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The relationships of sociodemographic factors, medical, psychiatric and substance-misuse comorbidities to neurocognition in short-term abstinent alcohol dependent individuals

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Abstract

Comorbidities that commonly accompany those afflicted with an alcohol use disorder (AUD) may promote variability in the pattern and magnitude of neurocognitive abnormalities demonstrated. The goal of this study was to investigate the influence of several common comorbid medical conditions (primarily hypertension and hepatitis C), psychiatric (primarily unipolar mood and anxiety disorders), and substance use (primarily psychostimulant and cannabis) disorders, and chronic cigarette smoking on the neurocognitive functioning in short-term abstinent, treatment-seeking individuals with AUD. Seventy-five alcohol dependent participants (ALC; 51 ± 9 years of age; 3 females) completed comprehensive neurocognitive testing after approximately one-month of abstinence. Multivariate multiple linear regression evaluated the relationships among neurocognitive variables and medical conditions, psychiatric and substance use disorders, controlling for sociodemographic factors. Sixty-four percent of ALC had at least one medical, psychiatric or substance abuse comorbidity (excluding smoking). Smoking status (smoker or non-smoker) and age were significant independent predictors of cognitive efficiency, general intelligence, postural stability, processing speed and visuospatial memory after age-normed adjustment and control for estimated premorbid verbal IQ, education, alcohol consumption, and medical, psychiatric, and substance misuse comorbidities. Results indicated that chronic smoking accounted for a significant portion of the variance in the neurocognitive performance of this middle-aged AUD cohort. The age-related findings for ALC suggest that alcohol dependence, per se, was associated with diminished neurocognitive functioning with increasing age. The study of participants who demonstrate common comorbidities observed in AUD is necessary to fully understand how AUD, as a clinical syndrome, affects neurocognition, brain neurobiology, and their changes with extended abstinence.

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Keywords

alcohol use disorders; alcohol dependence; cigarette smoking; age effects; comorbidities

INTRODUCTION

The adverse consequences of alcohol use disorders (i.e., alcohol abuse or dependence) on neurocognition, motor functions, and gait/balance, and their variable recovery with abstinence have been thoroughly documented (Reed et al., 1992; Rourke and Loberg, 1996; Rourke and Grant, 1999; Oscar-Berman, 2000; Sullivan et al., 2000a; Sullivan et al., 2000b). It is also widely recognized that a number of premorbid and/or comorbid participant characteristics can promote considerable variability in the pattern and magnitude of neurocognitive abnormalities demonstrated in AUD following detoxification and during sustained abstinence (Parsons and Nixon, 1993; Rourke and Loberg, 1996; Oscar-Berman, 2000; Sher et al., 2005). With respect to common comorbidities in AUD, chronic cigarette smoking (York and Hirsch, 1995; Daepfen et al., 2000; John et al., 2003; Room, 2004; Friend and Pagano, 2005), medical conditions, and psychiatric and substance use disorders are frequently observed (Pomerleau et al., 1997; Stein, 1999; John et al., 2003; Mertens et al., 2005; Stinson et al., 2005; Hasin et al., 2007). Prevalent comorbid medical conditions in AUD include hypertension (Klatsky, 1996; daLuz and Coimbra, 2001; Parekh and Klag, 2001), coronary artery disease (Hennekens, 1996; Tegos et al., 2001; Stinson et al., 2005), hepatitis C infection (Stein, 1999; Mertens et al., 2003), liver cirrhosis (Mertens et al., 2003; Stinson et al., 2005), and type-2 diabetes (Mansell et al., 2006). Common psychiatric comorbidities include anxiety disorders (Kranzler and Rosenthal, 2003; Hasin et al., 2007), unipolar and bipolar mood disorders (Raimo and Schuckit, 1998; Gilman and Abraham, 2001; Hasin and Grant, 2002; Lukassen and Beaudet, 2005; Hasin et al., 2007), and antisocial and borderline personality disorders (Kranzler and Rosenthal, 2003; Sher et al., 2005; Hasin et al., 2007). Comorbid illicit substance use disorders most frequently involve cannabis, cocaine, methamphetamine, and/or opioid use disorders (Wagner and Anthony, 2002; Degenhardt and Hall, 2003; Stinson et al., 2005).

In non-AUD samples, brain neurobiology and/or neurocognition are reported to be adversely affected by the foregoing medical (Hazell and Butterworth, 1999; Gispén and Biessels, 2000; Hilsabeck et al., 2002; Forton et al., 2003; Manolio et al., 2003), psychiatric (Veiel, 1997; Kramer-Ginsberg et al., 1999; Benes, 2000; Costa et al., 2000; Kanner, 2004; Campbell and MacQueen, 2006; Yildiz-Yesiloglu and Ankerst, 2006; Glahn et al., 2007), and substance use (Davis et al., 2002; Nordahl et al., 2003; Hester and Garavan, 2004; Lundqvist, 2005; Nordahl et al., 2005) disorders, as well as by chronic cigarette smoking (Durazzo and Meyerhoff, 2007; Swan and Lessov-Schlaggar, 2007). For this reason, participants who manifest hypertension, diabetes, hepatitis C, mood or anxiety disorders, and/or substance misuse disorders (other than nicotine dependence) are frequently excluded from study to reduce the potential influence of such comorbidities on outcome variables (Glenn et al., 1993; Oscar-Berman, 2000; Rosenbloom et al., 2005). However, recent large epidemiologic studies emphasize the very high prevalence of medical, psychiatric and substance misuse comorbidities in those with AUD (Mertens et al., 2003; Mertens et al., 2005; Stinson et al., 2005; Hasin et al., 2007). Furthermore, treatment-seeking AUD generally demonstrate a greater prevalence of comorbid mood, anxiety and personality disorders, psychiatric comorbidities, and a greater magnitude of lifetime alcohol consumption than their treatment-naïve counterparts (Kaskutas et al., 1997; Fein et al., 2002; Fein and Landman, 2005; Moss et al., 2007).

Given the high prevalence of medical, psychiatric and substance misuse comorbidities in AUD, it is important to understand to what extent these factors may contribute to the neurocognitive

abnormalities observed in AUD. Examination of samples that include participants who demonstrate comorbidities that commonly accompany AUD increases the clinical relevance and generalizability of the data, as such cohorts are more characteristic of the larger population of treatment-seeking alcoholics (Grant et al., 1984; Ham and Parsons, 2000; Rosenbloom et al., 2005). Grant and colleagues (Grant et al., 1984; Schafer et al., 1991) examined the influence of medical risk factors, liver function, nutrition and depression on neurocognition in 1–3 month abstinent, treatment-seeking individuals with AUD. The authors found that age, education, head injury risk factors, and severity of depressive symptoms were predictive of neurocognition. Parsons and colleagues reported that composite indexes of childhood behavior disorders, depressive symptomatology, and lifetime antisocial behaviors predicted different aspects of neurocognitive functioning in 3 – 6 week abstinent alcoholics (Glenn et al., 1993; Ham and Parsons, 2000). Beatty et al. (Beatty et al., 1997) reported that after approximately 3 weeks of abstinence, AUD with comorbid polysubstance demonstrated poorer performance on measures of geographical knowledge and spatial localization relative to controls; AUD-only and AUD-marijuana abusers were not different from controls. Studies investigating the effects of comorbid psychostimulant use disorders (i.e., amphetamine and/or cocaine) on neurocognitive dysfunction in recently detoxified AUD indicated potential additive adverse effects of psychostimulants (Bolla et al., 2000). Our group [see (Durazzo et al., 2006, 2007c)] and others (Friend et al., 2005; Glass et al., 2006) showed that chronic cigarette smoking is related to significantly lower neurocognition in multiple domains in treatment-seeking and non-treatment seeking AUD relative to their non-smoking counterparts. In contrast, several studies reported that comorbid medical, psychiatric, and/or substance abuse comorbidities did not influence neurocognition in AUD (Grant et al., 1984; Beatty et al., 1995; Eckardt et al., 1995; Lawton-Craddock et al., 2003; Uekermann et al., 2003; Rosenbloom et al., 2005). Given the inconsistent findings in the literature, the relationships of multiple common comorbidities to neurocognition in treatment-seeking AUD in early recovery is unclear.

The goal of this study was to specifically examine the relationships of several common comorbid medical conditions (primarily hypertension and hepatitis C), psychiatric (primarily unipolar mood and anxiety disorders), and substance use (primarily psychostimulant and cannabis) disorders, and chronic cigarette smoking on the neurocognitive functioning of one-month-abstinent, treatment-seeking AUD, while controlling for sociodemographic factors (i.e., age, education and estimated premorbid IQ) known to influence neurocognition. To our knowledge, a detailed examination of the relationships of the above factors with neurocognition in treatment-seeking alcohol-dependent individuals has not been reported.

METHODS

Participants

Recovering alcoholics (n = 75; 3 females) were recruited from the VA Medical Center Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program outpatient clinics in San Francisco for a longitudinal study on the effects chronic cigarette smoking on neurobiological and neurocognitive recovery from AUD. Recovering alcohol dependent individuals (ALC) were recruited from the VA Medical Center Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program outpatient clinics in San Francisco for a longitudinal study on the effects of abstinence from alcohol on brain structure, metabolism and function. Twenty-seven non-smoking light drinking controls (LD; 2 females) were recruited from the community. All participants were between the ages of 28 and 66 at the time of enrolment. ALC completed a comprehensive neuropsychological assessment battery after 33 ± 10 days of sustained abstinence (1 month assessment). Forty-one of the 75 ALC participants took part in studies described in our previous work (Durazzo et al., 2006). The majority of ALC participants first completed magnetic

resonance studies 6 ± 3 days after consumption of their last alcoholic drink as described in (Durazzo et al., 2004; Gazdzinski et al., 2005). Demographics, indices of alcohol consumption, smoking severity, depressive and anxiety symptomatology as well as select laboratory measures obtained at the 1-month assessment 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 greater than 150 alcoholic drinks per month (one alcoholic drink equivalent = 13.6 grams pure alcohol) for at least 8 years prior to enrolment for men, and consumption of greater than 80 drinks per month for at least 6 years prior to enrolment for women. Primary exclusion criteria are fully detailed in 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: hepatitis C, type-2 diabetes, hypertension, unipolar mood (major depression, substance-induced mood disorder), and anxiety (generalized anxiety disorder, panic disorder) disorders. ALC who met DSM-IV criteria for current or past substance abuse, and past substance dependence five or more years 5 prior to enrolment were allowed, whereas current opioid replacement therapy (e.g., methadone) was exclusionary. Approximately 88% of ALC participated in continued outpatient substance abuse treatment programs at the San Francisco VA Medical Center or Kaiser Permanente after their baseline magnetic resonance studies through the time of the 1-month assessment. ALC attended these programs 3–5 days per week, were given random weekly drug screens, and breath alcohol levels were acquired randomly or in the case of suspected or obvious intoxication. No participant reported alcohol or substance use between enrolment and comprehensive neuropsychological assessment and chart review of available records confirmed that no participant tested positive for illicit/non-prescribed substances or alcohol over this interval. Prior to all assessments, participants' urine was tested for five common illicit substances (i.e., THC, opiates, PCP, cocaine, and amphetamines), and they were evaluated for recent ethanol consumption via breathalyzer. No participant was positive for the above-listed substances or ethanol at the time of assessment.

Medical, Psychiatric, Substance, and Drinking History Assessment

At study enrolment and the 1-month assessment, ALC participant medical history was obtained from self-report and confirmed or amended via available medical records. At enrolment all 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 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 average number of drinks per month over 1, 3 and 8 years prior to enrolment, average number of drinks per month over lifetime, number of lifetime 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 lifetime in which the participant drank in excess of 100 drinks per month), and age of onset of heavy drinking. At the 1-month assessment point, ALC completed self-report measures of depressive [(Beck Depression Inventory, BDI; (Beck, 1978)] and anxiety symptomatology [(State-Trait Anxiety Inventory, form Y-2, STAI; (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) $\times$ number of years of smoking at level reported at enrolment]

calculated for smoking ALC. Smoking levels in ALC did not change between baseline and the 1-month assessment.

Neuropsychological Assessment

Participants completed comprehensive neuropsychological and motor/ataxia assessment (approximately 2.5 hours), which evaluated neurocognitive functions known to be adversely affected by alcohol-dependence (Rourke and Grant, 1999) and chronic cigarette smoking (Durazzo and Meyerhoff, 2007; Swan and Lessov-Schlaggar, 2007). Smoking ALC were allowed to smoke ad libitum prior to assessment and to take smoke breaks during the assessment. The domains evaluated and the constituent measures were as follows: *Executive skills*: Short Categories Test (Wetzel and Boll, 1987), Stroop Color-Word Test (Golden, 1978), Trail Making Test part B (Reitan and Wolfson, 1985), Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Similarities (Wechsler, 1997), Wisconsin Card Sorting Test-64: Computer Version 2-Research Edition (Heaton et al., 1993) non-perseverative errors, perseverative errors, and perseverative responses. *Fine motor skills*: Grooved Peg Board (Lafayette Instrument, Lafayette IN). *General intelligence*: Ward-7 Full Scale IQ [(Axelrod, Ryan & Ward, 2001; based on WAIS-III Arithmetic, Block Design, Digit Span, Digit Symbol, Information, Picture Completion, and Similarities subtests (Wechsler, 1997)]. *Learning and memory*: Auditory-verbal: California Verbal Learning Test-II (Delis et al., 2000), Immediate Recall trials 1–5 (learning), Short and Long Delay Free Recall (memory). Visuospatial: Brief Visuospatial Memory Test-Revised (Benedict, 1997), Total Recall (learning) and Delayed Recall (memory). *Postural stability*: Sharpened Romberg, eyes closed condition (Fregly and Graybiel, 1968). *Processing speed*: WAIS-III Digit Symbol, Stroop Color & Word (Golden, 1978), WAIS-III Symbol Search (Wechsler, 1997), Trail Making Test-A (Reitan and Wolfson, 1985). *Visuospatial skills*: WAIS-III Block Design; Luria-Nebraska Item 99 (Golden et al., 1978). *Working memory*: WAIS-III Arithmetic, WAIS-III Digit Span. *Cognitive efficiency*: This domain consisted of all tests that were timed, or in which the time to complete the task influenced the score achieved was calculated by averaging the individual z-scores of those measures (see below). Timed tests included the Luria-Nebraska Item 99 ratio, Stroop word, color, and color-word tests, Trails A and B and WAIS-III Arithmetic, Block Design, Digit Symbol, Picture Completion, and Symbol Search. Higher scores on these measures reflect better speed and accuracy on principally non-verbal tasks. The cognitive efficiency domain is an approximation of the concept of cognitive efficiency described by Glen and Parsons (Glen and Parsons, 1992) and Nixon and colleagues (Nixon et al., 1995; Nixon et al., 1998). Premorbid verbal intelligence was estimated with the American National Adult Reading Test (Grober and Sliwinski, 1991). The Sharpened Romberg task was administered as described in (Durazzo et al., 2006) and the score was log-transformed due to the highly skewed distributions.

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 (i.e., most participants achieved a score of 6 or better) for the number correct and the resultant highly skewed distribution. For both ALC and LD, raw scores for *all* neurocognitive measures, except the Fregly Sharpened Romberg and Luria-Nebraska Item 99 ratio, were converted to age-adjusted standardized scores via the normative data accompanying the particular measure (i.e., BVM-T-R, CVLT-II, Short Categories Test, Stroop Color-Word Test, WAIS-III subtests) or age and education [(Trails A and B, and WCST-64 variables via Heaton Compendium Norms (Heaton et al., 1991)]. Standardized scores were transformed to z-scores for formation of the above listed domains. For the Fregly Sharpened Romberg, eyes closed trial, and the Luria-Nebraska Item 99 ratio, raw scores were converted to z-scores based on the performance LD, as there are no appropriate norms for these measures. The summary score of domains with multiple measures represents the average of the individual z-scores of the constituent measures.

Laboratory Tests

Gamma-glutamyltransferase (GGT), liver function panels, prealbumin, complete blood count and common electrolytes were obtained at both assessments. GGT level served as a marker of recent heavy alcohol consumption (Sillanaukee and Olsson, 2001), and the plasma protein prealbumin provided information on nutritional status (Weinreb et al., 2002). See Table 1.

Data Analyses

In this report, our primary goal was to investigate the contribution of common comorbid medical, psychiatric, substance use disorders, and chronic cigarette smoking to the neurocognitive functioning of one-month abstinent ALC. In our primary analyses, the forgoing factors were treated as binary categorical variables in a multivariate multiple linear regression model. Specifically, if an ALC participant had any history of a non-exclusionary medical condition, they were considered to be positive for the medical comorbidity factor. To be considered positive for the substance use disorder comorbidity factor, the participant must have met current or lifetime DSM-IV criteria for substance abuse or past dependence (dependence must have ended ≥ 5 yrs prior to enrolment). Similarly, to be considered positive for a psychiatric comorbidity, the participant must have met current or lifetime DSM-IV criteria for a unipolar mood or anxiety disorder. ALC participants actively smoking at the time of assessment were considered to be positive for the smoking status factor. Age, education and estimated premorbid verbal intelligence (i.e., AMNART) were included as covariates in the model as these factors account for a significant amount of variance in neurocognitive functioning (Heaton et al., 1991; Gladsjo et al., 1999; Schretlen et al., 2005). Lifetime average drinks per month were also included as the main factor characterizing the effects of chronic and excessive alcohol consumption on brain function. Coding for all categorical comorbidities: 0 = negative for comorbidity, 1 = positive for comorbidity.

Multivariate multiple linear regression was used to control for the increased family-wise error rate that occurs when separately analyzing multiple dependent measures, and to account for the inter-relationships among dependent variables (in the ALC the average Spearman correlation coefficient among cognitive domains, excluding fine motor skills and postural stability, was 0.44). All dependent measures (i.e., neurocognitive domains), predictors and covariates were simultaneously entered into the omnibus model. In the omnibus model for AUD, we took the additional extremely conservative approach of adjusting the significance level for each predictor (.05) by the 8-neurocognitive domains evaluated (adjusted $\alpha = .0063$) to stringently control for the increased probability of making Type I errors with multiplicity of tests/comparisons. Results from follow-up univariate regressions were only considered for significant predictors in the omnibus model. The individual univariate regressions also controlled for the influence of all predictors, and an α level of .05 was considered statistically significant. Separate regression analyses were conducted for the domains of fine motor skills and postural stability. We view these sensorimotor functions as distinct from neurocognitive processes, as evidenced by their generally weak correlations among the neurocognitive domains evaluated in this study.

In secondary analyses for AUD, we included intracranial volume (ICV) with the above listed factors, as ICV has been reported to predict neurocognition in those with AUD (Di Sclafani et al., 1998; Schottenbauer et al., 2007). We also substituted average drinks per month over 1, 3, and 8 year prior to enrolment, and months of heavy drinking for lifetime average drinks per month to examine the association of these measures of drinking severity with neurocognition. The conditions that comprised the medical, psychiatric and substance abuse comorbidities factors were also individually entered as predictors. We also examined the relationships of age, education estimated premorbid IQ and ICV to neurocognition in LD with the above described statistical procedures.

RESULTS

Participant Characterization

Seventy-five percent (56/75) of ALC participants were Caucasian, 12% (9/75) African American, 6% (5/75) Latino, 4% (4/75), Native American, and 1% (1/75) Pacific Islander. Eighty percent of LD were Caucasian, 16% African American, and 4% Latino. See Table 1 for additional demographic information. Sixty-four percent of ALC had at least one medical, psychiatric or substance abuse comorbidity (excluding smoking). Fifty-nine percent of ALC were chronic smokers. Thirty-five percent of ALC participants met criteria for a comorbid medical condition, 36% for a psychiatric disorder, and 16% for a substance use disorder (see Table 2). Participants who met criteria for non-alcohol substance dependence had not used the compound in question for 160 ± 69 months (min = 120, max = 240). For ALC who met criteria for non-alcohol substance abuse, four were actively using at the time of assessment, and five had not used for 45 ± 40 months (min = 4, max = 252) and were in sustained full remission. At the one-month assessment, 50% of ALC took medications for a medical condition (primarily for hypertension) and 33% for a psychiatric disorder (primarily for major depression). Among non-smoking ALC, 24 reported never having used cigarettes consistently in their life (i.e., more than 10 cigarettes in one month). Seven non-smokers reported a previous history of chronic smoking, with five quitting more than 8 years and two 3 to 5 years prior to enrolment. All LD participants were never smokers.

Regression Analyses for ALC and LD

In the omnibus model, smoking status [$F(10, 52) = 7.92, p < .001$], age [$F(10, 52) = 2.90, p = .006$], and AMNART [$F(10, 52) = 7.92, p < .001$] were significant predictors of neurocognition. There were no significant interactions among predictors. In univariate regressions, smoking status, age, and AMNART were significant independent predictors of cognitive efficiency, general intelligence and processing speed (all $p < .05$; see Table 3). Age and AMNART predicted executive skills, and visuospatial skills, while smoking status and AMNART predicted auditory-verbal learning (all $p < .05$). Smoking status and age predicted visuospatial memory and postural stability (all $p < .05$). Smoking status uniquely predicted auditory-verbal memory, age predicted visuospatial learning, and AMNART uniquely predicted working memory (all $p < .05$). There was a trend for smoking status to predict executive skills ($p = .051$). Smoking status accounted for the greatest variance in auditory-verbal learning, auditory-verbal memory, and visuospatial memory, and age explained the most variance in visuospatial learning and postural stability. AMNART accounted for the greatest variance in cognitive efficiency, general intelligence, processing speed, visuospatial skills and working memory (see Table 3). Importantly in ALC, lifetime average drinks per month, education, and comorbid medical, psychiatric, and substance use disorders did not approach significance in the omnibus model, even at an alpha level of 0.05. None of the individual conditions (e.g., hypertension, cannabis abuse) that comprised the comorbid medical, psychiatric, and substance use factors were significant predictors. Other measures of drinking severity (e.g., 1, 3, 8-year average drinks/month, months of heavy drinking) and ICV were not predictive of neurocognition, and inclusion of these predictors did not appreciably alter the significance levels or variance accounted for by AMNART, age and smoking status reported above.

In separate analyses for LD, AMNART, age and education were not significant predictors of any neurocognitive of sensorimotor domain. The above results were unchanged when female participants were excluded from analyses for both ALC and LD.

Bivariate correlations (Spearman) for ALC between smoking status, age, AMNART, and neurocognitive domains are provided in Table 4. Significant positive correlations were observed between the AMNART and the neurocognitive domains where it was a significant

predictor, while age and positive smoking status were inversely related to the domains where they were significant predictors.

DISCUSSION

The main findings for this predominately Caucasian male Veteran sample of treatment-seeking ALC tested at approximately one-month of abstinence from alcohol were: 1) chronic cigarette smoking and age were significant independent predictors of multiple domains of neurocognition after age-normed adjustment and control for estimated premorbid verbal IQ, education and medical, psychiatric, and substance misuse comorbidities; 2) alcohol consumption levels and medical, psychiatric, and substance misuse comorbidities, as measured in this report, did not predict neurocognition.

In one-month abstinent ALC, chronic smoking was an independent predictor of auditory-verbal learning and memory, visuospatial memory, cognitive efficiency, general intelligence, processing speed, and postural stability, after controlling for the influence of common medical, psychiatric, and substance misuse comorbidities as well as sociodemographic factors. Overall, these results are a confirmation and a major extension of our earlier findings (Durazzo et al., 2006), where non-smoking ALC were superior to smoking ALC on measures of auditory-verbal and memory cognitive efficiency, processing speed, and static postural stability. The findings suggest chronic smoking accounts for a significant portion of the variance in the neurocognitive performance of our middle-age AUD cohort, and is consistent with the few other reports specifically investigating relationships among chronic smoking and brain function in AUD (Friend et al., 2005; Glass et al., 2006). In the present report, ICV in smoking (1460 ± 114 cc) and non-smoking ALC (1498 ± 141 cc) were not significantly different, and both were equivalent to LD ICV (1522 ± 144 cc). Age, education, AMNART and “ageing-resilient” measures (i.e., WAIS-III Information and Similarities subtests; data not shown) were not different among smoking and non-smoking ALC. These results suggest the smoking and non-smoking ALC groups were equivalent on sociodemographic and premorbid neurobiological and neurocognitive factors that are related to brain function in AUD and healthy controls (Heaton et al., 1991; Oscar-Berman, 2000; Fein and Di Sclafani, 2004; Schottenbauer et al., 2007). Smoking ALC participants were allowed to smoke ad libitum prior to, and during, the 2–2.5 hour neurocognitive assessment. The plasma half-life of nicotine in humans is approximately 2 – 3 hours (Nakajima and Yokoi, 2005), and, based on a 2-hour half-life, nicotine levels will accumulate (i.e., 3 or more half-lives) in the body with regular smoking during waking hours (Hukkanen et al., 2005). Consequently, the adverse effects of nicotine withdrawal on aspects of neurocognition do not typically manifest for 8–12 hours or longer after last nicotine consumption [for review see (Sacco et al., 2004)]. Therefore, we do not believe that potential nicotine withdrawal confounded our findings. Please see (Durazzo et al., 2007a; Durazzo et al., 2007b; Swan and Lessov-Schlaggar, 2007) for discussion of the potential mechanisms contributing to the greater neurobiological and neurocognitive abnormalities observed in chronically smoking AUD.

Notably, age was a significant predictor of multiple domains of functioning in ALC, despite *the use of age-adjusted norms*, while age did not predict neurocognition in LD. With the exception of visuospatial learning and memory, age explained a similar amount of variance in each domain for the smoking and non-smoking ALC groups when controlling for psychiatric, medical, substance misuse and demographic factors (age explained approximately 12% more variance for visuospatial learning and memory in smoking than non-smoking ALC; data not shown). Fast, flexible and accurate responses are required for better scores on the predominantly non-verbal/visuospatial tasks comprising the cognitive efficiency and processing speed domains, and on the WAIS-III Performance tasks contributing to the general intelligence domain. Research on normal age-related neurocognitive changes suggests

decreasing information processing speed is a major contributor to the declines in learning, memory and visuospatial abilities with increasing age (Salthouse, 1996, 2000; Christensen, 2001; Finkel et al., 2007). In this report, and our earlier work (Durazzo et al., 2006), measures of alcohol consumption severity showed no association with neurocognition. This is consistent with other studies that reported measures of alcohol consumption quantity/frequency were weakly or not significantly related to neurocognition (e.g., Schafer et al., 1991; Beatty et al., 1995; Eckardt et al., 1998; Horner et al., 1999; Beatty et al., 2000; Sullivan et al., 2000b). However, given that age did not predict performance in LD after accounting for AMNART and education, the age-related findings for ALC suggest that chronic alcohol dependence, per se, was associated with diminished neurocognitive functioning with increasing age on measures of cognitive efficiency, executive skills, general intelligence, processing speed, visuospatial learning and memory, and postural stability. Taken together, results for LD and ALC also are generally consistent with the “premature ageing” hypothesis of AUD [see (Oscar-Berman, 2000)].

In ALC, the AMNART accounted for the greatest variance across domains, followed by smoking status and age. The large amount of variance explained by AMNART, rather than education, across multiple domains in ALC is somewhat unexpected; the AMNART, and other similar indexes tend to show strong relationships to WAIS measures of Verbal and Full Scale IQ, and only moderately strong correlations with WAIS Performance measures and other neurocognitive domains (Gladsjo et al., 1999; Graves, 2000; Schretlen et al., 2005). Education may have not predicted neurocognition because of the relatively high level achieved (13.8 ± 2.1 years) and the restricted range in this ALC cohort. Multicollinearity diagnostics indicated the AMNART explained a portion of the variance in each domain that was unique from education.

The lack of association of psychiatric and substance misuse comorbidities with neurocognition in this report is consistent with studies of one-to-three-month-abstinent, younger (Eckardt et al., 1995) and middle aged (Rosenbloom et al., 2005) AUD cohorts, where these conditions did not adversely affect neurocognition. The findings for the substance misuse comorbidity are in line with Lawton-Craddock et al. (Lawton-Craddock et al., 2003), who reported comorbid psychostimulant dependence did not adversely affect neurocognition in one-month abstinent ALC. In the present study, comorbid medical conditions also did not predict neurocognition, which parallels Grant and colleagues (Grant et al., 1984), who reported that hypertension, diabetes or hepatic disease were not related to neurocognition in a large group of recently detoxified ALC. Conversely, comorbid mood disorders, which were the most prevalent psychiatric comorbidity in our sample predictors, were reported to predict neurocognition in short-term abstinent ALC in other studies (Schafer et al., 1991; Ham and Parsons, 2000).

This report has limitations that may influence the nature and generalizability of the findings. The lack of associations of psychiatric comorbidities with neurocognition in this cohort may have been influenced by the low frequency of anxiety disorders relative to that reported in epidemiological and treatment seeking samples (e.g., Baigent, 2005; Hasin et al., 2007), as well as the exclusion of those with bipolar disorder and schizophrenia-spectrum disorders. Similarly, the lack of associations of substance misuse comorbidities with neurocognition was likely influenced by low prevalence and severity in this cohort, compared to that reported in epidemiological studies (e.g., Stinson et al., 2005). Participants who met DSM-IV criteria for substance dependence in the 5 years preceding enrolment were excluded, which surely limited the prevalence and severity of substance use disorders in our cohort. It is also possible that the results were influenced by factors not directly assessed in this study, such as nutrition, exercise, and previous exposure to environmental cigarette smoke or genetic predispositions. Additionally, we did not assess for personality disorders in our cohort, which may contribute

to the neurobiological and neurocognitive abnormalities observed in AUD, particularly antisocial personality disorder (Eckardt et al., 1995; Kuruoglu et al., 1996; Giancola and Moss, 1998; Costa et al., 2000). Finally, 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.

In conclusion, after age-normed adjustment, and control for premorbid verbal IQ, education and comorbidities commonly observed in AUD, chronic cigarette smoking and age were independent and robust predictors of neurocognition in this cohort of 1-month-abstinent recovering alcoholics. In general, the psychiatric, medical and substance misuse comorbidities, as measured in this study, had little relationship to neurocognition at one month of abstinence from alcohol. Future studies that include a greater variety and severity of the psychiatric, medical and substance misuse comorbidities that are commonly observed in those with AUD are necessary to fully understand how the clinical syndrome of AUD affects brain neurobiology, neurocognition, and their changes with extended abstinence. The information generated from such studies will have greater generalizability and considerably more relevance to clinical researchers and treatment providers who strive to increase the efficacy of pharmacological and behavioral treatments for AUD.

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References

- Axelrod BN, Ryan JJ, Ward CL. Evaluation of seven-subtest short forms of the Wechsler Adult Intelligence Scale-III in a referred sample. *Arch Clin Neuropsychology* 2001;16:1–8.
- Baigent MF. Understanding alcohol misuse and comorbid psychiatric disorders. *Curr Opin Psychiatry* 2005;18:223–228. [PubMed: 16639144]
- Beatty WW, Katzung VM, Moreland VJ, Nixon SJ. Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend* 1995;37:247–253. [PubMed: 7796719]
- Beatty WW, Blanco CR, Hames KA, Nixon SJ. Spatial cognition in alcoholics: influence of concurrent abuse of other drugs. *Drug Alcohol Depend* 1997;44:167–174. [PubMed: 9088789]
- Beatty WW, Tivis R, Stott HD, Nixon SJ, Parsons OA. Neuropsychological deficits in sober alcoholics: influences of chronicity and recent alcohol consumption. *Alcohol Clin Exp Res* 2000;24:149–154. [PubMed: 10698365]
- Beck, AT. *Depression Inventory*. Center for Cognitive Therapy; Philadelphia: 1978.
- Benedict, R. *Brief Visuospatial Memory Test - Revised*. Psychological Assessment Resources, Inc.; Odessa, FL: 1997.
- Benes FM. Emerging principles of altered neural circuitry in schizophrenia. *Brain Res Brain Res Rev* 2000;31:251–269. [PubMed: 10719152]
- Bolla KI, Funderburk FR, Cadet JL. Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology* 2000;54:2285–2292. [PubMed: 10881254]
- Campbell S, MacQueen G. An update on regional brain volume differences associated with mood disorders. *Curr Opin Psychiatry* 2006;19:25–33. [PubMed: 16612175]
- Christensen H. What cognitive changes can be expected with normal ageing? *Aust N Z J Psychiatry* 2001;35:768–775. [PubMed: 11990887]

- Costa L, Bauer L, Kuperman S, Porjesz B, O'Connor S, Hesselbrock V, Rohrbaugh J, Begleiter H. Frontal P300 decrements, alcohol dependence, and antisocial personality disorder. *Biol Psychiatry* 2000;47:1064–1071. [PubMed: 10862806]
- Daepfen JB, Smith TL, Danko GP, Gordon L, Landi NA, Nurnberger JI Jr, Bucholz KK, Raimo E, Schuckit MA. Clinical correlates of cigarette smoking and nicotine dependence in alcohol-dependent men and women. The Collaborative Study Group on the Genetics of Alcoholism Alcohol Alcohol 2000;35:171–175.
- daLuz PL, Coimbra SR. Alcohol and atherosclerosis. *An Acad Bras Cienc* 2001;73:51–55. [PubMed: 11246269]
- Davis PE, Liddiard H, McMillan TM. Neuropsychological deficits and opiate abuse. *Drug Alcohol Depend* 2002;67:105–108. [PubMed: 12062785]
- Degenhardt L, Hall W. Patterns of co-morbidity between alcohol use and other substance use in the Australian population. *Drug Alcohol Rev* 2003;22:7–13. [PubMed: 12745353]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test. 2. The Psychological Corporation; San Antonio, TX: 2000.
- Di Sclafani V, Clark HW, Tolou-Shams M, Bloomer CW, Salas GA, Norman D, Fein G. Premorbid brain size is a determinant of functional reserve in abstinent crack-cocaine and crack-cocaine-alcohol-dependent adults. *J Int Neuropsychological Soc* 1998;4:559–565.
- Durazzo TC, Gazdzinski S, Banys P, Meyerhoff DJ. Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. *Alcohol Clin Exp Res* 2004;28:1849–1860. [PubMed: 15608601]
- Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. A comparison of neurocognitive function in nonsmoking and chronically smoking short-term abstinent alcoholics. *Alcohol* 2006;39:1–11. [PubMed: 16938624]
- Durazzo TC, Gazdzinski S, Meyerhoff DJ. The neurobiological and neurocognitive consequences of chronic cigarette smoking in alcohol use disorders. *Alcohol Alcohol* 2007a;42:174–185. [PubMed: 17526627]
- Durazzo TC, Meyerhoff DJ. Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. *Front Biosci* 2007;12:4079–4100. [PubMed: 17485360]
- Durazzo TC, Rothlind JC, Cardenas VA, Studholme C, Weiner MW, Meyerhoff DJ. Chronic cigarette smoking and heavy drinking in human immunodeficiency virus: consequences for neurocognition and brain morphology. *Alcohol* 2007b;41:489–501. [PubMed: 17923369]
- Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. Chronic smoking is associated with differential neurocognitive recovery in abstinent alcoholic patients: a preliminary investigation. *Alcohol Clin Exp Res* 2007c;31:1114–1127. [PubMed: 17451399]
- Eckardt MJ, Stapleton JM, Rawlings RR, Davis EZ, Grodin DM. Neuropsychological functioning in detoxified alcoholics between 18 and 35 years of age. *Am J Psychiatry* 1995;152:53–59. [PubMed: 7802120]
- Eckardt MJ, File SE, Gessa GL, Grant KA, Guerri C, Hoffman PL, Kalant H, Koob GF, Li TK, Tabakoff B. Effects of moderate alcohol consumption on the central nervous system. *Alcohol Clin Exp Res* 1998;22:998–1040. [PubMed: 9726269]
- Fagerstrom KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. *Ear Nose Throat J* 1991;69:763–765. [PubMed: 2276350]
- Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical gray matter loss in treatment-naïve alcohol dependent individuals. *Alcohol Clin Exp Res* 2002;26:558–564. [PubMed: 11981133]
- Fein G, Di Sclafani V. Cerebral reserve capacity: implications for alcohol and drug abuse. *Alcohol* 2004;32:63–67. [PubMed: 15066705]
- Fein G, Landman B. Treated and treatment-naïve alcoholics come from different populations. *Alcohol* 2005;35:19–26. [PubMed: 15922134]
- Finkel D, Reynolds CA, McArdle JJ, Pedersen NL. Age changes in processing speed as a leading indicator of cognitive aging. *Psychology and Aging* 2007;22:558–568. [PubMed: 17874954]

- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0, 8/98 revision). Biometrics Research Department; New York, NY: 1998.
- Forton DM, Taylor-Robinson SD, Thomas HC. Cerebral dysfunction in chronic hepatitis C infection. *J Viral Hepat* 2003;10:81–86. [PubMed: 12614463]
- Fregly AR, Graybiel A. An ataxia test battery not requiring rails. *Aerospace Med* 1968;39:277–282. [PubMed: 5636011]
- Friend KB, Malloy PF, Sindelar HA. The effects of chronic nicotine and alcohol use on neurocognitive function. *Addict Behav* 2005;30:193–202. [PubMed: 15561461]
- Friend KB, Pagano ME. Changes in cigarette consumption and drinking outcomes: findings from Project MATCH. *J Subst Abuse Treat* 2005;29:221–229. [PubMed: 16183471]
- Gazdzinski S, Durazzo TC, Studholme C, Song E, Banys P, Meyerhoff DJ. Quantitative brain MRI in alcohol dependence: preliminary evidence for effects of concurrent chronic cigarette smoking on regional brain volumes. *Alcohol Clin Exp Res* 2005;29:1484–1495. [PubMed: 16131857]
- Giancola PR, Moss HB. Executive cognitive functioning in alcohol use disorders. *Recent Dev Alcohol* 1998;14:227–251. [PubMed: 9751948]
- Gilman SE, Abraham HD. A longitudinal study of the order of onset of alcohol dependence and major depression. *Drug Alcohol Depend* 2001;63:277–286. [PubMed: 11418232]
- Gispén WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci* 2000;23:542–549. [PubMed: 11074263]
- Gladys JA, Heaton RK, Palmer BW, Taylor MJ, Jeste DV. Use of oral reading to estimate premorbid intellectual and neuropsychological functioning. *J Int Neuropsychological Soc* 1999;5:247–254.
- Glahn DC, Bearden CE, Barguil M, Barrett J, Reichenberg A, Bowden CL, Soares JC, Velligan DI. The neurocognitive signature of psychotic bipolar disorder. *Biol Psychiatry* 2007;62:910–916. [PubMed: 17543288]
- Glass JM, Adams KM, Nigg JT, Wong MM, Puttler LI, Buu A, Jester JM, Fitzgerald HE, Zucker RA. Smoking is associated with neurocognitive deficits in alcoholism. *Drug Alcohol Depend* 2006;82:119–126. [PubMed: 16169161]
- Glenn SW, Parsons OA. Neuropsychological efficiency measures in male and female alcoholics. *J Stud Alcohol* 1992;53:546–552. [PubMed: 1434630]
- Glenn SW, Errico AL, Parsons OA, King AC, Nixon SJ. The role of antisocial, affective, and childhood behavioral characteristics in alcoholics' neuropsychological performance. *Alcohol Clin Exp Res* 1993;17:162–169. [PubMed: 8452198]
- Golden, CJ. Stroop Color and Word Test. Stoelting Company; Chicago, IL: 1978.
- Golden CJ, Hammeke TA, Purisch AD. Diagnostic validity of a standardized neuropsychological battery derived from Luria's neuropsychological tests. *J Consult Clin Psychol* 1978;46:1258–1265. [PubMed: 730876]
- Grant I, Adams KM, Reed R. Aging, abstinence, and medical risk factors in the prediction of neuropsychologic deficit among long-term alcoholics. *Arch Gen Psychiatry* 1984;41:710–718. [PubMed: 6732429]
- Graves RE. Accuracy of regression equation prediction across the range of estimated premorbid IQ. *J Clin Exp Neuropsychology* 2000;22:316–324.
- Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *J Clin Exp Neuropsychology* 1991;13:933–949.
- Ham HP, Parsons OA. Predicting cognitive performance in alcoholics and nonalcoholics: specification of affective, childhood behavior disorders, and antisocial variables. *Appl Neuropsychol* 2000;7:90–95. [PubMed: 10863603]
- Hasin D, Grant B. Major depression in 6050 former drinkers: association with past alcohol dependence. *Arch Gen Psychiatry* 2002;59:794–800. [PubMed: 12215078]
- Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007;64:830–842. [PubMed: 17606817]

- Hazell AS, Butterworth RF. Hepatic encephalopathy: An update of pathophysiologic mechanisms. *Proc Soc Exp Biol Med* 1999;222:99–112. [PubMed: 10564534]
- Heaton, RK.; Grant, I.; Matthews, CG. Comprehensive norms for an expanded Halstead-Reitan Battery Demographic Corrections, Research Findings, and clinical applications. Psychological Assessment Resources, Inc.; Odessa, FL: 1991.
- Heaton, RK.; Staff, PAR. Wisconsin Card Sorting Test: ComputerVersion-2, Research Edition. Psychological Assessment Resources Inc; Lutz, FL: 1993.
- Hennekens, CH. Alcohol and Risk of Coronary Events. In: Zahkari, S.; Wassef, M., editors. Alcohol and the Cardiovascular System. 15. National Institutes of Health: National Institute on Alcohol Abuse and Alcoholism; Bethesda, MD: 1996.
- Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *J Neurosci* 2004;24:11017–11022. [PubMed: 15590917]
- Hilsabeck RC, Perry W, Hassanein TI. Neuropsychological impairment in patients with chronic hepatitis C. *Hepatology* 2002;35:440–446. [PubMed: 11826421]
- Horner MD, Waid LR, Johnson DE, Latham PK, Anton RF. The relationship of cognitive functioning to amount of recent and lifetime alcohol consumption in outpatient alcoholics. *Addict Behav* 1999;24:449–453. [PubMed: 10400285]
- Hukkanen J, Jacob P 3, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005;57:79–115. [PubMed: 15734728]
- John U, Meyer C, Rumpf HJ, Schumann A, Thyrian JR, Hapke U. Strength of the relationship between tobacco smoking, nicotine dependence and the severity of alcohol dependence syndrome criteria in a population-based sample. *Alcohol Alcohol* 2003;38:606–612. [PubMed: 14633650]
- Kanner AM. Is major depression a neurologic disorder with psychiatric symptoms? *Epilepsy Behav* 2004;5:636–644. [PubMed: 15380113]
- Kaskutas LA, Weisner C, Caetano R. Predictors of help seeking among a longitudinal sample of the general population, 1984–1992. *J Stud Alcohol* 1997;58:155–161. [PubMed: 9065893]
- Klatsky, AL. Blood Pressure and Alcohol Intake: Clinical Aspects. In: Zahkari, S.; Wassef, M., editors. Alcohol and the Cardiovascular System. 173. National Institutes of Health: National Institute on Alcohol Abuse and Alcoholism; Bethesda, MD: 1996.
- Kramer-Ginsberg E, Greenwald BS, Krishnan KR, et al. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. *Am J Psychiatry* 1999;156:438–444. [PubMed: 10080561]
- Kranzler HR, Rosenthal RN. Dual diagnosis: alcoholism and co-morbid psychiatric disorders. *Am J Addict* 2003;12(Suppl 1):S26–40. [PubMed: 14972778]
- Kuruoglu AC, Arikan Z, Vural G, Karatas M, Arac M, Isik E. Single photon emission computerised tomography in chronic alcoholism. Antisocial personality disorder may be associated with decreased frontal perfusion. *Br J Psychiatry* 1996;169:348–354. [PubMed: 8879722]
- Lawton-Craddock A, Nixon SJ, Tivis R. Cognitive efficiency in stimulant abusers with and without alcohol dependence. *Alcohol Clin Exp Res* 2003;27:457–464. [PubMed: 12658111]
- Lafayette Instrument. Grooved Pegboard Test, Model 32025. Lafayette IN: 1989.
- Lukassen J, Beaudet MP. Alcohol dependence and depression among heavy drinkers in Canada. *Soc Sci Med* 2005;61:1658–1667. [PubMed: 15869834]
- Lundqvist T. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav* 2005;81:319–330. [PubMed: 15925403]
- Manolio TA, Olson J, Longstreth WT. Hypertension and cognitive function: pathophysiologic effects of hypertension on the brain. *Curr Hypertens Rep* 2003;5:255–261. [PubMed: 12724059]
- Mansell D, Penk W, Hankin CS, Lee A, Spiro A 3rd, Skinner KM, Hsieh J, Kazis LE. The illness burden of alcohol-related disorders among VA patients: the veterans health study. *J Ambul Care Manage* 2006;29:61–70. [PubMed: 16340620]
- Mertens JR, Lu YW, Parthasarathy S, Moore C, Weisner CM. Medical and psychiatric conditions of alcohol and drug treatment patients in an HMO: comparison with matched controls. *Arch Intern Med* 2003;163:2511–2517. [PubMed: 14609789]

- Mertens JR, Weisner C, Ray GT, Fireman B, Walsh K. Hazardous drinkers and drug users in HMO primary care: prevalence, medical conditions, and costs. *Alcohol Clin Exp Res* 2005;29:989–998. [PubMed: 15976525]
- Moss HB, Chen CM, Yi HY. Subtypes of alcohol dependence in a nationally representative sample. *Drug Alcohol Depend* 2007;91:149–158. [PubMed: 17597309]
- Nakajima M, Yokoi T. Interindividual variability in nicotine metabolism: C-oxidation and glucuronidation. *Drug Metab Pharmacokinet* 2005;20:227–235. [PubMed: 16141602]
- Nixon SJ, Tivis R, Parsons OA. Behavioral dysfunction and cognitive efficiency in male and female alcoholics. *Alcohol Clin Exp Res* 1995;19:577–581. [PubMed: 7573777]
- Nixon SJ, Paul R, Phillips M. Cognitive efficiency in alcoholics and polysubstance abusers. *Alcohol Clin Exp Res* 1998;22:1414–1420. [PubMed: 9802522]
- Nordahl TE, Salo R, Leamon M. Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. *J Neuropsychiatry Clin Neurosci* 2003;15:317–325. [PubMed: 12928507]
- Nordahl TE, Salo R, Natsuaki Y, Galloway GP, Waters C, Moore CD, Kile S, Buonocore MH. Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study. *Arch Gen Psychiatry* 2005;62:444–452. [PubMed: 15809412]
- Oscar-Berman, M. Review of NIAAA's Neuroscience and Behavioral Research Portfolio. NIAAA; Bethesda, MD: 2000. NIAAA Research Monograph No. 34: Neuropsychological vulnerabilities in chronic alcoholism; p. 437–472.
- Parekh RS, Klag MJ. Alcohol: role in the development of hypertension and end-stage renal disease. *Curr Opin Nephrol Hypertens* 2001;10:385–390. [PubMed: 11342802]
- Parsons OA, Nixon SJ. Neurobehavioral sequelae of alcoholism. *Neurol Clin* 1993;11:205–218. [PubMed: 8441371]
- Pomerleau CS, Aubin HJ, Pomerleau OF. Self-reported alcohol use patterns in a sample of male and female heavy smokers. *J Addict Dis* 1997;16:19–24. [PubMed: 9243336]
- Raimo EB, Schuckit MA. Alcohol dependence and mood disorders. *Addict Behav* 1998;23:933–946. [PubMed: 9801727]
- Reed RJ, Grant I, Rourke SB. Long-term abstinent alcoholics have normal memory. *Alcohol Clin Exp Res* 1992;16:677–683. [PubMed: 1530129]
- Reitan, RM.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Interpretation. Neuropsychological Press; Tucson, AZ: 1985.
- Room R. Smoking and drinking as complementary behaviours. *Biomed Pharmacother* 2004;58:111–115. [PubMed: 14992792]
- Rosenbloom MJ, O'Reilly A, Sassoon SA, Sullivan EV, Pfefferbaum A. Persistent cognitive deficits in community-treated alcoholic men and women volunteering for research: limited contribution from psychiatric comorbidity. *J Stud Alcohol* 2005;66:254–265. [PubMed: 15957677]
- Rourke, SB.; Loberg, T. Neurobehavioral correlates of alcoholism. In: Grant, I.; Adams, KM., editors. *Neuropsychological Assessment of Neuropsychiatric Disorders: Revised*. Oxford University Press; 1996. p. 423–485.
- Rourke SB, Grant I. The interactive effects of age and length of abstinence on the recovery of neuropsychological functioning in chronic male alcoholics: a 2-year follow-up study. *J Int Neuropsychological Soc* 1999;5:234–246.
- Sacco KA, Bannon KL, George TP. Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. *J Psychopharmacol* 2004;18:457–474. [PubMed: 15582913]
- Salthouse TA. The processing-speed theory of adult age differences in cognition. *Psychol Rev* 1996;103:403–428. [PubMed: 8759042]
- Salthouse TA. Aging and measures of processing speed. *Biol Psychol* 2000;54:35–54. [PubMed: 11035219]
- Schafer K, Butters N, Smith T, Irwin M, Brown S, Hanger P, Grant I, Schuckit M. Cognitive performance of alcoholics: a longitudinal evaluation of the role of drinking history, depression, liver function, nutrition, and family history. *Alcohol Clin Exp Res* 1991;15:653–660. [PubMed: 1928640]

- Schottenbauer MA, Momenan R, Kerick M, Hommer DW. Relationships among aging, IQ, and intracranial volume in alcoholics and control subjects. *Neuropsychology* 2007;21:337–345. [PubMed: 17484597]
- Schretlen DJ, Buffington AL, Meyer SM, Pearlson GD. The use of word-reading to estimate “premorbid” ability in cognitive domains other than intelligence. *J Int Neuropsychological Soc* 2005;11:784–787.
- Sher KJ, Grekin ER, Williams NA. The development of alcohol use disorders. *Annu Rev Clin Psychol* 2005;1:493–523. [PubMed: 17716097]
- Sillanaukee P, Olsson U. Improved diagnostic classification of alcohol abusers by combining carbohydrate-deficient transferrin and gamma-glutamyltransferase. *Clin Chem* 2001;47:681–685. [PubMed: 11274018]
- Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. *J Stud Alcohol* 1982;43:1157–1170. [PubMed: 7182675]
- Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Self-Evaluation Questionnaire. 1977
- Stein MD. Medical consequences of substance abuse. *Psychiatric Clinics of North America* 1999;22:351–370. [PubMed: 10385938]
- Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend* 2005;80:105–116. [PubMed: 16157233]
- Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Brain Vulnerability to Alcoholism: Evidence from Neuroimaging studies. NIAAA. 2000a
- Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin Exp Res* 2000b;24:611–621. [PubMed: 10832902]
- Swan GE, Lessov-Schlaggar CN. The Effects of Tobacco Smoke and Nicotine on Cognition and the Brain. *Neuropsychology Rev.* 2007
- Tegos TJ, Kalodiki E, Sabetai MM, Nicolaides AN. The genesis of atherosclerosis and risk factors: a review. *Angiology* 2001;52:89–98. [PubMed: 11228092]
- Uekermann J, Daum I, Schlebusch P, Wiebel B, Trenckmann U. Depression and cognitive functioning in alcoholism. *Addiction* 2003;98:1521–1529. [PubMed: 14616178]
- Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. *J Clin Exp Neuropsychology* 1997;19:587–603.
- Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *Am J Epidemiol* 2002;155:918–925. [PubMed: 11994231]
- Wechsler, D. The Wechsler Adult Intelligence Scale-Third Edition. The Psychological Corporation; San Antonio, TX: 1997.
- Weinreb W, Graf-Gruss R, Schwabe R, Stippler D, Fusgen I. The two-factor method--a new approach to categorizing the clinical stages of malnutrition in geriatric patients. *J Am Geriatrics Soc* 2002;50:2105–2107.
- Wetzel, L.; Boll, T. Short Category Test, Booklet Format. Western Psychological Services; Los Angeles: 1987.
- Yildiz-Yesiloglu A, Ankerst DP. Review of 1H magnetic resonance spectroscopy findings in major depressive disorder: a meta-analysis. *Psychiatry Res* 2006;147:1–25. [PubMed: 16806850]
- York JL, Hirsch JA. Drinking patterns and health status in smoking and nonsmoking alcoholics. *Alcohol Clin Exp Res* 1995;19:666–673. [PubMed: 7573791]

Table 1**Participant Demographics and Clinical Measures**

Measure	LD (n = 27)	ALC (n = 75)
Age	45.3 ± 9.0	50.6 ± 9.2 [*]
Education	15.8 ± 2.4	13.8 ± 2.1 [#]
AMNART	119 ± 6	112 ± 9 [#]
1-yr ave drinks/month	19 ± 24	412 ± 207 [*]
8-yr ave drinks/month	19 ± 22	328 ± 161 [*]
Lifetime ave drinks/month	19 ± 18	232 ± 125 [*]
Months heavy drinking	NA	267 ± 114
Age onset heavy drinking	NA	25 ± 10
FTND	NA	6.3 ± 4.0
Cigarette pack years	NA	29 ± 20
BDI	4.2 ± 4.2	9.0 ± 7.1 [*]
STAI-trait	33.4 ± 7.4	42.8 ± 11.0 [*]
GGT	25 ± 10	44 ± 25 [*]
prealbumin	30 ± 7	27 ± 6
ICV (cc)	1522 ± 144	1479 ± 129

^{*} Note. ALC > LD, $p < .05$;

[#] ALC < LD, $p < .05$;

AMNART: American National Adult Reading Test; BDI: Beck Depression Inventory; FTND: Fagerstrom Test for Nicotine Dependence, for smoking ALC only; GGT: gamma glutamyltransferase, normal range 7–64 institutional units; ICV: intracranial volume; NA: not applicable; prealbumin, normal range 18 – 45 mg/dL; STAI: State-trait Anxiety Inventory (all values mean ± SD).

Table 2

Frequency of psychiatric, medical and substance abuse comorbidities in ALC

Comorbidity	n (%)	Subcategory	n	Number of participants with current diagnosis
Psychiatric disorder	27 (36)	Major depression	13	10
		Substance induced mood disorder	14	14
		Generalized anxiety disorder	3	3
		Participants with > 1 subcategory	3	3
Medical condition	36 (35)	Hypertension	16	16
		Hepatitis C	15	15
		Type-2 Diabetes	2	2
		Other medical conditions	3	3
		Participants with > 1 subcategory	10	9
Substance use disorder	12 (16)	Methamphetamine dependence	1	0
		Cocaine dependence	2	0
		Methamphetamine abuse	2	0
		Cocaine abuse	3	1
		Cannabis abuse	6	3
		Participants with > 1 subcategory	2	2
Smoker	44 (59)	Current smoker	44	na
		Former smoker	7	na

Table 3
Significance levels and eta squared for smoking status, age, and AMNART for ALC

Domain	Smoking Status			Age			AMNART		
	B	p	Eta ²	B	p	Eta ²	B	p	Eta ²
AV learning	-.955	<.001	.210	-.009	.468	.006	.020	.027	.061
AV memory	-.907	<.001	.185	-.017	.458	.007	.037	.191	.021
Cognitive efficiency	-.403	<.001	.111	-.020	.002	.065	.042	<.001	.214
Executive skills	-.261	.051	.036	-.025	.004	.079	.029	<.001	.207
General Intelligence	-.283	.024	.021	-.023	.005	.046	.070	<.001	.284
Processing speed	-.427	.001	.100	-.014	.038	.037	.044	<.001	.241
VS learning	-.402	.089	.027	-.034	.049	.064	.014	.323	.008
VS memory	-.770	.010	.081	-.039	.040	.068	.026	.162	.020
VS skills	-.044	.632	.001	-.024	.012	.057	.051	<.001	.180
Working memory	-.025	.297	.001	-.012	.489	.014	.051	.012	.176
Fine motor skills	-.061	.722	.001	-.006	.609	.004	.006	.709	.002
Postural stability	-1.53	.040	.069	-.110	.005	.135	.039	.432	.010

Note. AV: Auditory-verbal; Eta²: Eta squared; VS: visuospatial

Table 4

Correlations among neurocognitive domains and AMNART, age and smoking status for ALC

Domain	AMNART	Age	Smoking status
AV learning	.31**	.04	-.48**
AV memory	.21	-.05	-.42**
Cognitive efficiency	.55**	-.23*	-.32**
Executive skills	.53**	-.33**	-.16
General Intelligence	.77**	-.18	-.16
Processing speed	.52**	-.29*	-.33**
VS learning	.25	-.27*	-.24*
VS memory	.22	-.28*	-.26*
VS skills	.53**	-.33**	-.01
Working memory	.60**	-.13	-.05
Fine motor skills	.11	-.01	-.09
Postural stability	.19	-.31*	-.39**

* Note. $p < .05$;**
 $p < .01$;

AMNART: American National Adult Reading Test; AV: auditory-verbal; VS: visuospatial; all values are Spearman's rho.

Table 5

Neurocognitive performance of ALC

Domain	ALC
AV learning	.49 ± .95
AV memory	.30 ± .92
Cognitive efficiency	-.30 ± .60
Executive skills	-.31 ± .62
General Intelligence	.19 ± .88
Processing speed	-.20 ± .60
VS learning	-.62 ± 1.11
VS memory	-.54 ± 1.19
VS skills	-.27 ± .81
Working memory	.16 ± 1.06
Fine motor skills	-.96 ± .79
Postural stability	-2.07 ± 2.45

Note. ALC: alcohol dependent participant; AV: auditory-verbal; VS: visuospatial; all values are age corrected z-scores (mean ± SD).