final analysis. Neither balancing the target color nor balancing the order had any effect on either task; the participants performed equally well across the four combinations that balanced the target colors and the task order.

Associative PI

Accuracy. The performance of alcoholic and control groups did not differ on the baseline color pairs, $t(32) = 1.18$, $p = .25$. There was a significant Alcohol Status × Task Condition interaction, $F(1, 32) = 5.29$, $p = .03$ (illustrated in Figure 2A); the control group made significantly fewer correct responses than the alcoholic group at the point of transfer. There was a marginally significant overall effect of alcohol status, $F(1, 32) = 3.93$, $p = .056$, indicating that control group tended to perform at a lower level than the alcoholic group in acquiring the interfering color pairs. There was a main effect of task condition, $F(1, 32) = 22.65$, $p = .0001$, indicating significantly lower correct responses in the PI condition relative to the baseline condition.

Response time. The performance of alcoholic and control groups did not differ on the baseline color pairs, $t(32) = 0.78$, $p = .44$. There was no overall difference between the control and alcoholic participants in response

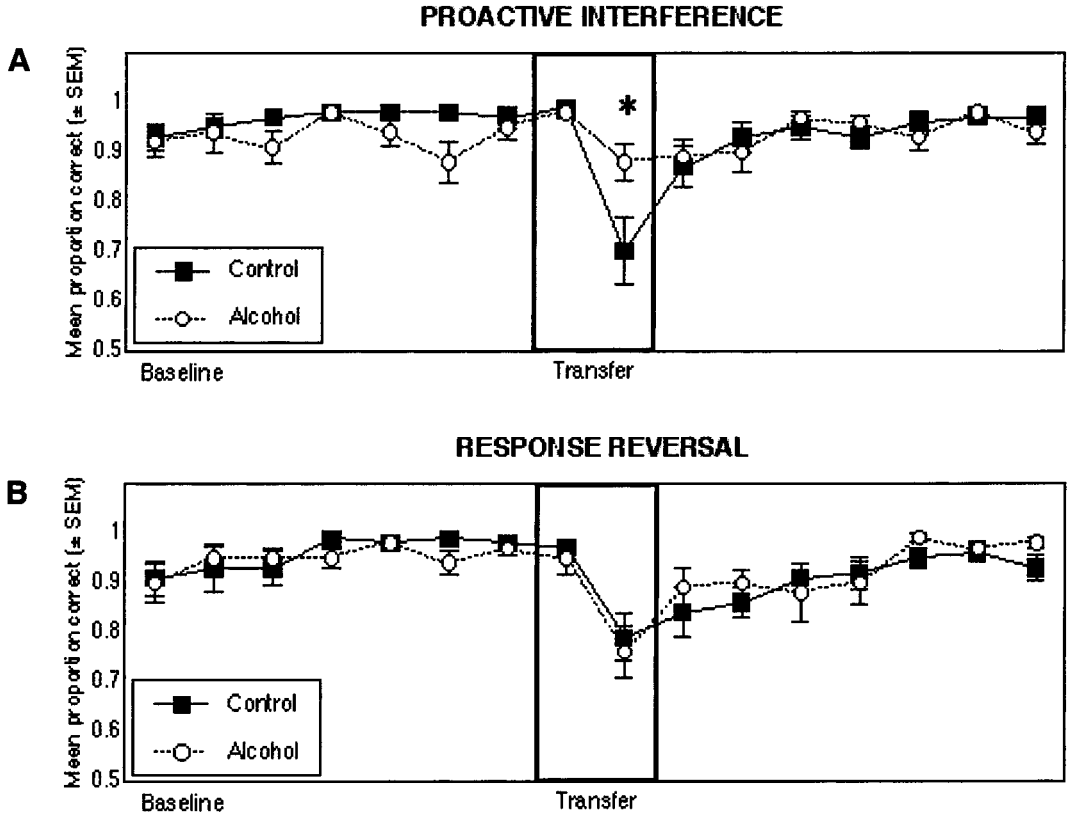


Figure 2. A: Performance on the associative proactive interference (PI) task as mean proportion of correct responses; acquisition of the baseline color pairs (A+B−) and then the proactive interference color pairs (A−C+). * $p < .05$. B: Performance on the response reversal task as mean proportion of correct responses; acquisition of the baseline color pairs (A+B−) and then the reversal color pairs (B+A−). Analyses were performed on the point of transfer, where PI or reversal was expected to be maximal.

time, $F(1, 32) = 0.56$. All of the participants slowed their response time in the PI condition relative to their baseline performance, evidenced in a main effect of task condition, $F(1, 32) = 26.85$, $p = .0001$. There was a marginally significant Alcohol Status × Task Condition interaction, $F(1, 32) = 3.70$, $p = .06$, with the control participants tending to respond more slowly than the alcoholic participants did.

Response Reversal

Accuracy. The alcoholic and control participants did not differ on their performance on the baseline color pairs, $t(32) = 0.35$, $p = .73$. There was a main effect of task condition, $F(1, 32) = 23.04$, $p = .0001$, indicating a difference between baseline and the acquisition of the response reversal task. There was no overall effect of alcohol status, $F(1, 32) = 0.23$, nor a significant Response Reversal × Alcohol Status interaction, $F(1, 32) = 0.04$. Figure 2B shows that there was not a differential sensitivity to response reversal between the two groups.

Response time. The alcoholic and control participants did not differ in their performance on the baseline color pairs, $t(32) = 1.22$, $p = .23$. There was a main effect of alcohol status, $F(1, 32) = 4.30$, $p = .05$, where the alcoholic participants responded significantly faster ($M = 445.60$ ms, $SD = 76.97$) than the control participants did ($M = 407.31$ ms, $SD = 61.73$). Again, there was a main effect of task condition, $F(1, 32) = 27.18$, $p = .0001$. All of the participants slowed down when responding to the response reversal stimuli, but there was no relative difference in slowing between the groups, evidenced in the absence of a Response Reversal × Alcohol Status interaction, $F(1, 32) = 0.89$.

Relationship Between PI and Response Reversal

As an additional assessment of a task dissociation in alcoholic participants, separate correlations were calculated within each group to test the relationship between the two tasks. Differences between correlations were submitted to a Fisher's Z transformation and then to a Z test.

Accuracy. In control participants, accuracy scores of the PI and response reversal tests were not significantly correlated ($r = .32$, $p = .19$). When an outlier in the response reversal condition (3.73 *SD* from the mean) was removed from the control correlation analysis, the relation-

ship became significantly correlated ($r = .69$, $p = .002$). In alcoholic participants, accuracy scores of the PI and reversal test were not significantly correlated ($r = -.23$, $p = .39$). The Z test computed with all of the participants revealed a modest difference between the groups ($Z = 1.49$, $p = .07$). The Z test computed without the one outlier in the control group revealed a significant difference between the groups ($Z = 2.85$, $p = .002$; see Figure 3).

Response time. Controls showed a significant relationship between the magnitude of their PI and response reversal response times ($r = .57$, $p = .01$). Again, the alcoholic participants demonstrated a poor relationship between the two tasks ($r = .31$, $p = .24$). The Z test revealed a significant ($Z = 2.55$, $p = .005$) difference between the correlation of the two groups.

ANCOVA for Demographic and Neuropsychological Variables

Given the significant group differences in age, education, NART IQ, and the GMI (see Table 1), the effect of each of these variables on the four principal dependent measures was tested as covariates with ANCOVA. In all but one instance, the homogeneity-of-variance assumption was met; the exception involved the PI accuracy measure and education, thus precluding an ANCOVA for this measure. When the effects of age, education, NART IQ, and GMI were used as covariates for the remaining comparisons, the group differences observed with the simple ANOVAs persisted in all but one case. Specifically, the ANOVA for response time in the associative PI task indicated that the alcoholic participants were marginally significantly faster than the controls ($p = .06$); however, when age was entered as a covariate in the ANCOVA, the response time of the groups was no longer significantly different, $F(1, 31) = 1.91$, $p = .18$. Thus, group differences in response time in the PI task were accounted by differences in age.

Additional analyses on a subset of alcoholic ($n = 11$) and control ($n = 11$) participants matched for age, education, NART, and Dementia Rating Scale yielded the same behavioral effects as when data from all available participants were included in the analysis; the alcoholic participants showed greater release from PI, although comparable response reversal, relative to controls (see the Appendix).

Discussion

With this associative learning paradigm adapted from one previously used in rats, detoxified alcoholic participants showed significantly less PI than control participants but performed like controls on a simple response reversal task. This task dissociation in alcoholic participants was further supported by correlational analyses (see Figure 3), where, unlike the pattern observed in controls, performance levels in the PI and response reversal tasks were not significantly correlated in the alcoholic participants. Examination of the baseline performance alone could not help to determine whether either group had learned anything about the B context with the A+B− paired associate until they were confronted with A in the context of C (A−C+). When participants were challenged this way, control participants demonstrated significantly more PI than alcoholic participants. Associative PI is a reflection of past learning and may serve as an index of mnemonic binding of paired-associate stimuli. Thus, we propose that the alcoholic participants' lack of persisting interference may reflect a form of memory abnormality.

Although there were no explicit task demands to do so, we speculate that the control participants, and not the alcoholic participants, may have naturally formed a configural representation of the baseline paired-associate stimuli. We theorize that the two stimuli presented as paired associates independently entered into an association with the response in both groups. However, what is proposed to be deficient in alcoholic participants is the ability to create a unitary representation of the paired associates and associatively bind that configural information as a single association to the response. This would not necessarily be revealed in the response reversal task because A is re-presented in its

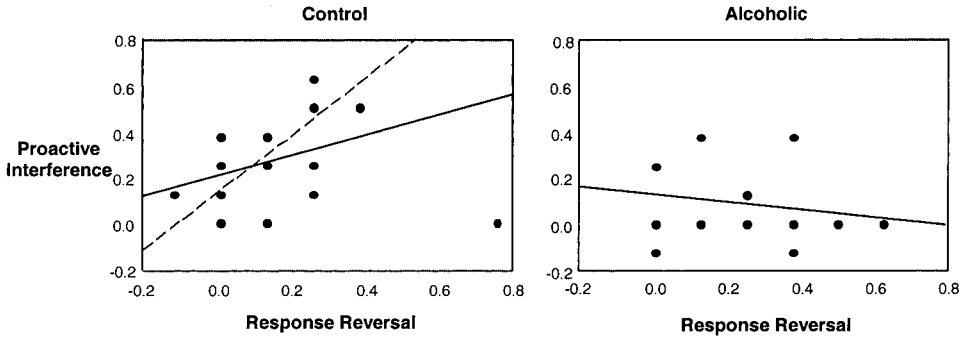


Figure 3. Scatter plot of the relationship between proportion of correct responses on the associative proactive interference and the response reversal tasks. A Z test computed with all of the participants (solid line) revealed a modest difference between control and alcoholic groups ($Z = 1.49$, $p = .07$). A Z test computed without the one outlier (3.73 *SD* from the mean) in the control group (dotted line) revealed a significant difference between controls and alcoholics ($Z = 2.85$, $p = .002$).

original context and therefore the context can act as a retrieval cue for the original stimulus–response memory for both groups. This interpretation stems from the alcoholic participants' inappropriate release from associative PI and intact response reversal impairment. We further theorize that learning with a compromised cholinergic system, which may occur in chronic alcoholism, may impair configural processing of paired-associate stimuli while sparing elemental processing of both components.

It has been argued that patients with alcoholic Korsakoff's syndrome, who have demonstrated pathology in the basal forebrain nuclei, have an encoding dysfunction. This interpretation stems from Korsakoff patients' significantly greater release from PI when compared with controls to shallow-level contextual changes, such as changes in word color (Winocur, Kinsbourne, & Moscovitch, 1981). In light of this result, the lack of PI release typically attributed to Korsakoff patients (Butters & Cermak, 1980) may reflect relatively poor processing of complex information, and the shallow level of contextual cuing, used in the Winocur et al. study, may have permitted more effective encoding or less buildup of PI in the Korsakoff patients than occurred in controls. In the present study, the new target colors appeared in a new context, and the alcoholic participants showed a greater release from PI than controls. This inappropriate release from PI parallels the benefits of contextual cuing observed in Korsakoff patients. By contrast, when the new target colors appeared in the old context, both alcoholic participants and controls demonstrated comparable difficulty transferring to the new response.

Theoretical Model of Associative Learning in Humans

We have developed a model (see Figures 4 and 5) that depicts associative binding of paired-associate stimuli and its theoretical effect on the learning of new, related information. We propose that the mechanism that strengthens this associative binding is cholinergic activity from afferents arising from the basal forebrain. Confirmation of our speculations regarding the presence and influence of cho-

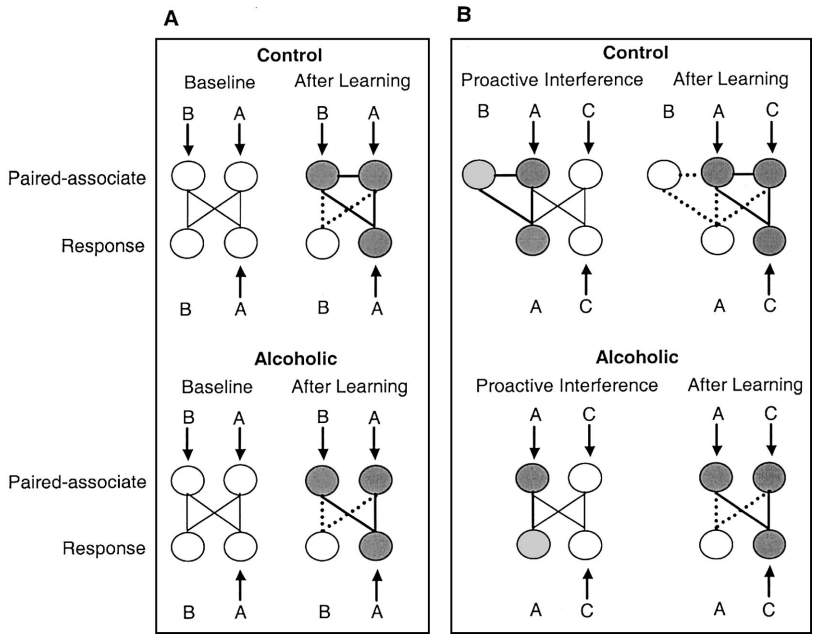


Figure 4. A simplified representation of the hypothesized role of acetylcholine in binding the paired-associate stimuli during learning. In these groups of neurons, the degrees of shading represent levels of neuronal excitatory activation, the thickness of the lines represents the strengthening of the excitatory connections to the correct responses through learning, and the dotted lines represent the strengthening of the inhibitory connections to the incorrect responses through learning. A: During learning of the initial baseline paired-associate stimuli (A+B−), Colors A and B activate the neurons on the top row, and those neurons strengthen connections to the correct response A. Unlike the alcoholic group, the control group strengthens the connections between the sensory stimuli A and B on the top row that associatively bind the paired-associate stimuli to each other and to the correct response to A. B: During learning of the interfering paired-associate stimuli (A−C+), Colors A and C activate the neurons on the top row but because of the strength of the connections between A and B in control participants, the neural activity spreads along the previously strengthened connection from A to B (not physically present). Therefore, the incorrect response to A receives activation from A and the past learning experience of B; this strong incorrect response to A initially competes with acquiring the correct response C. Because the alcoholic participants do not bind A and B together, learning the interfering paired-associate stimuli is less affected by their past learning of B.

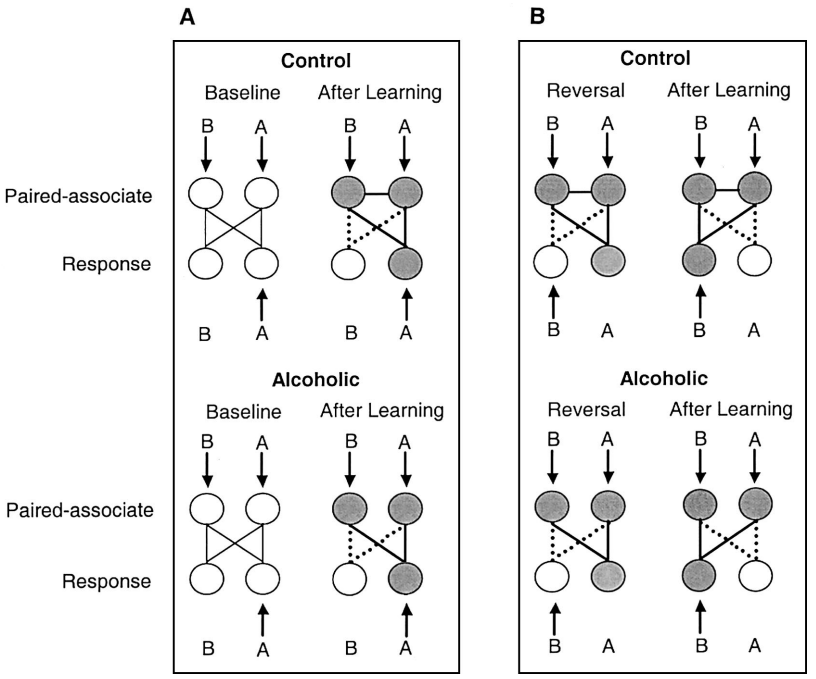


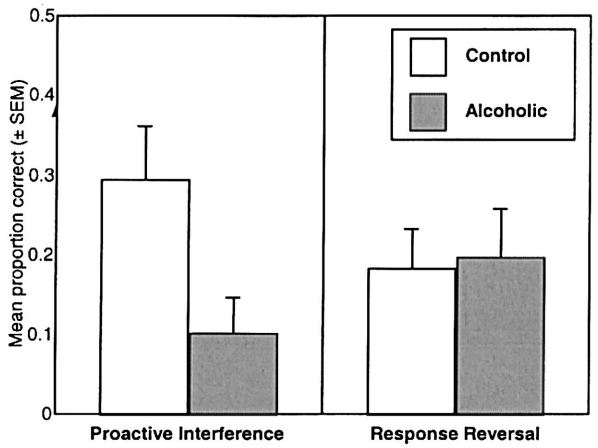
Figure 5. A simplified representation of the hypothesized role of acetylcholine in binding the paired-associate stimuli during learning. In these groups of neurons, the degrees of shading represent levels of excitatory neuronal activation, the thickness of the lines represents the strengthening of the excitatory connections to the correct responses through learning, and the dotted lines represent the strengthening of the inhibitory connections to the incorrect responses through learning. A: During learning of the initial baseline paired-associate stimuli (A+B−), Colors A and B activate the neurons on the top row, and those neurons strengthen connections to the correct response A. Unlike the alcoholic group, the control group strengthens the connections between the sensory stimuli A and B on the top row that associatively bind the paired-associate stimuli to each other and to the correct response to A. B: During learning of the response reversal (A−B+), the control and alcoholic groups have been equated because the exact same stimuli are present in the baseline and response reversal conditions and therefore show an equal response reversal impairment.

linergic dysfunction on associative binding requires future experiments in which the cholinergic system is pharmacologically challenged.

The model applies to the present study as follows: The control participants showed a larger magnitude of an associative PI effect than a response reversal effect, $t(17) = 2.24$, $p = .04$ (see Figure 6A). We theorize that in controls, the associative interference task involves suppressing a past association with Color B while switching the response from Color A to Color C. With ACh present, the model depicts strong associative binding of the paired-associate stimuli to each other (see Figure 4A). Although the Color B component of the baseline paired-associate stimuli was not physically present while they learned the interfering paired associate, the controls were strongly influenced by the memory of Color B while trying to acquire Color C. We further theorize that the controls, in contrast to the alcoholic participants, implicitly learned the significance of the target color in a specific color context by binding the paired-associate stimuli together. The alcoholic participants may have learned only the direct stimulus–response association (see Figure 4B). The data reveal, and the model depicts, that learning paired-associate stimuli with a compromised cholinergic system can impair true associative stimulus–stimulus binding of the baseline paired associates and therefore generate less PI to surmount. We speculate that the alcoholic participants were able to suppress their response to the old target color better than the control participants did because they lacked strong associative binding of the paired-associate stimuli to each other.

The model (see Figure 5) is able to account for the fact that alcoholic participants and controls show equivalent performance on the response reversal task, $t(32) = 0.48$, $p = .60$; the same paired-associate stimuli were represented in the test condition, so the physical presence of the original stimulus context acted as the retrieval cue of the previous target for both groups. The correlational analyses support the notion that the associative PI and response reversal tasks are dissociable in alcoholic participants. Figure 6B details how intact and compromised cholinergic modulation would influence learning of paired-associate stimuli and affect the magnitude of associative PI and response reversal.

A



B

	Control	Alcoholic
Associative Proactive Interference		
Unlearn strengthened response to A	YES	YES
Unlearn inhibited response to B	YES	NO
Unbind AB paired-associate configuration	YES	NO
Response Reversal		
Unlearn strengthened response to A	YES	YES
Unlearn inhibited response to B	YES	YES
Unbind AB paired-associate configuration	NO	NO

Figure 6. Summary of fit for behavioral data to the models. A: Magnitude of proactive interference and response reversal effects in control and alcoholic participants. B: Cognitive processes involved in acquiring the interfering stimuli and the response reversal.

Dysfunction of Associative Binding in Nonamnesic Chronic Alcoholic Individuals

Chronic alcoholic individuals have been described (Butters & Cermak, 1980) as having a "subtle, but real, information-processing deficit that impairs their ability to learn and remember efficiently" (p. 164). This observation is supported by the PI data presented here. Associative learning, as examined in the present study, entails selectively learning relevant cues in a particular stimulus array and then selecting and learning the relevant response to make based on those attended-to cues. This ability increases the chances of learning new information rapidly without "overwriting" previously acquired knowledge. On the basis of the similarity between the stimulus representations, inappropriate responses were predicted to transfer into a new learning situation in the associative PI condition; this was the case for the control participants. The alcoholic participants' performance pattern suggests that they did not reinstate their previously acquired knowledge from the baseline condition while acquiring the interfering stimuli. We propose that the psychological mechanism underlying acquisition of a stimulus–stimulus relationship and interference between two stimuli is associative binding. Further, we hypothesize that the proposed lack of associative binding in detoxified nonamnesic alcoholic participants reflects an alcohol-related alteration in cholinergic function in the basal forebrain.

In conclusion, the results supported our hypothesis that alcoholic participants would demonstrate an inappropriate release from PI; nonetheless, this finding requires replication and extension with larger samples that include men and women. In light of the known reduction of cholinergic function in the basal forebrain arising from chronic alcohol consumption, future studies that manipulate the cholinergic system pharmacologically are required to confirm our speculations regarding the essential role of ACh in associative binding processes and the interleaving of temporally distinct memories. Additional investigation focusing on parsing the psychological mechanisms of associative binding could target whether chronic alcoholism decreases the processing of specific stimulus features during ongoing perception (attention), decreases the availability of information for future reference (memory), or both.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Arendt, T. (1994). Impairment in memory function and neurodegenerative changes in the cholinergic basal forebrain system induced by chronic intake of ethanol. *Journal of Neural Transmission, 44,* 173–187.

Arendt, T., Allen, Y., Marchbank, R. M., Schugens, M. M., Sinden, J., Lantos, P. L., & Gray, J. A. (1989). Cholinergic system and memory in the rat: Effects of chronic ethanol, embryonic basal forebrain transplants and excitotoxic lesions of the cholinergic basal forebrain projection system. *Neuroscience, 33,* 435–462.

Baxter, M. G., & Chiba, A. A. (1999). Cognitive functions of the basal forebrain. *Current Opinion in Neurobiology, 9,* 178–183.

Butters, N., & Cermak, L. S. (1980). Memory and cognitive disorders of chronic alcoholics. In *Alcoholic Korsakoff's syndrome: An information-processing approach to amnesia* (pp. 157–169). New York: Academic Press.

Casamenti, F., Scali, C., Vannucchi, M., Bartolini, L., & Pepeu, G. (1993). Long-term ethanol consumption by rats: Effect on acetylcholine release *in vivo,* choline acetylcholine activity, and behavior. *Neuroscience, 56,* 465–471.

Cohen, J. D., MacWhinney, B., Flatt, M., & Provost, J. (1993). PsyScope: A raw graphic interaction environment for designing psychology experiments. *Behavioral Research Methods, Instruments, & Computers, 25,* 257–271.

De Rosa, E., & Baxter, M. G. (2002). The basal forebrain. In L. Nadel (Ed.), *Encyclopedia of cognitive science* (Vol. 1, pp. 322–328). London: Macmillan Reference Ltd.

De Rosa, E., & Hasselmo, M. E. (2000). Muscarinic cholinergic neuromodulation reduces proactive interference between stored odor memories during associative learning in rats. *Behavioral Neuroscience, 114,* 32–41.

De Rosa, E., Hasselmo, M. E., & Baxter, M. G. (2001). Contribution of the cholinergic basal forebrain to proactive interference from stored odor memories during associative learning in rats. *Behavioral Neuroscience, 115,* 314–327.

Everitt, B. J., & Robbins, T. W. (1997). Central cholinergic systems and cognition. *Annual Review of Psychology, 48,* 649–684.

Floyd, E. A., Young-Seigler, A. C., Ford, B. D., Reasor, J. D., Moore, E. L., Townsel, J. G., & Rucker, H. K. (1997). Chronic ethanol ingestion produces cholinergic hypofunction in the rat brain. *Alcohol, 14,* 93–98.

Freund, G., & Ballinger, W. (1989). Loss of cholinergic muscarinic and benzodiazepine neuroreceptors from hippocampus of alcohol abusers. *Alcohol, 6,* 23–31.

Frye, G. D., Taylor, L., Grover, C. A., Fincher, A. S., & Griffith, W. H. (1995). Acute ethanol dependence or long-term ethanol treatment and abstinence do not reduce hippocampal responses to carbachol. *Alcohol, 12,* 29–36.

Hasselmo, M. E., & Bower, J. M. (1993). Acetylcholine and memory. *Trends in Neuroscience, 16,* 218–222.

Ishihara, S. (2000). *Ishihara's test for colour deficiency* (Rev. ed.). Tokyo: Kanehara.

Jernigan, T. L., Butters, N., DiTraglia, G., Schafer, K., Smith, T., Irwin, M., et al. (1991). Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. *Alcoholism: Clinical and Experimental Research, 15,* 418–427.

Kausler, D. H. (1974). *Psychology of verbal learning and memory.* New York: Academic Press.

Little, H. J. (1999). The contribution of electrophysiology to knowledge of the acute and chronic effects of ethanol. *Pharmacology & Therapeutics, 84,* 333–353.

Mackintosh, N. J. (1983). *Conditioning and associative learning.* New York: Clarendon Press.

Mattis, S. (1998). *Dementia Rating Scale (DRS) professional manual*. Odessa, FL: Psychological Assessment Resources.

Melis, F., Stancampiano, R., Imperato, A., Carta, G., & Fadda, F. (1996). Chronic ethanol consumption in rats: Correlation between memory performance and hippocampal acetylcholine release *in vivo. Neuroscience, 74,* 155–159.

Nelson, H. E. (1982). *National Adult Reading Test (NART): Test manual.* Windsor, England: NFER-Nelson.

Nixon, S. J., & Parsons, O. A. (1991). Alcohol-related efficiency deficits using an ecologically valid test. *Alcoholism: Clinical and Experimental Research, 15,* 601–606.

Nixon, S. J., Tivis, R. D., Jenkins, M. R., & Parsons, O. A. (1998). Effects of cues on memory in alcoholics and controls. *Alcoholism: Clinical and Experimental Research, 22,* 1065–1069.

Nordberg, A., Larsson, C., Perdahl, E., & Winblad, B. (1982). Changes in cholinergic activity in human hippocampus following chronic alcohol abuse. *Pharmacology, Biochemistry and Behavior, 18,* 297–400.

Nordberg, A., & Wahlstrom, G. (1992). Cholinergic mechanisms in physical dependence on barbiturates, ethanol and benzodiazepines. *Journal of Neural Transmission, 88,* 199–221.

Oscar-Berman, M. (2000). Neuropsychological vulnerabilities in chronic alcoholism. In A. Noronha, M. Eckardt, & K. Warren (Eds.), *Review of NIAAA neuroscience and behavioral research portfolio* (NIAAA Research Monograph No. 34, pp. 437–471). Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism.

Oscar-Berman, M., Clancy, J. P., & Weber, D. A. (1993). Discrepancies between IQ and memory scores in alcoholism and aging. *Clinical Neuropsychologist, 7,* 281–296.

Oscar-Berman, M., & Ellis, R. J. (1987). Cognitive deficits related to memory impairments in alcoholism. In M. Galanter (Ed.), *Recent developments in alcoholism* (pp. 59–80). New York: Plenum.

Parsons, O. A., & Nixon, S. J. (1993). Neurobehavioral sequelae of alcoholism. *Neurologic Clinics, 11,* 205–218.

Pfefferbaum, A., Lim, K. O., Zipursky, R. B., Mathalon, D. H., Rosenbloom, M. J., Lane, B., et al. (1992). Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: A quantitative MRI study. *Alcoholism: Clinical and Experimental Research, 16,* 1078–1089.

Pfefferbaum, A., Rosenbloom, M., Crusan, K., & Jernigan, T. L. (1988). Brain CT changes in alcoholics: Effects of age and alcohol consumption. *Alcoholism: Clinical and Experimental Research, 12,* 81–87.

Rothberg, B. S., Yasuda, R. P., Satkus, S. A., Wolfe, B. B., & Hunter, B. E. (1993). Effects of chronic ethanol on cholinergic actions in rat hippocampus: Electrophysiological studies and quantification of m1–m5 muscarinic receptor subtypes. *Brain Research, 631,* 227–234.

Rye, D. B., Wainer, B. H., Mesulam, M. M., Mufson, E. J., & Saper, C. B. (1984). Cortical projections arising from the basal forebrain: A study of cholinergic and noncholinergic components employing combined retrograde tracing and immunochemical localization of choline acetyltransferase. *Neuroscience, 13,* 627–643.

Salmon, D. P., & Butters, N. (1987). The etiology and neuropathology of alcoholic Korsakoff's syndrome: Some evidence for the role of the basal forebrain. In M. Galanter (Ed.), *Recent developments in alcoholism* (pp. 27–58). New York: Plenum.

Sarter, M., & Bruno, J. P. (1997). Cognitive functions of cortical acetylcholine: Toward a unifying hypothesis. *Brain Research Review, 23,* 28–46.

Sullivan, E. V., Fama, R., Rosenbloom, M. J., & Pfefferbaum, A. (2002). A profile of neuropsychological deficits in alcoholic women. *Neuropsychology, 16,* 74–83.

Sullivan, E. V., Mathalon, D. H., Lim, K. O., Marsh, L., & Pfefferbaum, A. (1998). Patterns of regional cortical dysmorphology distinguishing schizophrenia and chronic alcoholism. *Biological Psychiatry, 15,* 43, 118–131.

Sullivan, E. V., Mathalon, D. H., Zipursky, R. B., Kersteen-Tucker, Z., Knight, R. T., & Pfefferbaum, A. (1993). Factors of the Wisconsin Card Sorting Test as measures of frontal-lobe function in schizophrenia and in chronic alcoholism. *Psychiatry Research, 46,* 175–199.

Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (2000). Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcoholism: Clinical and Experimental Research, 24,* 611–625.

Wechsler, D. (1987). *Wechsler Memory Scale—Revised.* San Antonio, TX: Psychological Corporation.

Winocur, G., Kinsbourne, M., & Moscovitch, M. (1981). The effect of cueing on release from proactive interference in Korsakoff amnesic patients. *Journal of Experimental Psychology: Human Learning and Memory, 7,* 56–65.

(*Appendix follows*)

Appendix

Matched Participant Appendix

Table A1
Matched Participant Characteristics

Variable	Alcoholic		Control		Comparison	
	M	*SD*	*M*	*SD*	*t*(20)	*p*
Age (years)	55.1	9.0	55.2	9.6	0.03	.98
Education (years)	15.9	2.5	17.0	1.3	1.3	.21
NART	110.0	8.6	114.6	4.8	1.6	.13
General Memory Index	112.8	12.5	122.9	7.0	2.3	.03
Delayed Memory Index	114.1	13.7	126.9	6.2	2.8	.01
Dementia Rating Scale	140.2	2.6	141.4	1.5	1.3	.21

	Matched participant alcohol history			
	Alcoholic		Control	
	M	*SD*	*M*	*SD*
Median length of sobriety (days)	71			
Total lifetime alcohol consumption (kg)	1,358.2	1,301.0	114.0	83.9

Note. $n = 11$ for alcoholic and control participants. For median length of sobriety, range = 11–742 days. General Memory Index and Delayed Memory Index measured by Wechsler Memory Scale—Revised (Wechsler, 1987). NART = premorbid estimation of IQ, measured by the National Adult Reading Test (Nelson, 1982).

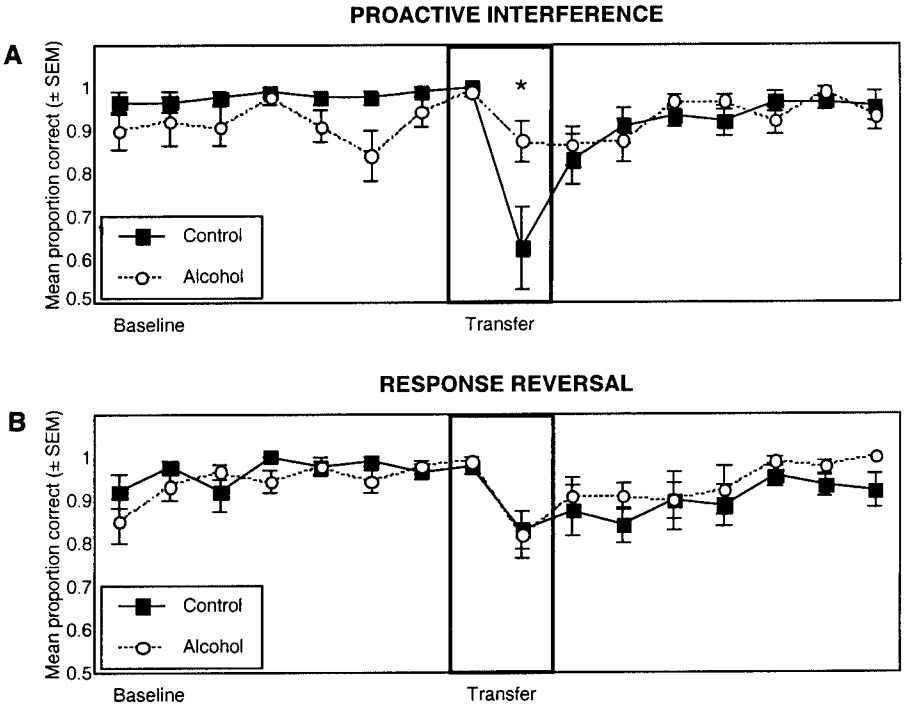


Figure A1. Participants matched for age, education, National Adult Reading Test IQ, and dementia. A: Performance on the associative proactive interference (PI) task as mean proportion of correct responses; acquisition of the baseline color pairs (A+B−) and then the proactive interference color pairs (A−C+). * $p < .05$. B: Performance on the response reversal task as mean proportion of correct responses; acquisition of the baseline color pairs (A+B−) and then the reversal color pairs (B+A−). Analyses were performed on the point of transfer, where PI or reversal was expected to be maximal.

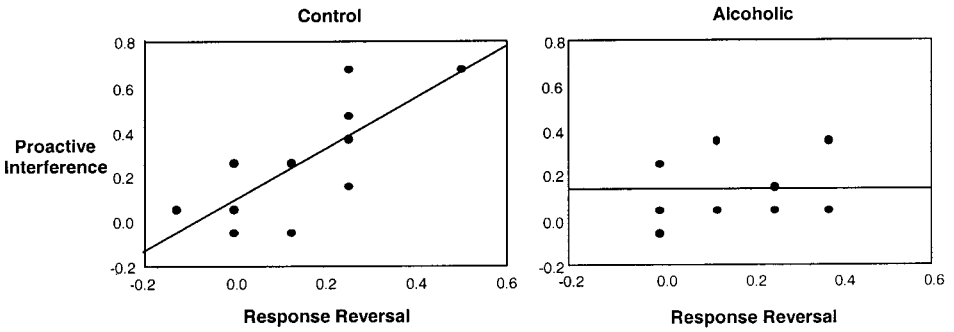


Figure A2. Scatter plot of the relationship between proportion of correct responses on the associative proactive interference and the response reversal tasks in participants matched for age, education, the National Adult Reading Test IQ, and the Dementia Rating Scale. A *Z* test indicated a significant difference between control and alcoholic participants ($Z = 1.95$, $p = .03$).

Received July 26, 2002
Revision received November 15, 2002
Accepted November 21, 2002 ■