Published in final edited form as:

J Clin Exp Neuropsychol. 2011 July ; 33(6): 609–618. doi:10.1080/13803395.2010.543887.

Nicotine Effects on Immediate and Delayed Verbal Memory After Substance Use Detoxification

Rebecca Gilbertson, Ph.D.^{1,2}, Jeff Boissoneault, B.A.¹, Robert Prather, B.A.¹, and Sara Jo Nixon, Ph.D.¹

¹ Department of Psychiatry, University of Florida, Gainesville FL 32610 USA

² Department of Psychology, Lycoming College, Williamsport, PA 17701 USA

Abstract

Decrements in verbal memory are commonly reported by detoxified treatment-seeking individuals. Although acute nicotine has been shown to improve attentional performance, its effects on verbal memory in substance abusers have not been addressed. Treatment-seeking alcohol dependent (ALCS N=29; 14 male), illicit stimulant (predominantly cocaine) dependent (STIMS N = 25; 15 male) and alcohol and illicit stimulant dependent (ALC/STIMS N = 50; 35 male) participants with co-morbid nicotine dependence were studied. Subjects had been abstinent from their drugs of choice for 41(±18) days and were in short-term abstinence from tobacco (~8–10 hours). Subjects received double-blind administration of either transdermal nicotine (High dose: 21/14 mg for men and women, respectively or Low dose: 7 mg) or placebo. The Logical Memory (LM) subtest from the Wechsler Memory Scale -Revised (WMS-R) was used to assess immediate and delayed verbal memory recall. Results indicated that STIMS receiving the high dose of nicotine recalled more words at immediate recall than STIMS who received placebo. Trend level differences were also noted at delayed recall between STIM nicotine and placebo doses. Nicotine failed to impact either recall in alcoholic subgroups. Although not the primary focus, results also revealed differences in the forgetting rates between the groups with the ALC/STIMS demonstrating the steepest forgetting slope. In summary, this study suggests that nicotine effects may be differentially experienced by substance using subgroups; that nicotine may have a direct effect on memory and, that considering neurocognitive processes (e.g., encoding vs. retrieval) underlying endpoint indicators (e.g. correct recall) may be critical in predicting outcomes.

Introduction

There is considerable heterogeneity in the breadth and severity of neuropsychological and cognitive deficits among detoxified substance abusers (Lawton-Craddock et al., 2003; Nixon and Phillips, 1999; Oscar-Berman & Ellis, 1987; Parsons & Nixon, 1993; Sullivan et al., 2002). One domain with considerable real-world relevance, but notable empirical variability is verbal memory performance (Beatty et al., 1995; Nixon et al., 1987; Nixon et al., 1998; Rosenbloom et al., 2004; Ardila et al., 1991; Mittenberg and Motta, 1993; Massman, 1979; Parsons and Prigatano, 1977; Medina et al., 2006). Inconsistency among empirical studies may be related to task-dependent factors such as difficulty and the fact that many verbal tasks involve highly practiced information or processes. However, it may also be related to previously understudied drug-related issues such as drug of choice (Beatty et al., 1995; Horner, 1997; Oscar-Berman & Ellis, 1987; Selby and Azrin, 1998) and drug use

comorbidities including nicotine. Nicotine use, while highly prevalent among treatment seeking substance abusers, has been largely ignored in laboratory studies of long-term substance-related cognitive deficits. Given nicotine's cognitive enhancing properties, this oversight may have resulted in an underestimation of alcohol and other drug-related deficits by failing to control for nicotine's potential to mask or compensate for such deficits (Ceballos, 2006a; Levin et al., 2006).

Recent studies comparing the cognitive effects of nicotine among detoxified substance abusers and community controls who also smoke have revealed that acute nicotine administration affects controls' performance less robustly than alcoholics (Nixon, et al; 2007), that subgroups defined on the basis of their drugs of choice vary in their sensitivity to acute nicotine (Ceballos, et al, 2006b), and that nicotine may affect neuropsychological and neurophysiological processes differently, perhaps in conjunction with drug of choice (Ceballos, et al; 2008). The majority of these findings concern tasks with strong attentional demands (Nixon et al., 2007).

However, nicotine's effects on verbal memory are less clear. Nicotine generally improves verbal memory function (Warburton and Mancuso, 1998; Rusted et al., 1992; 1998) among community controls. However the mechanism for this action remains unclear, with some studies suggesting the effect is mediated through enhanced attentional mechanisms during initial acquisition (Warburton and Mancuso, 1998) while others support a more direct effect on memory retrieval (Rusted et al., 1992, 1998).

Given the import of verbal memory in post-treatment adaptation and the understudied impact of nicotine on these processes, the current study was designed to examine acute nicotine effects on verbal memory among treatment-seeking substance abusers, subgrouped on the basis of their drugs of choice. Based on the "real-world" relevance of processing short vignettes of current events, we elected to focus on logical semantic memory; selecting the Logical Memory (LM) subtest from the Wechsler Memory Scale Revised (WMS-R; Wechsler, 1987). To disentangle encoding from consolidation or retrieval processes, we included both immediate and delayed recall (Russell, 1975; Nixon, et al, 1987). Immediate recall, occurring immediately after story presentation, relies heavily on initial encoding processes which in turn rely on attention functions, semantic activation, and event sequencing. In comparison, delayed recall, when unannounced, allows for the passage of time without the benefit of rehearsal strategies and relies more heavily on consolidation and retrieval processes/strategies which are less dependent on attention and working memory (see Nixon et al, 1987).

Therefore, based on our previous work (Nixon, et al, 2007; Ceballos, et al 2005) demonstrating nicotine's effects on attention, we predicted that nicotine's acute effect on verbal memory would occur through attentional mechanisms and thus be visible at immediate recall. In contrast, if nicotine directly affected higher order components of memory, positive effects of nicotine administration would be evident on delayed recall and/or both recall tasks. As noted previously, some of our work suggests that nicotine effects may be affected by the specific drug of abuse (Ceballos, et al, 2006b). However, given the task differences between this and previous work, we felt strong hypotheses were premature. Therefore, we asked the question of whether the three groups would differ in their response to nicotine.

Methods

Subjects

All procedures were approved by the University of Kentucky Medical Institutional Review Board and the University of Florida Medical Institutional Review Board. Subjects gave written informed consent prior to study involvement and were compensated for their time for both the screening and laboratory phases. Subjects were detoxified substance dependent males and females between the ages of 25 and 59 with a minimum of 10 years of education ($N = 104$). Based on the cDIS, subjects met DSM-IV (APA, 1994) criteria for current alcohol (ALCS $n=29$; 14 male), illicit stimulant (STIMS $n = 25$; 15 male) or alcohol and illicit stimulant dependence (ALC/STIMS $n = 50$; 35 male) in addition to current nicotine dependence. All subjects were recruited from inpatient drug and alcohol treatment facilities and were between 15–99 days sober at the time of testing. Illicit stimulant individuals were predominately cocaine dependent (96%; 3% amphetamine dependent; 1% other). Females who were pregnant or breast feeding as determined by self-report and urine analysis at the time of testing were not allowed to participate in the study.

Screening Procedures—Subjects were asked to complete a multi-tiered screening protocol including a screening packet, medical, and psychiatric interviews. The packet administered during the initial screening phase included depression (BDI- II; Beck, 1996) and state anxiety (STAI; Spielberger et al., 1983) inventories, assessment of general intellectual abilities (the Shipley Institute of Living Vocabulary and Abstracting Tests (Zachary, 1986)), and an overview of health conditions and medications. They also complete a questionnaire developed in and used by our laboratory for over a decade detailing past (lifetime) and current (6 months prior to treatment entry) history of marijuana, alcohol, nicotine, and other drug use including chronicity and frequency of use. Lifetime use data is largely applied for selection purposes (except for chronicity measures) whereas the current use data are used to quantify recent exposure.

Blood pressure and expired carbon monoxide (CO) (VitalographR Inc., Lenexa, KS) were also measured to establish baseline levels. Subjects continuing to meet criteria and remaining interested were further screened for psychiatric disorders which could interfere with neurocognitive function. Subjects meeting study eligibility criteria were scheduled for the laboratory study day.

Laboratory Study—Consistent with previous studies (Nixon et al., 2007; Ceballos et al., 2005; 2006b; 2008) and suggested procedure, subjects were instructed to refrain from smoking overnight prior to the study. The abstinence period both facilitates performance effects due to acute nicotine administration (independent from withdrawal alleviation), and ensures that extraneous nicotine from cigarette use is fully metabolized prior to study participation (Hughes, 1991; Pritchard & Robinson, 1998; Heishman, Kleykamp, & Singleton, 2010). Subjects were transported to the laboratory by research personnel. Prior to transport, CO levels were ascertained to verify smoking abstinence. Subjects were required to produce CO measures of < 12 ppm if baseline measures had been < 25 ppm. If baseline measures were > 25 ppm, at least a 50% reduction in CO was required. After arriving at the laboratory, subjects provided urine (OnTrak TestCup 5R, Varian Inc., Cary, NC) and breath samples (IntoxilyzerR Model 400, CMI Inc., Owensboro, KY) to confirm alcohol and drug sobriety from tetrahydrocannabinol, cocaine, benzodiazepines, morphine, and methamphetamine. Transdermal nicotine administration occurred at ~7:20 a.m.. Neurobehavioral assessments included the Logical Memory subtest (LM) from the WMS-R and on-going assessments of withdrawal symptoms.

Transdermal Nicotine Patch Administration—Transdermal administration of nicotine was selected because its pharmacokinetics are well studied and not dependent upon the subjects' response to the vehicle (i.e. smoking topography, gum chewing, inhalation process, etc). Transdermal administration provides steady state nicotine plasma concentrations of 17, 12 and 6 ng/mL for 21, 14, and 7 mg doses, respectively (Transdermal Nicotine Study Group, 1991). While these levels are lower than ad libitum smoking, they are biologically active.

Subjects were randomly assigned to either a placebo, or one of two active doses (patches). Patches were placed on the upper left shoulder where they were not visible and could not be inadvertently removed. Placebo patches matched the size and shape of active patches. The low dose was a 7 mg patch. The high dose was gender-specific as a result of previous experience in our laboratory as well as other data (Evans et al., 2006) suggesting that female subjects experienced intolerance to the 21 mg patch (extreme nausea and other side-effects). Therefore, a 14 mg patch was used as the high dose for women and a 21mg patch for men. Active patches are commercially available (EquateR). The 14 and 21 mg patches did not differ statistically on any dependent variables of interest, thus further justifying the gender-specific dosing.

The LM was administered as part of a larger neurobehavioral assessment (Ceballos et al., 2005, 2006; Nixon et al., 2007) and was administered approximately 6 hours after patch administration ensuring nicotine stabilization (see Gorsline et al, 1993). Given the intent of the larger project, the figural memory component of the WMS-R was not administered. Following laboratory testing, subjects were fully debriefed as to which patch they had received. Subjects receiving nicotine were advised to refrain from smoking for several hours and were then transported to their treatment facility by laboratory personnel.

Logical Memory subtest of the WMS-R—Subjects were asked to listen to audio-tapes of the two stories to ensure standard story administration. Consistent with standard instructions, subjects were asked to repeat what they remembered following each story as an assessment for immediate recall. Standard substitutions in the absence of verbatim recall were accepted (Wechsler, 1987). Using Russell's adaptation (1975), thirty minutes following initial administration, subjects were asked to give an unannounced recall of both stories. Between the two tests, subjects completed unrelated tasks. Recall was audio-taped and scored independently by two research assistants according to LM subtest scoring criteria. When scores differed, tapes were re-scored until consensus was reached. Dependent variables included summary scores of immediate and delayed recall.

Self-reported Measures of Nicotine Dependence and Withdrawal—The Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) and the Smoking Consequences Questionnaire (SCQ; Copeland et al., 1995) are two widely used pencil/paper measures in nicotine research. The FTND measures nicotine dependence severity using items such as number of cigarettes smoked per day and latency between waking and smoking (Heatherton et al., 1991). The SCQ measures smoking expectancies, organizing items into 10 different subscales including craving/addiction and negative affect reduction (Copeland et al., 1995).

Nicotine withdrawal symptomatology could occur at either nicotine dose due to differences in nicotine pharmacokinetics between smoking and transdermal nicotine administration (Benowitz, 1993; Garrett et al., 2001). Given the potential effect of nicotine withdrawal symptomatology on performance (Jacobsen et al., 2005; Kelemen & Fulton, 2008), a nicotine withdrawal symptoms checklist (WSC; adapted from the American Psychiatric

Association, 1994 and Hughes and Hatsukami, 1986) was administered prior to the LM subtest.

Data Analysis

Demographic data comparing ALCS, STIMS, and ALC/STIMS were analyzed with univariate analysis of variance (ANOVA). For the LM, recall scores for immediate and delayed conditions were separately analyzed by a 3 Group (ALCS, STIMS, ALC/STIMS) x 3 Dose (Placebo, Low, High) univariate ANOVA to assess main and interaction effects. Immediate and delayed memory recall were also analyzed by a repeated measures ANOVA to assess change across time for immediate and delayed LM recall and possible interaction effects with Group or Dose. Because analyses showed a significant Time x Group interaction, a measure of forgetting rate over time ($[\text{immediate recall} - \text{delayed recall}] / 30$ minutes) was calculated for each participant and subjected to analysis. Although the more traditional forgetting rate is calculated as immediate recall-delayed recall/immediate recall, the current approach allows examination of a process oriented examination of forgetting (Kaplan, 1988) which could be modified for elapsed time between immediate versus delayed memory recall. Forgetting rates were assessed with a univariate ANOVA. Self-reported measures of nicotine withdrawal symptoms during memory testing were also assessed with a 3 Group (ALCS, STIMS, ALC/STIMS) x 3 Dose (Placebo, Low, High) ANOVA to assess main and interaction effects. When interactions occurred, post hoc analyses (Tukey's HSD) were conducted to determine group significance. Type III sum of squares F statistics are reported for all ANOVAs to account for unequal sample sizes. Degrees of freedom differences indicate missing data. Statistical analyses were completed using SAS Version 9.1 (SAS Institute, 2008).

Results

Demographics

Demographic and tobacco smoking characteristics for substance dependent subgroups (ALCS, STIMS, ALC/STIMS) are presented in Table I and Table II, respectively. Results showed that substance dependent subgroups were similar on age, years of education, state anxiety symptoms and verbal and abstracting ages from the Shipley Institute of Living Scale (p 's > .37). Subgroups differed on depressive symptoms [$F(2,88) = 5.95$, $p = .004$]. Post-hoc analyses showed that ALCS reported more depressive symptoms than ALC/STIMS (p 's < .05). Importantly, depressive symptoms did not correlate with either immediate or delayed recall scores in (p 's > .35).

As expected, subjects differed on the quantity and frequency of alcohol consumed in the last six months before treatment [$F(2,95) = 20.38$, $p < .0001$]; a difference that existed between all groups (ALCS > ALC/STIMS > STIMS, p 's > .001). Stimulant use history among STIM and ALC/STIM subgroups was similar with groups having between 9.25 and 11.78 years (SD = 6.84–8.13 years) of use.

Smoking characteristics for subgroups were similar for chronicity, FTND, withdrawal symptoms prior to the task, average cigarettes smoked per day and expired CO levels for the laboratory study day. Furthermore, withdrawal symptoms were not correlated with performance (p 's > .05). Illustrating the effectiveness of the randomization process, individuals within the drug subgroups did not significantly differ on the demographic or pre-administration substance related variables. In the interest of clarity, we note that abstracting ages approached significance among ALC/STIMS [$F(2,46) = 3.04$, $p = .06$]. For all other comparisons, $F < 2.3$ and $p > .12$.

Logical Memory subtest of the WMS-R

Based on our conceptual model concerning encoding processes versus retrieval or consolidation processes, nicotine effects on immediate and delayed verbal memory recall were first assessed separately in 3 Group (ALCS, STIMS, ALC/STIMS) x 3 Dose (Placebo, low, high) univariate ANOVAs. These analyses revealed a significant Group x Dose interaction [$F(4,95) = 3.52, p = .01$] for immediate memory recall, as well as an effect at the trend level for delayed memory recall [$F(4,92) = 2.35, p = .06$] (see Figure I and II). Post-hoc analyses were conducted on each substance dependent subgroup to assess the effects of nicotine dose on immediate memory recall. STIMS showed a significant effect of dose for the immediate memory recall, [$F(2,22) = 7.55, p = .003$] with individuals who received the high dose of nicotine having significantly better immediate recall than those who received placebo. Delayed memory recall in STIMS also showed differences between the high dose of nicotine and placebo at the trend level [$F(2,22) = 3.30, p = .06$]. No other main or interactive effects were obtained.

To examine group differences between immediate and delayed verbal memory recall, a mixed model ANOVA was also applied. As illustrated in Figure 3, analyses indicated that verbal memory recall decreased from immediate to delayed memory recall (Time main effect [$F(1,92) = 196.76, p < .0001$]), and that the subgroups differed in their sensitivity to time (Time x Group interaction [$F(2,92) = 3.42, p = .04$]), as described earlier. As might be expected from the between groups analyses, nicotine had consistent effects on immediate and delayed memory recall (Time x Dose interaction, p 's $> .05$).

The Time x Group interaction from the mixed model ANOVA (see above) was explored via the measure of forgetting rate (immediate recall – delayed recall) / 30 minutes). These analyses revealed that ALC/STIMS had significantly greater forgetting rates as compared to ALCS [$F(1,74) = 5.64, p = .02$]; other comparisons were not significant. Forgetting rates were not modulated by nicotine dose (p 's $> .17$),

Self-reported Measures of Nicotine Dependence and Withdrawal—Assessment of nicotine withdrawal symptoms during LM testing showed no differences between Group, Dose or Group x Dose interaction (p 's $> .28$). Further, nicotine withdrawal symptoms were not correlated with immediate or delayed recall scores; neither did they differ as a result of time or its interaction with dose or group.

Discussion

Memory decrements are a frequent clinical complaint in recently sober alcohol and/or stimulant dependent individuals (Massman, 1979; Parsons and Prigatano, 1977; Medina et al., 2006). These clinical complaints are inconsistently affirmed by empirical data (Beatty et al., 1995; Mittenberg et al., 1993; Nixon et al., 1987; Selby and Azrin, 1998). One possible reason for this inconsistency may be the high prevalence of nicotine use among substance dependent individuals (DiFranza and Guerrera, 1990; Le, 2002; Littleton et al., 2007) which historically was not controlled in memory studies.

Nicotine's cognitive enhancing effects are recognized in clinical populations; with the most robust effects being shown on attentional tasks (Koelega, 1998; Nixon et al., 2007; Rezvani & Levin, 2001). Despite the clinical rationale, nicotine's effects on verbal memory function have not previously been systemically examined in substance dependent individuals. To that end, the current study was designed to assess the role of transdermal nicotine on logical verbal memory recall in substance dependent subgroups including detoxified, treatment-seeking alcoholics (ALCS), stimulant dependent (STIMS), and ALC/STIMS. Subjects completed immediate and delayed (30 min) recall of the Logical Memory subtest of the

WMS-R (Wechsler, 1987; Russell, 1975) six hours following transdermal nicotine patch (low or high dose or placebo).

Interestingly, nicotine effects were demonstrated in both immediate and delayed verbal memory recall, but only for STIMS. STIMS who received the high dose of nicotine recalled significantly more words at immediate recall than did STIMS receiving placebo ($p = .01$). Similar findings were detected at the trend level for delayed recall ($p = .06$). Consistent with a nicotine dose effect are the data showing that the recall levels for the STIM low dose group fell intermediate to the other two doses on both immediate and delayed verbal memory recall.

The positive nicotine effect at both tests among STIMS suggests the effects may be due to enhanced (relative to placebo dosing) encoding processes which then benefited delayed recall. While requiring sufficient attentional application as noted in the introduction, encoding complex verbal material such as stories is also dependent on higher order cortical processes such as activating effective semantic associations and event sequencing. The absence of an effect among the ALCS at immediate recall and the previous literature suggesting nicotine's differential effect on attentional processes among this group leads us to conclude that the nicotine effect observed in the STIM group here is unlikely to be related to attentional enhancement. Instead, we propose that nicotine may have *direct* effects on semantic and integrative processes essential to verbal memory among specific groups such as detoxified stimulant dependent persons.

In the interest of model development, we speculate that alcoholics engaged compensatory mechanisms not readily available to stimulant dependent persons through non-attentional processes. This conclusion is consistent with the better performance of the ALC placebo group relative to the other placebo groups at both tests. The capacity to activate this level of compensatory process might provide a cognitive override for the nicotine effects, resulting in its administration being of no significant behavioral benefit. While the nature of these compensatory mechanisms is unknown, they may be an integral part of the recovery process and remain an active area of on-going study (Parks et al., 2010). Furthermore, if specific compensatory processes are less available or less effective among subgroups, identifying effective interventions would be a significant advance.

An alternative explanation is that these findings reflect amelioration of nicotine withdrawal symptoms in STIMS; symptoms not experienced by alcohol subgroups. However, demographic data regarding cigarette use and assessment of nicotine withdrawal symptomatology indicated subgroup similarities. Further, the mean number of reported symptoms was well below the maximum of 33, suggesting that withdrawal was not a significant influence in performance for either group. This conclusion is consistent with anecdotal reports by participants who noted an absence of desire to smoke during the laboratory testing.

Also of interest are the group data regarding forgetting rates observed in exploratory analyses. Although groups performed similarly following the immediate recall, ALC/STIMS had poorer delayed recall than all other groups. Thus, the "forgetting slope" was steeper for ALC/STIMS than other groups. Poorer performance on episodic memory tasks in ALC/STIMS as compared to other substance dependent subgroups has been noted previously (Beatty et al., 1995; Horner et al., 1997; O'Malley et al., 1992; Selby & Azrin 1998), and is of obvious clinical significance. This standardized test of verbal memory recall demonstrates that following a thirty minute retention period, the rate of verbal memory loss is substantial. Nearly one-third of the immediate recall material was forgotten by ALC/STIMS in the current study. In comparison, controls from a similar study displayed only a 10 percent

decline in immediate versus delayed verbal memory recall (Nixon et al., 1987). Identifying factors contributing to these subgroup differences in forgetting rates is an important clinical and research issue.

Limitations of the current study include this study's administration of only one test of verbal memory. We recognize that one assessment of verbal memory does not fully characterize the complexity of verbal memory processes and urge that more comprehensive studies be conducted. It might also be argued that the absence of a baseline performance measure taken prior to nicotine administration complicates interpretation, potentially confounding withdrawal relief and cognitive enhancement. We suggest that our inclusion of a placebo group as well as the consistent absence of significant withdrawal symptoms mitigates, although perhaps not eliminates, this concern. Additionally, the absence of a community control group of smokers restricts broad statements regarding nicotine's differential effect among substance abusers as compared to "normal" smokers. The absence of this group, however, does not impact the conclusions regarding the between group differences of primary concern in the current study. Finally, a potential limitation regarding the generalization of these findings is the fact that nicotine patch administration produces active nicotine levels below those typically achieved by smoking. It might be argued that if significant effects are observed at these relatively low levels, one might expect similar if not greater effects at higher levels. On the other hand, it is likely that the positive effects are non-linearly associated with drug level, at least at higher levels. Additional research is needed to define the nature of this relationship. In conclusion, on a traditional test of verbal memory, stimulant dependent individuals who received a high dose of transdermal nicotine showed better performance than other stimulant dependent individuals in a dose-dependent manner. Interestingly, nicotine had no significant effect among alcohol subgroups. Further work is needed to clarify the mechanism underlying this memory enhancement. However, the results, in combination with a growing literature, suggest that nicotine effects in substance dependent individuals may be dependent on the substance of primary use, the nature of the specific task and the dose.

Acknowledgments

Research was performed in the Neurocognitive Laboratory (SJM) director, at the Department of Psychology, University of Kentucky, Lexington, KY and Department of Psychiatry, University of Florida, Gainesville FL. Support was provided in part from NIDA #R01 DA-13677 (to SJM). A preliminary abstract of this work was published in *Alcoholism: Clinical and Experimental Research* (2008, Supplement 6, pg. 175A). Additional salary support was provided through U54RR025208 (D. Nelson, PI, Nixon, Co-I).

The authors would like to thank Christine Stolz, Amanda Ross, M.S. and Andy Shelton, M.S., for their assistance in data collection.

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Figure I.

Nicotine dose effects in immediate recall from the Logical Memory subtest (Wechsler, 1987; Russell, 1975). STIMS who received the high dose of nicotine had better immediate verbal memory recall as compared to STIMS who received placebo [$F(2,22) = 7.55$, $p = .003$; post hoc $p < .05$]. This effect was non-significant in ALCS and ALC/STIMS. Data are means and standard errors (std.err)

Figure II.

Delayed recall from Logical Memory subtest (Wechsler, 1987; Russell, 1975) in ALCS, for STIMS, and ALC/STIMS who received nicotine or placebo. Analyses revealed a Group x Dose interaction at the trend level ($p = .06$). Data are means and std. err.

Figure III.

Immediate and delayed recall from Logical Memory subtest (Wechsler, 1987) in ALCS, for STIMS, and ALC/STIMS collapsed across dose. ALC/STIMS had significantly greater forgetting rates as compared to ALCS [$F(1,74) = 5.64, p = .02$], a difference that was not found between any other group. Data are means and std. err.

Table 1
Demographic characteristics of subjects by substance dependent subgroup Means and Standard Deviations

	ALCS			ALC/STIM			STIM		
	Placebo (N=8)	Low (N=11)	High (N=10)	Placebo (N=19)	Low (N=13)	High (N=18)	Placebo (N=8)	Low (N=8)	High (N=9)
Age (years)	38.13(8.44)	39.09(9.35)	41.00(9.23)	38.26(8.96)	40.46(10.69)	36.11(6.65)	39.50(9.58)	37.00(7.37)	37.44(6.98)
Education (years)	13.50(1.77)	12.91(2.26)	13.30(1.64)	12.79(1.96)	12.69(1.11)	12.50(1.76)	12.25(1.67)	12.50(1.85)	13.33(2.12)
Depression symptoms (test) ^a	13.57(9.45)	14.50(5.74)	14.67(9.30)	9.41(5.95)	11.09(7.79)	7.06(5.21)	6.25(7.40)	10.37(6.39)	8.22(5.61)
Anxiety symptoms (prior to task)	46.13(4.42)	50.27(12.00)	48.30(8.77)	47.16(8.66)	50.50(7.99)	43.06(6.80)	49.00(6.89)	49.50(7.44)	52.22(7.50)
Verbal age	17.44(2.44)	19.26(7.07)	16.36(0.95)	16.07(0.99)	17.13(2.08)	16.27(1.79)	16.15(2.28)	15.69(1.08)	15.76(2.39)
Abstracting age	15.89(2.70)	14.75(2.34)	15.89(3.03)	14.59(2.49)	15.97(2.50)	13.68(2.59)	14.45(2.00)	15.22(3.05)	14.39(2.49)
Quantity frequency index ^b (alcohol)	8.60(4.92)	15.75(10.18)	13.08(7.67)	13.08(7.67)	7.62(4.93)	9.66(5.97)	0.98(1.18)	0.85(0.76)	1.94(3.57)
Sobriety (days)	53.20(25.41)	30.00(12.96)	45.00(16.63)	48.00(22.61)	45.38(21.04)	39.17(15.65)	32.43(11.43)	39.88(10.67)	37.50(16.26)

Depression symptoms: Beck Depression Inventory (Beck et al., 1996); **Anxiety symptoms:** Spielberger State Anxiety Inventory (Spielberger, 1983); **Verbal and abstracting age:** Shipley Institute of Living Scale (Zachary, 1986); **Quantity frequency index** (Cahalan, et al., 1969)

^aSignificant effect of group [$F(2,88) = 5.95, p = .004$]; ALCS differed significantly from other groups ($p's < .05$).

^bSignificant effect of group [$F(2,95) = 20.38, p < .0001$]; Groups differed significantly from one another ($p's < .05$).

Table II
Tobacco smoking characteristics of subjects by substance dependent subgroup Means and Standard Deviations

	ALCS			ALC/STIM			STIM		
	Placebo (N=8)	Low (N=11)	High (N=10)	Placebo (N=19)	Low (N=13)	High (N=18)	Placebo (N=8)	Low (N=8)	High (N=9)
Smoking Chronicity (years)	21.63(10.93)	23.18(7.78)	25.50(10.06)	22.21(9.84)	23.61(11.33)	19.77(9.08)	21.63(10.95)	18.50(9.21)	18.67(9.00)
Average cigarettes (per day)	21.88(11.63)	17.54(8.96)	21.22(12.54)	23.06(11.84)	18.46(5.15)	16.43(6.54)	18.38(8.18)	16.63(8.31)	20.89(4.28)
Carbon monoxide (testing)	11.87(7.22)	9.10(3.73)	10.40(4.25)	8.21(3.19)	9.92(3.90)	7.50(3.47)	8.13(3.48)	6.13(2.36)	9.22(4.47)
Fagerström (total score)	6.25(2.19)	5.09(1.76)	3.70(2.31)	4.37(2.54)	5.23(2.39)	4.72(2.02)	4.63(1.69)	4.75(1.98)	5.11(1.76)
Smoking consequences (total score)	49.17(6.96)	55.91(13.84)	52.90(7.54)	49.48(13.05)	45.19(12.26)	49.85(10.03)	43.04(6.62)	53.37(15.42)	47.89(11.39)
Withdrawal symptoms (prior to task)	4.00(2.78)	7.18(3.95)	6.20(2.82)	5.84(3.70)	6.77(5.83)	5.22(5.02)	5.25(4.65)	6.13(3.09)	4.67(4.44)

Fagerström: Fagerström Test for Nicotine Dependence (Heatherton et al., 1991); **Smoking consequences:** Smoking Consequences Questionnaire (Copeland et al., 1995); **Withdrawal symptoms:** Withdrawal Symptoms Checklist (Hughes and Hatsukami, 1986)

Logical Memory subtest scores of subjects by substance dependent subgroup and nicotine dose Means and Standard Deviations

Table III

	ALCS			ALC/STIM			STIM		
	Placebo (N=8)	Low (N=11)	High (N=10)	Placebo (N=19)	Low (N=13)	High (N=18)	Placebo (N=8)	Low (N=8)	High (N=9)
Immediate recall	25.13(8.58)	22.36(5.35)	24.00(7.70)	22.95(5.19)	25.23(6.93)	21.06(6.45)	17.13(5.33)	22.00(4.5)	27.00(5.72)
	ALCS immediate recall Grand Average = 23.69(7.00)			ALC/STIM immediate recall Grand Average = 22.86(6.22)			STIM immediate recall Grand Average = 22.24(6.50)		
Delayed recall	22.66(8.28)	18.09(7.20)	19.00(8.22)	16.21(7.01)	19.36(7.19)	16.05(4.75)	13.97(5.96)	16.63(4.47)	21.56(7.72)
	ALCS delayed recall Grand Average = 19.66(7.81)			ALC/STIM delayed recall Grand Average = 16.89(6.34)			STIM delayed recall Grand Average = 17.52(6.84)		