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COGNITIVE ASPECTS

Measures of Learning, Memory and Processing Speed Accurately Predict Smoking Status in Short-term Abstinent Treatment-seeking Alcohol-dependent Individuals

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Abstract — Aim: Chronic cigarette smoking appears to adversely affect several domains of neurocognition in those with alcohol use disorders (AUDs). The primary goal of this study was to identify which measures commonly used to assess neurocognition in AUDs accurately predict smoking status of individuals seeking treatment of alcohol dependence. **Methods:** Treatment-seeking alcohol-dependent participants (ALC; $n = 92$) completed a comprehensive neuropsychological battery after 33 ± 9 days of abstinence. Measures significantly different between smoking and non-smoking ALC were entered as predictors in binary logistic regression and discriminant analysis models, with smoking status as the dependent variable. **Results:** Smoking ALC performed significantly worse than non-smoking ALC on measures assessing processing speed, auditory–verbal and visuospatial learning and memory. Using these measures as predictors, a logistic regression model accurately classified 91% of smokers and non-smokers into their respective groups overall and accounted for 68% of the variance in smoking status. The discriminant analysis confirmed the findings from the logistic regression. In smoking ALC, smoking chronicity was inversely related to performance on multiple measures after controlling for lifetime alcohol consumption. **Conclusions:** Measures of processing speed, learning and memory robustly predicted the smoking status of ALC with high sensitivity and specificity during early abstinence. The results identified specific measures within a comprehensive neurocognitive battery that discriminated smoking and non-smoking alcohol-dependent individuals with a high sensitivity and specificity. The association of greater smoking chronicity and poorer performance on multiple measures after control for alcohol consumption suggests that chronic smoking adds an additional burden to neurocognitive function in those with alcohol dependence.

INTRODUCTION

Considerable variability exists in the type and magnitude of neurocognitive abnormalities exhibited by individuals with alcohol use disorders (AUDs) following detoxification (Oscar-Berman, 2000; Rourke and Loberg, 1996; Sher *et al*., 2005). Comorbid behaviors/conditions such as chronic smoking in AUDs may contribute to this variability in neurocognition. Approximately 60–90% of individuals in North America seeking treatment for AUDs are chronic smokers (Durazzo and Meyerhoff, 2007; Room, 2004). Our group (Durazzo *et al*., 2006b, 2008) and others (Friend *et al*., 2005; Glass *et al*., 2006, 2009) found that chronic cigarette smoking among individuals with an AUD is associated with adverse effects on multiple neurocognitive domains of functioning, in particular executive skills, learning and memory, processing speed and cognitive efficiency. These studies (Durazzo *et al*., 2006b, 2008) also showed that not all aspects of neurocognition (e.g. visuospatial skills, working memory) are necessarily modulated by chronic smoking in those with an AUD.

To better understand the scope and magnitude of the neurocognitive consequences associated with chronic smoking in AUDs, we have employed a neurocognitive battery composed of common clinical and research measures to comprehensively assess the domains of functioning reported to be adversely affected by both AUDs (Oscar-Berman, 2000) and comorbid chronic smoking (Swan and Lessov-Schlaggar, 2007). The primary goal of this study was to identify individual measures in our battery that can be combined to parsimoniously and specifically discriminate smoking from non-smoking alcohol-dependent individuals, rather than strictly examining for mean differences between smokers and non-smokers across general domains of function (e.g. visuospatial skills, working memory) or use smoking status as a predictor of general domain function. Identification of the specific measures that predict smoking status may provide more precise information on the nature and magnitude of neurocognitive consequences associated with chronic smoking in AUDs. This approach also permits examination of the sensitivity and specificity of the measures used to predict smoking status, which is not possible when utilizing standard parametric linear methods. Finally, identification of the specific measures that accurately and uniquely discriminate smokers and non-smokers can be used to determine whether the 'hallmark' neurocognitive profile associated with chronic smoking in this AUD cohort is reproducible in independent samples. Such replication studies are imperative to ensure that previous findings (e.g. Durazzo *et al*., 2006a,b, 2008) are generalizable to the larger population of treatment-seeking AUDs. A secondary goal of this study was to explore the relationships between the measures of smoking chronicity and the performance on individual neurocognitive tests, controlled for alcohol consumption in the smoking AUD participants.

METHODS

Participants

Individuals seeking treatment for AUDs ($n = 92$; four females) were recruited from the VA Medical Center Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program outpatient clinics

Table 1. Demographics, alcohol and cigarette use histories, self-report questionnaires and comorbidity frequency for nsALC and sALC (mean ± SD)

Measure	nsALC ($n = 36$)	sALC ($n = 56$)
Age (years)	52.1 ± 9.8 (min = 31; max = 68)	50.1 ± 8.9 (min = 28; max = 68)
Education (years)	14.3 ± 2.3 (min = 10; max = 19)	13.5 ± 2.0 (min = 10; max = 20)
% Caucasian	75	74
Number of days abstinent	32 ± 10 (min = 16; max = 58)	33 ± 9 (min = 16; max = 57)
Average drinks/month over past year	370 ± 201 (min = 96; max = 920)	416 ± 206 (min = 106; max = 920)
Lifetime average drinks/month	179 ± 119 (min = 69; max = 532)	258 ± 116* (min = 90; max = 543)
% with medical comorbidity	42	47
% with substance use disorder comorbidity	22	21
% with psychiatric comorbidity	53	41
FTND	NA	6.2 ± 3.9 (min = 2; max = 10)
Cigarettes per day	NA	19.5 ± 8.8 (min = 5; max = 50)
Pack years	NA	29.1 ± 20.1 (min = 5; max = 87.5)
Smoking duration (years)	NA	26.2 ± 12.4 (min = 5; max = 54)
BDI	7.7 ± 8.1 (min = 1; max = 28)	10.8 ± 7.6 (min = 1; max = 33)
STAI	43.1 ± 11.0 (min = 24; max = 62)	43.8 ± 10.9 (min = 21; max = 68)

BDI, Beck Depression Inventory; FTND, Fagerstrom Tolerance Test for Nicotine Dependence; Max, maximum; Min, minimum; NA, not applicable; STAI, State-trait Anxiety Inventory—Trait.
*$P < 0.05$.

in San Francisco. All participants were between the ages of 28 and 68 at the time of study, and all met the diagnostic and statistical manual of mental disorders - fourth edition (DSM-IV) criteria for alcohol dependence (95% with physiological dependence). The alcohol-dependent participants (ALC) completed a comprehensive neuropsychological assessment battery after 33 ± 9 days of sustained abstinence. There was no difference between smoking (sALC; $n = 56$) and non-smoking (nsALC; $n = 36$) alcohol-dependent individuals in the duration of abstinence prior to assessment. All sALC were actively smoking at the time of assessment. No sALC appreciably changed their cigarette consumption from the onset of abstinence to the time of assessment. Eight nsALC reported a previous history of chronic smoking, with five quitting more than 8 years and three more than 3 years prior to enrollment. The performance of the former smokers was within ±0.5 standard deviations of the nsALC group mean across measures. Demographics, indices of alcohol consumption, smoking severity, depressive and anxiety symptomatology and frequency of medical, psychiatric and substance use comorbidities for sALC and nsALC are given in Table 1.

Primary inclusion criteria were current DSM-IV diagnosis of alcohol dependence or abuse (American Psychiatric Association, 1994), fluency in English, consumption of more than 150 alcoholic drinks per month (one alcoholic drink equivalent = 13.6 g pure ethanol) for at least 8 years prior to enrollment for men, and consumption of more than 80 drinks per month for at least 6 years prior to enrollment for women. Primary exclusion criteria are fully detailed in our previous work (Durazzo *et al.*, 2004). In brief, no participant had a history of a neurologic (e.g. non-alcohol-related seizure disorder, neurodegenerative disorder, demyelinating disorder), general medical (e.g. myocardial infarction, type-1 diabetes, cerebrovascular accident) or psychiatric (i.e. schizophrenia spectrum, bipolar disorder, post-traumatic stress disorder) conditions known or suspected to influence neurocognition. The following comorbidities were permitted in ALC participants due to their prevalence in AUDs (Gilman and Abraham, 2001; Stinson *et al.*, 2005): hepatitis C, type-2 diabetes, hypertension, unipolar mood (major depression, substance-induced mood disorder) and anxiety disorders (generalized anxiety disorder, panic disorder). ALC who met DSM-IV criteria for current or past substance abuse, and past substance dependence that occured at least five prior to enrollment were also included. Current opioid replacement therapy (e.g. methadone) was exclusionary.

Medical, psychiatric, substance and drinking history assessment

Participant medical history was obtained from self-report and confirmed or amended via available medical records. Participants completed the Structured Clinical Interview for DSM-IV Axis I disorders, Patient Edition, Version 2.0 (SCID-I/P; First *et al.*, 1998), and standardized questionnaires assessing lifetime (LT) alcohol consumption [lifetime drinking history (LDH); Skinner and Sheu, 1982] and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use). From the LDH, we derived the average number of drinks per month over 1, 3 and 8 years prior to enrollment, average number of drinks per month over LT, number of LT years of regular drinking (i.e. duration for which the participant began consuming at least one alcoholic drink per month), number of months of heavy drinking (i.e. total number of months over LT in which the participant drank in excess of 100 drinks per month) and age of onset of heavy drinking. All participants completed self-report measures of depressive [Beck Depression Inventory (BDI); Beck, 1978] and anxiety symptomatology [State-Trait Anxiety Inventory (STAI), form Y-2; Spielberger *et al.*, 1977] and nicotine dependence [Fagerstrom Tolerance Test for Nicotine Dependency (FTND); Fagerstrom *et al.*, 1991]. The total number of cigarettes currently smoked per day and the number of years of smoking at the current level were also recorded and pack years [i.e. (number of cigarettes per day/20) × number of years of smoking at level reported at enrollment] were calculated for sALC.

Neuropsychological assessment

Participants completed a comprehensive battery, which evaluated neurocognitive and motor functions adversely affected by alcohol dependence (Oscar-Berman, 2000; Rourke and

Table 2. Individual measure *z*-scores for nsALC and sALC (mean ± SD)

Measure	nsALC ($n = 36$)	sALC ($n = 56$)	Effect size (Cohen's *d*)
AMNART	112.2 ± 9.1	113.0 ± 9.2	0.09
BVMT-R Total Recall	−0.36 ± 0.98	−0.90 ± 1.07*	0.53
BVMT-R Delayed Recall	−0.27 ± 1.09	−0.78 ± 1.12*	0.47
CVLT-II Immediate Recall (trials 1–5)	0.99 ± 0.89	−0.04 ± 0.98***	1.10
CVLT-II Short Delayed Free Recall	0.63 ± 0.88	−0.15 ± 0.90***	0.88
CVLT-II Long Delayed Free Recall	0.79 ± 0.77	−0.23 ± 0.94***	1.17
Grooved Peg Board Dominant Hand	−0.86 ± 1.07	−0.92 ± 0.96	0.06
Grooved Peg Board Non-Dominant Hand	−0.94 ± 0.85	−0.88 ± 0.79	0.07
Luria Item 99	−0.81 ± 0.98	−0.71 ± 1.01	0.11
Short Categories Test	−0.74 ± 1.07	−0.69 ± 1.15	0.05
Stroop Word	−0.32 ± 0.67	−0.53 ± 0.56	0.35
Stroop Color	−0.34 ± 0.63	−0.69 ± 0.59**	0.58
Stroop Color-Word	−0.17 ± 0.85	−0.68 ± 0.97**	0.56
Trail Making Test, part A	−0.16 ± 0.93	−0.56 ± 0.86*	0.46
Trail Making Test, part B	−0.22 ± 0.96	−0.34 ± 0.93	0.13
WAIS-III Arithmetic	−0.10 ± 1.01	−0.27 ± 0.81	0.19
WAIS-III Block Design	0.20 ± 0.92	−0.04 ± 0.90	0.26
WAIS-III Digit Span	0.15 ± 0.88	0.25 ± 0.92	0.11
WAIS-III Digit Symbol	0.02 ± 0.77	−0.57 ± 0.87***	0.72
WAIS-III Information	0.55 ± 0.87	0.55 ± 0.86	0.00
WAIS-III Picture Completion	0.21 ± 0.99	−0.36 ± 0.84**	0.64
WAIS-III Similarities	0.91 ± 1.00	0.59 ± 1.00	0.32
WAIS-III Symbol Search	0.53 ± 0.80	0.03 ± 0.83**	0.62
WCST-64 Total Errors	−0.30 ± 1.03	−0.53 ± 1.04	0.22
WCST-64 Perseverative Responses	−0.22 ± 0.82	−0.51 ± 0.87	0.34
WCST-64 Perseverative Errors	−0.30 ± 0.87	−0.51 ± 0.94	0.23
WCST-64 Non-Perseverative Errors	−0.53 ± 0.99	−0.58 ± 0.98	0.05

Note: Asterisks indicate statistically significant differences (two-tailed *t*-test) between and nsALC and sALC, *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$.

Grant, 1999) and chronic cigarette smoking (Durazzo *et al*., 2007; Swan and Lessov-Schlaggar, 2007). sALC were allowed to smoke ad libitum prior to assessment and to take smoke breaks during the assessment. The individual measures that comprised our battery were as follows (Table 2): Brief Visuospatial Memory Test-Revised (Benedict, 1997), Total Recall and Delayed Recall; California Verbal Learning Test-II (Delis *et al*., 2000), Immediate Recall trials 1-5, Short and Long Delay Free Recall; Grooved Pegboard Test (Lafayette Instrument, Lafayette, IN, USA); Luria-Nebraska Item 99 (Golden *et al*., 1978); Short Categories Test (Wetzel and Boll, 1987); Stroop Color-Word Test (Golden, 1978); Trail Making Test, parts A and B (Reitan and Wolfson, 1985); Wechsler Adult Intelligence Scale, 3rd edn (WAIS-III) (Wechsler, 1997), Arithmetic, Block Design, Digit Span, Digit Symbol, Information, Picture Completion, and Similarities and Symbol Search subtests; Wisconsin Card Sorting Test-64: Computer Version 2-Research Edition (Heaton and Staff, 1993) total errors, non-perseverative errors, perseverative errors and perseverative responses. Premorbid verbal intelligence was estimated with the American National Adult Reading Test (Grober and Sliwinski, 1991). For the Luria-Nebraska Item 99, the number correct (maximum possible = 8) was divided by the time required to complete the task. This ratio was used due to the low ceiling for the number correct (i.e. most participants achieved a score of 6 or better) and the resultant highly skewed distribution.

Raw scores for all neurocognitive measures, except the Luria-Nebraska Item 99 ratio, were converted to age-adjusted standardized scores via the normative data accompanying the particular measure (i.e. BVMT-R, CVLT-II, Short Categories Test, Stroop Color-Word Test, WAIS-III subtests) or age and education [WCST-64 variables; Trails A and B via Heaton Compendium Norms (Heaton *et al*., 1991)]. Standardized scores were transformed to *z*-scores for all measures. For the Luria-Nebraska Item 99 ratio, raw scores were converted to *z*-scores based on the performance of 30 non-smoking light drinking controls, as there are no norms available for this measure.

Data analyses

Independent sample *t*-tests were used to evaluate for differences between nsALC and sALC on all individual neurocognitive measures, age, education, predicted premorbid IQ and measures of alcohol consumption. Fisher's exact test was used to determine whether nsALC and sALC differed in the frequency of comorbid medical conditions (primarily hypertension and hepatitis C), psychiatric disorders (primarily unipolar mood and anxiety disorders) and substance abuse (primarily psychostimulant and cannabis abuse). Although sALC and nsALC were not significantly different on age and AMNART, these measures accounted for a significant amount of the variance in neurocognition in both nsALC and sALC cohorts in our previous work (Durazzo *et al*., 2008) and, therefore, were used as covariates in the present study. Measures that were different between nsALC and sALC at $P < 0.05$ were entered as predictors in a binary logistic regression model, with smoking status (i.e. nsALC and sALC) as the dependent measure. In addition, a discriminant analysis, with smoking status as the grouping variable, was also conducted with the same predictors used in the binary logistic regression. The rationale for this analysis was to seek confirmation of our logistic regression-based findings using a different method to predict the smoking

status of participants. The sensitivity of the model is the percent of smokers accurately classified, whereas specificity is the percent of non-smokers correctly classified.

To explore the relationships among the measures of smoking chronicity and individual cognitive tests, we examined partial correlations, controlling for LT average drinks per month, between LT number of years of smoking and the individual measures comprising the battery. Total number of years of smoking over LT was chosen as this measure of smoking was most robustly related to several domains of neurocognition in our previous work (Durazzo *et al.*, 2006b). Alpha levels ($P \leq 0.05$) in these exploratory comparisons were not corrected for multiplicity of tests. Factor analysis (principle component analysis, varimax rotation) was conducted with predictors used in the best-fitting logistic regression model to identify the latent functions assessed by these factors. All analyses were completed with SPSS, v17.0.

RESULTS

Participant performance on outcome measures

nsALC and sALC were not significantly different on age, education, average number of drinks per month 1 and 3 years prior to enrollment, self-report measures of depressive (BDI) and anxiety symptomatology (STAI) or on the frequency of comorbid medical, psychiatric disorders or substance misuse (Table 1). sALC performed significantly worse than nsALC on the following 11 measures: BVMT-R Total Recall and Delayed Recall; CVLT-II Immediate Recall (Trials 1–5), Short and Long Delayed Free Recall; Stroop Color and Color-Word trials; Trail Making Test, Part A (Trails A); WAIS-III Digit Symbol, Picture Completion and Symbol Search subtests (Table 2). sALC consumed significantly more drinks per month over LT (LT average drinks; $P < 0.05$) than nsALC. These variables were entered into the models described subsequently.

Prediction of group membership: logistic regression and discriminant analysis

For the logistic regression analyses, we initially compared the fit accuracy and explanatory power in two primary models. Model 1 included LT average drinks, age and AMNART. In Model 2, the 11 individual neurocognitive measures that were significantly different between sALC and nsALC (see above) were added to LT average drinks, age and AMNART to determine whether the addition of the 11 neurocognitive measures provided an increased explanatory power, fit and classification accuracy. Model 1, with LT average drinks, age and AMNART as predictors, was significant [χ^2 (3) = 12.77, $P < 0.005$, $r^2 = 0.18$] and accurately classified 50% of nsALC (i.e. specificity) and 83% of sALC (i.e. sensitivity) into their respective groups, with an overall classification accuracy of 71%. This basic model accounted for 18% of the variance in classification of smoking status. Model 2, which included the addition of the 11 neurocognitive measures as predictors, was significant [χ^2 (14) = 61.6, $P < 0.001$, $r^2 = 0.68$]. Model 2 accurately classified 86% of nsALC and 95% of sALC into their respective groups, with an overall classification accuracy of 91% and accounted for 68% of the variance in classification of smoking status. Model 2, compared with Model 1, demonstrated significantly better fit [χ^2 (9) = 48.7, $P < 0.01$], accounted for 50% more variance in the group membership (68 vs. 18%) and demonstrated a 20% better overall classification accuracy (91 vs. 71%). The discriminant analysis using the variables included in Model 2 was also significant [χ^2 (14) = 57.3, $P < 0.001$], and the combination of predictors accurately classified 91% of nsALC and 86% of sALC, with an overall classification accuracy of 89%. Collinearity diagnostics indicated that all predictors in the logistic regression model made unique contributions to classification of smoking status in the ALC cohort.

To develop a potentially more parsimonious model, we conducted a third binary logistic regression (Model 3) with only those neurocognitive measures that showed moderate to strong effect sizes (i.e. effect size >0.70; see Table 2). In Model 3, LT average drinks, age and AMNART, CVLT-II Immediate, Short and Long Delayed Free Recall and WAIS-III Digit Symbol were simultaneously entered. Model 3 was significant [χ^2 (6) = 53.2, $P < 0.001$, $r^2 = 0.61$], accounted for 61% of the variance, accurately classified 80% of nsALC and 89% of sALC into their respective groups, with an overall classification accuracy of 85%. However, relative to Model 2, Model 3 showed a lower overall classification accuracy (85 vs. 91%). Additionally, Model 3 did not demonstrate a significant reduction in residual error relative to Model 2 [χ^2 (7) = 8.1, $P > 0.50$], indicating that Model 3 did not provide a more accurate fit of the data. Discriminant analysis with the same predictors as Model 3 was also significant [χ^2 (6) = 52.4, $P < 0.001$], but also resulted in a less accurate prediction of the group membership compared with the original discriminant analysis model (see above), with 82% of non-smokers and 78% of smokers correctly classified.

Factor analysis of the 11 neurocognitive measures used as predictors in the above logistic regression and discriminant analyses resolved into three components. Trails A, Stroop Color and Color-Word and WAIS-III Digit symbol, Symbol Search and Picture Completion showed high loadings on Component 1; CVLT-II Immediate Recall, Short and Long Delayed Free Recall showed high loadings on Component 2; BVMT-R Total and Delayed Recall had high loadings on Component 3. Thus, the factor analysis suggests that the principal indices are processing speed, auditory–verbal learning/memory and visuospatial learning/memory.

Relationships between smoking chronicity and individual cognitive measures in smoking ALC

After controlling for LT average drinks per month, greater LT number of years of smoking in sALC was significantly related to lower scores on 13 of 27 measures (Table 3). Additionally, greater LT number of years of smoking was significantly associated with lower scores on 10 of 11 neurocognitive measures where sALC demonstrated significantly lower performance than nsALC. Conversely, after controlling for LT number of years of smoking, LT average drinks per month was related to 3 of 27 measures and was not related to any measures that discriminated sALC from nsALC.

Table 3. Partial correlations between lifetime number of years of smoking, lifetime average drinks per month and individual measure *z*-scores in sALC ($n = 56$)

Measure	Lifetime number of years of smoking[a]	Lifetime average drinks per month[b]
AMNART	−0.04	−0.41**
BVMT-R Total Recall	−0.41**	−0.02
BVMT-R Delayed Recall	−0.38**	0.03
CVLT-II Immediate Recall (trials 1-5)	−0.29*	−0.08
CVLT-II Short Delayed Free Recall	−0.38**	0.02
CVLT-II Long Delayed Free Recall	−0.27*	−0.03
Grooved Peg Board Dominant Hand	−0.20	−0.07
Grooved Peg Board Non-Dominant Hand	−0.23	0.01
Luria Item 99	−0.38**	−0.16
Short Categories Test	−0.30*	−0.24
Stroop Word	−0.17	−0.09
Stroop Color	−0.14	−0.23
Stroop Color-Word	−0.26*	−0.01
Trail Making Test, part A	−0.38**	−0.02
Trail Making Test, part B	−0.25	−0.07
WAIS-III Arithmetic	−0.16	−0.36**
WAIS-III Block Design	−0.29*	−0.08
WAIS-III Digit Span	−0.12	−0.18
WAIS-III Digit Symbol	−0.17	−0.20
WAIS-III Information	−0.09	−0.24
WAIS-III Picture Completion	−0.39**	−0.20
WAIS-III Similarities	−0.13	−0.32*
WAIS-III Symbol Search	−0.29*	−0.18
WCST-64 Total Errors	−0.19	−0.04
WCST-64 Perseverative Responses	−0.26*	−0.23
WCST-64 Perseverative Errors	−0.24	−0.20
WCST-64 Non-Perseverative Errors	−0.11	−0.14

Note: Asterisks indicate significant two-tailed tests *$P \leq 0.05$, **$P \leq 0.01$.
[a]Controlled for lifetime average drinks per month.
[b]Controlled for lifetime number of years of smoking.

DISCUSSION

The main findings from this cohort of 92 predominantly Caucasian male US Armed Services Veterans seeking treatment for alcohol dependence were as follows: (a) sALC performed significantly worse than nsALC on 11 of 27 standard clinical and research neurocognitive measures; (b) using two independent methods, the combination of these 11 measures robustly predicted smoking status and demonstrated high sensitivity and specificity in group classification, while controlling for the influence of age, estimated premorbid intelligence and LT alcohol consumption; (c) the 11 measures appear to primarily represent indices of processing speed, auditory–verbal and visuospatial learning and memory; (d) greater smoking chronicity in sALC was related to poorer performance on multiple measures after controlling for LT alcohol consumption.

The 11 measures assessing learning, memory and processing speed demonstrated high sensitivity and specificity in the prediction the smoking status as well as medium to large effect sizes for mean differences between sALC and nsALC during early abstinence from alcohol. These results extend our previous work by identifying the specific measures within a comprehensive battery of commonly used clinical and research tests that accurately and robustly discriminated smokers from non-smokers with alcohol dependence. The findings from this study are also consistent with earlier work (e.g. Durazzo *et al*., 2006b, 2008; Glass *et al*., 2006) demonstrating that chronic smoking in AUDs does not appear to adversely affect all domains of neurocognition. Previous neuroimaging studies in this cohort at ~1-month of abstinence showed lower frontal gray matter perfusion and lower *N*-acetylaspartate level (NAA; marker of neuronal integrity) in the frontal white matter, lower NAA and choline-containing compounds (Cho; marker of membrane synthesis/turnover) in mesial temporal/hippocampal subregions and lower hippocampal volume in sALC compared with nsALC (Durazzo *et al*., 2006a; Gazdzinski *et al*., 2008; Mon *et al*., 2009). These regional neuroimaging findings provide a potential neurobiological basis for the general pattern of performance demonstrated by sALC and nsALC as well as for the ability of indices of learning, memory and processing speed to accurately predict smoking status in this alcohol-dependent cohort during early abstinence. See Durazzo and Meyerhoff (2007) for review of the mechanisms by which chronic cigarette smoking may adversely affect neurobiology and neurocognition in AUDs.

It is noteworthy that the performance on measures generally fell in the average range of functioning or higher for both nsALC and sALC, with the exception of the Grooved Pegboard, Short Categories Test and Luria Item 99, which were all in the low average range for both groups. These findings are consistent with our earlier work (see Durazzo *et al*., 2006b, 2008) and congruent with the observation that only 50% of individuals with AUDs exhibit clinically significant neurocognitive dysfunction after 2–3 weeks of abstinence from alcohol (Rourke and Loberg, 1996). This highlights the considerable variability in the vulnerability/resiliency to the effects of AUDs, which may be influenced by such factors as chronic smoking, psychiatric disorders, medical comorbidities and genetic predispositions. The associations of poorer performance on multiple age-adjusted

measures with longer smoking duration after controlling for alcohol consumption in sALC converges with our previous work (Durazzo *et al*., 2006b) as well as with Glass *et al*. (2009) who found that higher pack years was related to poorer performance on components of the Trail Making and Stroop Tests in a large community-recruited cohort of AUD participants. Additionally, our neuroimaging findings in this cohort (Durazzo *et al*., 2004, 2006a) showed higher cigarette consumption was associated with lower thalamic and lenticular nuclei NAA levels and lower frontal and parietal white matter Cho levels in sALC during early recovery. Overall, these findings suggest that the direct and/or indirect effects of chronic smoking place an additional burden on neurocognitive function in AUD or compound a potentially preexisting vulnerability in smoking AUD.

This report has limitations that may influence the generalizability of the findings. We did not assess for personality disorders, which may contribute to the neurocognitive and neurobiological abnormalities observed in AUD (Costa *et al*., 2000; Eckardt *et al*., 1995; Giancola and Moss, 1998; Kuruoglu *et al*., 1996). The results were also potentially influenced by other factors not directly assessed in this study, such as nutrition, exercise and previous exposure to environmental cigarette smoke or premorbid/genetic predispositions. The majority of participants were males recruited from the San Francisco VA Medical Center, which did not allow for the examination of the potential effects of sex on neurocognition. Future research comparing smoking and non-smoking AUDs on tasks specifically assessing decision making, risk taking and impulsivity is warranted because such measures have been reported to be adversely affected by AUD and chronic cigarette smoking (Bobova *et al*., 2009; Fein *et al*., 2006; Lejuez *et al*., 2003; Li *et al*., 2009). Assessment of decision-making, risk taking and impulsivity is critical for understanding the full scope of the neurocognitive consequences associated with chronic smoking in AUD.

In summary, an estimated 60–90% of individuals seeking treatment for AUD in North America are chronic cigarette smokers (Durazzo and Meyerhoff, 2007; Room, 2004). Chronic cigarette smoking is a modifiable health risk that is associated with at least 440,000 deaths in the USA alone, with increasing mortality among individuals with AUD, substance use disorders and other neuropsychiatric conditions (see Durazzo and Meyerhoff, 2007 for review). These results offer treatment providers additional psychoeducational information on the consequences of chronic smoking in treatment-seeking AUD samples. Evidence from this report, combined with our earlier neurocognitive and neuroimaging studies (Durazzo and Meyerhoff, 2007; Mon *et al*., 2009) and the high mortality associated with cigarette smoking in AUD (Hurt *et al*., 1996), lend strong support to the growing clinical movement (which is a routine practice at the San Francisco VA Medical Center) to make smoking cessation programs available to chronic smokers entering treatment for substance use disorders.

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