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Neurocognition in 1-Month-Abstinent Treatment-Seeking Alcohol Dependent Individuals: Interactive Effects of Age and Chronic Cigarette Smoking

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Abstract

Background—Increasing age and chronic cigarette smoking are independently associated with adverse effects on multiple aspects of neurocognition in those seeking treatment for alcohol use disorders. However, the potential interactive effects of age and cigarette smoking on neurocognition in early abstinent alcohol dependent individuals have not investigated.

Methods—Cross-sectional performances of never-smoking healthy comparison participants (nvsCOM; n = 39) and 1-month-abstinent, treatment-seeking, never-smoking (nvsALC; n = 30), former-smoking (fsALC; n = 21) and actively smoking (asALC; n = 68) alcohol dependent individuals (ALC) were compared on a comprehensive neurocognitive battery. Domains of functioning evaluated were cognitive efficiency, executive functions, fine motor skills, general intelligence, learning and memory, processing speed, visuospatial functions and working memory. Participants were between 26 and 71 years-of-age at the time of assessment.

Results—asALC showed steeper age-related effects than nvsCOM on the domains of visuospatial learning, auditory-verbal memory, cognitive efficiency, executive functions, processing speed, and fine motor skills. In pairwise comparisons, fsALC and asALC performed more poorly than both nvsCOM and nvsALC on multiple domains; nvsCOM and nvsALC showed no significant differences. Domain scores for the ALC groups generally fell in the low-to-high-average range of functioning. A clinically significant level of impairment was apparent in only 25% of ALC participants on visuospatial learning, visuospatial memory and fine motor skills domains. Measures of alcohol use or consumption were not significantly related to neurocognition in the ALC cohorts.

Conclusions—The age-related findings suggest that the *combination* of active chronic smoking and alcohol dependence in this 1-month-abstinent ALC cohort was associated with greater-than-normal age-related effects in multiple domains. In general, a low level of clinically significant impairment was observed in the alcohol dependent participants. The findings from this study, in conjunction with previous research, strongly support smoking cessation interventions for those seeking treatment for alcohol and substance use disorders.

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Keywords

Alcohol use disorders; cigarette smoking; neurocognition; alcohol dependence; age

INTRODUCTION

Numerous studies have shown that those seeking treatment for an alcohol use disorder (i.e., alcohol abuse or dependence) perform more poorly than healthy comparison participants on multiple neurocognitive domains of function during the early phase of abstinence from alcohol (i.e., approximately 1 – 3 months) [see (Durazzo and Meyerhoff, 2007; Oscar-Berman, 2000; Stavro et al., 2012) for review]. However, it is estimated that only approximately 55% of those with an alcohol use disorders manifest measurable neurocognitive *impairment* during early abstinence, and the clinical severity of the deficits are typically in the mild-to-moderate range [see (Rourke and Grant, 2009) for review]. Therefore, it is clear there are multiple factors that influence the type and magnitude of neurocognitive abnormalities demonstrated during early abstinence by those seeking treatment for alcohol use disorders. Chronic cigarette smoking (Durazzo et al., 2010a; Durazzo et al., 2006; Durazzo et al., 2008b; Friend et al., 2005; Glass et al., 2006; Glass et al., 2009; Rosenbloom et al., 2005), increasing age [see (Nixon, 1998; Oscar-Berman, 2000) for review], and concurrent illicit substance misuse (Beatty et al., 1997; Bolla et al., 2000; Nixon et al., 1998) are factors prominently associated with adverse affects on multiple aspects of neurocognition in treatment-seeking individuals during early abstinence.

Several cross-sectional studies have reported that in adult non-clinical cohorts (i.e., no history of biomedical, psychiatric or alcohol/substance use disorders), the performance of former-smokers was intermediate to active-smokers and never-smokers on measures of executive functions, general intelligence, learning and memory, processing speed, and working memory [see (Durazzo et al., 2010b) for review]. In treatment-seeking alcohol dependent individuals (ALC), we observed that former-smokers (fsALC) performed worse than never-smokers (nvsALC) on a measure of auditory-verbal memory at 1-week and 1-month of abstinence (Pennington et al., 2013). However, in that longitudinal study, comparisons were restricted to nvsALC and fsALC, and the brief battery was limited to measures of learning, memory and basic processing speed. Therefore, it is unclear if there are significant differences between nvsALC, fsALC and active-smokers (asALC) at 1-month of abstinence on other major neurocognitive and motor functions (e.g., executive functions, general intelligence, fine motor skills). Importantly, it is also unknown if there is a differential effect of age on neurocognitive abilities and fine motor skills in nvsALC, fsALC and asALC during early abstinence relative to healthy, non-substance abusing controls. Given any neurocognitive impairment in older age is related to significantly higher risk for dementia (DeCarli, 2003) and chronic cigarette smoking during midlife is strongly associated with significantly increased risk for Alzheimer's disease (Rusanen et al., 2010), it is critical to determine if chronic smoking is related to increased age-related effects on neurocognition in alcohol use disorders. Accordingly, this cross-sectional study compared the performances of never-smoking, non-substance-abusing, healthy comparison participants (nvsCOM) and treatment-seeking nvsALC, fsALC, and asALC with approximately 1-month of abstinence from alcohol on a comprehensive neurocognitive battery. The analyses also focused on testing for greater age-related effects on neurocognition across the age range in nvsALC, fsALC and asALC relative to nvsCOM. We predicted that: 1) groups will be ranked with respect to the level of age-related effects on neurocognitive domains of function as follows: asALC > fsALC > nvsALC > nvsCOM (i.e., asALC manifest the greatest decrease in neurocognitive performance with increasing age compared to nvsCOM); 2) pairwise comparisons of groups across domains will show the following ranking of

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performance: nvsCOM > nvsALC > fsALC > asALC (i.e., nvsCOM show the best performance and asALC demonstrate the poorest performance).

METHODS

Participants

ALC participants (n = 119) in this cross-sectional study were recruited from the VA Medical Center Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program outpatient clinics in San Francisco, CA. All ALC met DSM-IV criteria for alcohol dependence (95% with physiological dependence). ALC were cross-sectionally assessed after 33 ± 8 days of monitored abstinence and stratified according to smoking status: nvsALC (n = 30; 4 females), fsALC (n = 21; 4 females), and asALC (n = 68; 2 females). nvsALC never smoked or smoked < 50 cigarettes during lifetime, with no smoking within 30 years of study. fsALC smoked for 15 ± 12 years and were abstinent from cigarettes for 13 ± 10 years at the time of study. All asALC were actively smoking at the time of assessment and reported no significant fluctuations in their cigarette consumption over the 2-years prior to study. The asALC cohort smoked 19 ± 9 cigarettes/day, over 27 ± 12 years (28 ± 18 pack years) and demonstrated a moderate to high level of nicotine dependence (Fagerstrom Test for Nicotine Dependence = 5.3 ± 2.0). Most ALC in this study participated in our previous research (Durazzo et al., 2010a; Durazzo et al., 2008b). nvsCOM (n = 39; 6 females) were recruited from the local community, and never smoked or smoked less than 50 cigarettes during lifetime, with no smoking within 30 years of study. nvsCOM were fluent in English and screened for history of any DSM-IV Axis I disorder or biomedical conditions that may have adversely affected neurocognition. All participants were between the ages of 26 and 71 at the time of study and provided written informed consent prior to study according to the Declaration of Helsinki. The informed consent document and study procedures were approved by the University of California San Francisco and the San Francisco VA Medical Center. Demographics, indices of alcohol consumption, smoking severity, depressive and anxiety symptomatology and frequency of medical, psychiatric and substance use comorbidities for groups are given in Table 1.

Primary inclusion criteria for ALC were current DSM-IV diagnosis of alcohol dependence or abuse, fluency in English, consumption of greater than 150 alcoholic drinks-per-month (one alcoholic drink equivalent = 13.6 grams pure ethanol) for at least 8 years prior to enrollment for men, and consumption of greater than 80 drinks-per-month for at least 8 years prior to enrollment for women. Exclusion criteria are fully detailed in our previous work (Durazzo et al., 2004). In summary, no ALC participant had a history of neurologic, general medical or psychiatric conditions known or suspected to influence neurocognition. The following comorbidities were permitted in ALC due to their high prevalence in alcohol use disorders (Gilman and Abraham, 2001; Stinson et al., 2005): hepatitis C, type-2 diabetes, hypertension, unipolar mood disorders (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 were included, given the high prevalence of comorbid substance abuse in alcohol use disorders (Hasin et al., 2007; Stinson et al., 2005).

Medical, Psychiatric, Substance, and Drinking History Assessment

Medical history for ALC was obtained from self-report and confirmed via available medical records. ALC completed the Structured Clinical Interview (SCID) for DSM-IV Axis I disorders, Patient Edition, Version 2.0. nvsCOM were screened for exclusionary conditions with an in-house instrument that incorporated elements of the SCID-screen and an in-house interview that screened for current/past history of DSM-IV Axis I disorders and medical

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conditions know or suspected to influence neurobiology or neurocognition. All participants completed standardized questionnaires assessing lifetime alcohol consumption (Lifetime Drinking History; LDH) and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use). From the LDH we derived average number of alcohol-containing drinks-per-month over 1-year prior to enrollment, average number of drinks-per-month over lifetime, and number of months-of-heavy drinking (i.e., total number of months over lifetime of consuming >100 drinks/month). All participants completed measures of depressive (Beck Depression Inventory; BDI) and anxiety symptomatology (State-Trait Anxiety Inventory, form Y-2, STAI), and nicotine dependence [Fagerstrom Tolerance Test for Nicotine Dependency (FTND)]. The total number of cigarettes currently smoked per day, number of years of smoking at the current level and over lifetime were also recorded and pack years [i.e., (number of cigarettes per day/20) × lifetime number of years of smoking] were calculated for asALC. See (Durazzo et al., 2010a) for references corresponding to the above measures.

Neuropsychological Assessment

Participants completed a comprehensive battery, which evaluated the adverse consequences of alcohol dependence (Rourke and Grant, 2009) and chronic cigarette smoking (Durazzo et al., 2007a; Swan and Lessov-Schlaggar, 2007) on neurocognition. Smoking ALC were allowed to smoke *ad libitum* before and during neurocognitive testing to reduce the potential confound of nicotine withdrawal [for review see (Sacco et al., 2004)]. Approximately, 33% of asALC took one smoke break during testing and all smoked one cigarette.

The neurocognitive domains evaluated and the constituent measures were as follows [See (Durazzo et al., 2010a) for references corresponding to the above measures]: Executive functions: Short Categories Test, color-word portion of the Stroop Test, Trail Making Test part B, Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Similarities, Wisconsin Card Sorting Test-64: Computer Version 2-Research Edition non-perseverative errors, perseverative errors, and perseverative responses General intelligence: Ward-7 Full Scale IQ (based on WAIS-III Arithmetic, Block Design, Digit Span, Digit Symbol, Information, Picture Completion, and Similarities subtests). Learning and memory: *Auditory-verbal*: California Verbal Learning Test-II, Immediate Recall trials 1-5 (learning), Short and Long Delay Free Recall (memory). *Visuospatial*: Brief Visuospatial Memory Test-Revised, Total Recall (learning) and Delayed Recall (memory). Processing speed: WAIS-III Digit Symbol, Stroop Color & Word, WAIS-III Symbol Search, Trail Making Test-A. Visuospatial functions: WAIS-III Block Design; Luria-Nebraska Item 99. 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, and was calculated by averaging the individual z-scores of those measures (see below). Timed tests included the Luria-Nebraska Item 99, 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 previously described by Glen and Parsons (Glenn and Parsons, 1992) and Nixon and colleagues (Nixon et al., 1998; Nixon et al., 1995). Premorbid verbal intelligence was estimated with the American National Adult Reading Test.

Raw score conversion to standardized scores—Raw scores for each measure were converted to z-scores to form the domains described above. Domain scores with multiple measures represent the average of the individual z-scores of the constituent measures of the domain. A global neurocognitive functioning score was calculated from the arithmetic mean of z-scores for all of the individual domains (excluding fine motor skills). Two methods

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were used to convert raw scores for the individual measures to z-scores to form domains for all groups: 1) based on the performance of nvsCOM (n = 39); 2) based on 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), age and education (WCST-64), or age, education and sex [Trails A and B via Heaton Compendium Norms (Heaton et al., 1991)].

Data Analyses

Analysis 1: *Primary analyses*—These analyses tested our predicted ordered magnitude of age-related effects on neurocognitive function across study groups (i.e., asALC > fsALC > nvsALC > nvsCOM). Greater age-related effects on neurocognition in each of the ALC groups relative to nvsCOM would be reflected in a significant group × age interaction, where the slope (i.e., change in neurocognitive performance per unit change in age) for the ALC cohorts were steeper than for nvsCOM. For Analysis 1, the domain score dependent measures represent the z-scores formed from the standardization to nvsCOM. The linear effects of group, age and AMNART, and the group × age interaction were modeled. Linear/main and interaction effects were considered statistically significant at $p < .05$. First, an omnibus MANCOVA was conducted to test for interaction effects [4 group (nvsCOM, nvsALC, fsALC, asALC) × age]. However, irrespective of the outcome of the omnibus MANCOVA, follow-up MANCOVAs were conducted on specific group pairings (e.g., nvsCOM vs. asALC, nvsALC vs. fsALC) to fully evaluate our *a priori* age-effects hypothesis.

Covariates: The AMNART (estimated premorbid verbal IQ) was used as a covariate as it has been shown to be a robust predictor of multiple neurocognitive domains in those with alcohol use disorders (Durazzo et al., 2010a; Durazzo et al., 2008b), and in chronically smoking controls (Durazzo et al., 2012b); AMNART also accounted for neurocognitive differences in comparisons between controls and those treatment-seeking for an alcohol use disorder (Sullivan et al., 2000). Although education has been reported to be robustly associated with neurocognition (e.g., Heaton et al., 1991), it was not a significant predictor of neurocognition when the AMNART was concurrently used as a covariate in our previous work (Durazzo et al., 2008, 2010a); therefore education was not included in the primary analyses and considered in secondary analyses (see below). Separate univariate analyses of covariance (ANCOVA) were conducted for global neurocognition domain and fine motor skills, with AMNART as a covariate. Since global neurocognition was formed from the average of all domains, it was artificially related to all individual domains, and may bias the omnibus statistics of a multivariate analysis containing the 10 individual domains. The fine motor skill domain was analyzed separately with ANCOVA because it is not a neurocognitive measure.

Secondary analyses for Analysis 1: Comparisons between nvsALC, fsALC and asALC were conducted separately using alcohol consumption variables (groups were significantly different on lifetime average drinks/month), education, as well as comorbid substance abuse, psychiatric, and medical disorders as covariates to determine if these variables predicted neurocognition in ALC. These additional variables were entered individually as covariates in models that also contained AMNART, age, study group and the study group × age interaction as predictors; this served to maintain a greater than 10:1 participant-to-predictor ratio in order to minimize the risk of model over-parameterization (Babyak, 2004)

Analysis 2: *Primary analyses*—MANCOVA, with AMNART as a covariate, was used to test our prediction of ordered cross-sectional performance of groups across neurocognitive domains (i.e., nvsCOM > nvsALC > fsALC > asALC). Significant

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univariate linear effects for group ($p < .05$) were followed up with pairwise t-tests. In these analyses, domain z-scores formed from standardization to the demographically corrected normative data were employed as dependent measures. The use of the domains standardized to the appropriate normative data allowed for the mean performances of study groups to be evaluated in terms of clinically relevant functional ranges of ability (e.g., average, below average, mildly impaired, etc) (Heaton et al., 1991; Lezak et al., 2004). As for Analysis 1, separate ANCOVAs were conducted for global neurocognition and fine motor skills.

Secondary analyses for Analysis 2: Significant pairwise differences observed in comparisons between the ALC cohorts were reanalyzed using the variables described in secondary analyses for Analysis 1.*Correction for multiple comparisons in Analysis 2:* Although we made *a priori* predictions, in follow-up pairwise comparisons among groups, we chose the conservative approach of using two-tailed t-tests and employed correction for multiple tests ($p = .05$) for these pairwise t-tests in Analysis 2 were corrected for multiple comparisons using a modified Bonferroni procedure [see (Sankoh et al., 1997)]. This procedure adjusted alpha level accounting for the number of neurocognitive domains (i.e. 10) in the MANCOVA and the average inter-correlation of the normative age-corrected domain scores for all groups combined ($r = 0.57$); the resulting adjusted alpha level from the modified Bonferroni procedure was $p \leq 0.019$; this corrected p-value was also applied to the pairwise t-tests for the global neurocognition and fine motor skills domains.

Analysis 3: Associations between Neurocognitive Domains and Smoking Measures in asALC and fsALC—In asALC, associations among domain scores and measures of smoking severity (lifetime years of smoking, pack-years, FTND score) were examined with multiple linear regression (semi-partial coefficients reported) controlling for lifetime average drinks-per-month. In fsALC, length of smoking cessation was related to neurocognitive domains (z-scores based on the normative data) with multiple linear regression controlling for lifetime average drinks-per-month. A p-value of $\leq .05$ was considered statistically significant and domain z-scores based on the normative data were used in all analyses.

RESULTS

Participant Characteristics

See Table 1 for group comparisons on demographic, self-report mood and anxiety symptomatology questionnaires, alcohol consumption variables, and frequency of comorbid conditions.

Analysis 1: Age-related effects

The ANCOVAs for global neurocognition [$F (3, 149) = 6.10$, $p = .03$] and fine motor skils [$F (3, 143) = 6.14$, $p = .03$] yielded significant group × age interactions for both domains. The omnibus MANCOVA for the 10 domains showed main effects for age [$F (10, 140) = 7.27$, $p < .001$] and AMNART [$F (10, 140) = 21.53$, $p < .001$]. In the ANCOVAs and MANCOVA, increasing age was associated with poorer performance, and increasing AMNART score with better performance, across all domains. The omnibus group × age interaction was not significant in the MANCOVA [$F (30, 426) = 1.21$, $p = .29$]; however, in planned comparisons, asALC demonstrated significantly steeper slopes than nvsCOM, indicating greater age-related effects compared to nvsCOM on the following domains: visuospatial learning ($p = .035$), auditory-verbal memory ($p = .049$), cognitive efficiency ($p = .029$), executive functions ($p = .025$), processing speed ($p = .043$), global neurocognition ($p = .014$), and fine motor skills ($p = .014$), with a trend for visuospatial memory ($p = .072$). nvsALC and fsALC and nvsCOM showed equivalent age-related effects across all domains

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(i.e., statistically parallel slopes). nvsALC, fsALC, and asALC all showed commensurate age-related effects across domains except for visuospatial functions, where asALC showed steeper age-related effects than nvsALC ($p = .022$). In comparisons among nvsALC, fsALC, and asALC, education, alcohol consumption variables (1-year and lifetime average drinks/month, months of heavy drinking), medical, psychiatric, and substance abuse comorbidities were not significant predictors of any domain. See Figure 1 for the general pattern displayed by groups across domains. See Table 2 for slopes of age-related effects on domain performance in nvsALC, fsALC, and asALC relative to nvsCOM.

Analysis 2: Comparisons of Group Performance on Domains (see Table 2)

ANCOVA for global neurocognition yielded significant main effects for group [$F (3, 153) = 10.49$, $p < .001$] and AMNART [$F (1, 153) = 52.85$, $p < .001$]. Similarly, ANCOVA for fine motor skills showed main effects for group [$F (3, 143) = 4.66$, $p = .003$] and AMNART [$F (1, 143) = 4.69$, $p = .03$]. The omnibus MANCOVA for the 10 domains indicated significant main effects for group [$F (30, 438) = 2.40$, $p < .001$] and AMNART [$F (10, 140) = 20.16$, $p < .001$]. Higher AMNART scores were related to better performance across all domains. In pairwise comparisons ($p \leq .019$ considered statistically significant), asALC were inferior to nvsCOM on all domains (all $p \leq .008$) except working memory. fsALC performed worse than nvsCOM on all domains (all $p \leq .009$) except executive functions and processing speed ($p = .05$). Moderate-to-strong effects sizes were apparent for domains where asALC and fsALC performed significantly worse than nvsCOM. There were no significant differences between nvsCOM and nvsALC on any domain (all $p > .32$, with weak effect sizes). asALC were inferior to nvsALC on auditory-verbal and visuospatial learning, auditory-verbal memory, cognitive efficiency, general intelligence, processing speed, and global neurocognition (all $p \leq .015$). fsALC performed worse than nvsALC on auditory-verbal and visuospatial learning, auditory-verbal and visuospatial memory, general intelligence, global neurocognition (all $p \leq .014$), and tended to perform worse on working memory ($p = .05$). Moderate-to-strong effects sizes were apparent for domains where asALC and fsALC performed worse than nvsALC. asALC and fsALC were not different on any domain. In comparisons among nvsALC, fsALC, and asALC, alcohol consumption variables, education, medical, psychiatric, and substance abuse comorbidities were not significant predictors of any domain.

Clinical Impairment across Groups—There is no universally agreed-upon cutoff for where clinically significant impairment *begins*, but 1.5 standard deviations (STD) below the mean (approximately the 7th percentile) is typically designated as the lower limit for the mildly impaired range of functioning [see (Lezak et al., 2004)]. From Table 2, it is apparent that the mean performance across domains for *all groups* fell in the low-average to high-average range (i.e., ± 1 STD of the mean). Using ≥ 1.5 STD below the mean as a cutoff for clinically significant impairment, in the combined ALC group (i.e., nvsALC, fsALC and asALC), approximately 25% of participants were showed a clinical level of impairment on the domains of fine motor skills, visuospatial learning, and visuospatial memory. nvsALC had the lowest percentage of participants at or below the cutoff. Very few participants (1 – 6 %) of the total ALC group were ≥ 1.5 STD on other domains. Even among nvsCOM, 13% and 8% were ≥ 1.5 STD below the mean on visuospatial learning and visuospatial memory, respectively.

Analysis 3: Associations between Neurocognitive Domains and Smoking Measures in asALC and fsALC

For asALC, greater lifetime years of smoking showed overall moderate to strong inverse relationships with performance on multiple neurocognitive domains after controlling for lifetime average drinks/month (see Table 3). There were no significant associations between

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FTND score (i.e., level of nicotine dependence), cigarettes smoked/day or pack-years, and any neurocognitive domain after controlling for lifetime average drinks/month. After controlling for lifetime years of smoking, higher lifetime average drinks/month was significantly, but weakly associated with poorer working memory ($r = -0.26$, $p = .04$). In fsALC, duration of smoking cessation was not significantly associated with any neurocognitive domain.

The findings reported for Analyses 1, 2, and 3 were essentially unchanged when female participants were excluded from the analyses.

DISCUSSION

The primary findings from this cross-sectional study of 119 alcohol dependent, primarily Veteran males with approximately 1-month of abstinence from alcohol were as follows: 1) asALC showed greater age-related effects over their age range than nvsCOM on the domains of visuospatial learning, auditory-verbal memory, cognitive efficiency, executive functions, processing speed and fine motor skills; 2) Comparisons of group performance across domains indicated nvsCOM and nvsALC were not significantly different on any domain, while fsALC and asALC performed more poorly than both nvsCOM and nvsALC on multiple domains; 3) The steeper age-related effects in asALC, compared to nvsCOM, were unchanged after controlling for estimated premorbid verbal IQ (AMNART). Similarly, the significantly poorer performance of fsALC and sALC compared to nvsALC on multiple domains was not attributable to AMNART, education, or alcohol consumption; 4) Mean scores for the nvsALC, fsALC and asALC generally fell in the low-average to high-average range of functioning for all domains. A clinically significant level of impairment (i.e., ≥1.5 STD below the mean) was apparent in only 25% of ALC participants on visuospatial learning, visuospatial memory and fine motor skills domains; 5) Measures of alcohol consumption, were weakly associated with performance across domains in the ALC groups. In asALC, greater number of lifetime years of smoking was significantly related to poorer performance in multiple domains, after controlling for alcohol consumption.

The significantly steeper age-related effects in asALC relative to nvsCOM on visuospatial learning, auditory-verbal memory, cognitive efficiency, executive functions, processing speed, and fine motor skills indicate greater-than-normal deterioration of these abilities in asALC with advancing age. It is notable that asALC demonstrated greater age-related effects in processing speed, given research on normal aging suggests decreasing information processing speed is a major contributor to diminishing performance on measures of learning, memory, and visuospatial abilities with increasing age (Finkel et al., 2007; Salthouse, 2000). The overall age-related findings suggest that the *combination* of active chronic smoking and alcohol dependence in this treatment-seeking ALC cohort was associated with greater-than-normal deterioration in performance with increasing age on multiple domains.

Group comparisons on domains calculated from age- or age- and education-corrected norms showed no significant differences between nvsCOM and nvsALC on any domain, while fsALC and asALC performed worse than both of these groups on many of the same domains. Moderate-to-strong effect sizes were apparent for the inferior performance of fsALC and asALC relative to nvsCOM and nvsALC. These findings indicated *combined* active chronic smoking (i.e., asALC) and previous history of chronic smoking (i.e., fsALC) with alcohol dependence, were associated with inferior performance relative to nvsCOM and nvsALC on multiple domains. Notably, nvsALC showed no differences from nvsCOM on any domain. The overall results for group comparisons on domains calculated from age- or age- and education-corrected norms showed alcohol dependence alone (i.e., nvsALC) was not associated with adverse effects on neurocognition in this 1-month-abstinent ALC cohort.

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Active chronic smoking in this alcohol dependent cohort was associated with greater age-related neurocognitive effects relative to nvsCOM and poorer performance on multiple domains relative to nvsALC and nvsCOM. However, it is of high clinical relevance that only approximately 25% of all ALC participants demonstrated a clinically significant level of functional *impairment*, which was confined to the domains of visuospatial learning, visuospatial memory, and fine motor skills. A trivial number of all ALC participants (1 to 6%) performed in the impaired range on other domains, despite consuming approximately 200 ± 100 drinks/month over lifetime. Additionally, the mean performance for nvsALC, fsALC and asALC generally fell in the low-average to high-average range of functioning across domains. It is also noteworthy that 13% and 8% of nvsCOM performed in the impaired range on visuospatial learning and visuospatial memory, respectively.

Measures of alcohol consumption (i.e., 1-year average drinks/month, lifetime average drinks/month, and months-of-heavy-drinking) were not significant predictors of any domain in age-related analyses or pairwise comparisons among nvsALC, fsALC, and asALC. Additionally, higher lifetime average drinks/month in ALC was weakly related to poorer performance in working memory in bivariate correlations. This was consistent with our earlier studies (Durazzo et al., 2012a; Durazzo et al., 2010a; Durazzo et al., 2007b; Durazzo et al., 2008b), and other research that found measures of alcohol consumption quantity/frequency were weakly or not significantly related to neurocognition (Beatty et al., 1995; Beatty et al., 2000; Eckardt et al., 1998; Horner et al., 1999; Schafer et al., 1991; Sullivan et al., 2000). Conversely, in asALC, a greater number of lifetime years of smoking (controlling for lifetime average drinks/month) were related to poorer performance on multiple domains, which is congruent with our previous work with this cohort (Durazzo et al., 2012a; Durazzo et al., 2010a; Durazzo et al., 2007b; Durazzo et al., 2008b).

Clinical and Treatment Implications

The overall low level of clinical impairment in this 1-month-abstinent ALC sample was encouraging, as better performance on select domains of functioning during early abstinence was related to better treatment outcome in several studies (Bates et al., 2006; Cunha and Novaes, 2004; Durazzo et al., 2008a; Tapert et al., 2004). Our findings highlight the clinical salience of also providing scores in research reports, when possible, that are based on the appropriate normative data in order to determine the participants' functional level of ability. The ALC sample overall demonstrated a low frequency of clinical level of impairment as previously reported [see Rourke and Grant (2009) for review]. However, asALC demonstrated significantly poorer performance with increasing age on multiple domains compared to nvsCOM. Also, both fsALC and asALC performed significantly worse than both nvsCOM and nvsALC on most of the domains assessed in this study. These findings may help guide the development of targeted cognitive remediation techniques to maximize neurocognitive recovery with abstinence from alcohol for these subgroups of alcohol dependent treatment seekers (Fadardi and Cox, 2009). Cigarette smoking is a modifiable health risk that is directly associated with at least 440,000 annual deaths in the United States, with ever increasing mortality and morbidity among those with alcohol/substance use and other neuropsychiatric conditions [see (Durazzo and Meyerhoff, 2007) for review]. Additionally, chronic smoking during midlife is associated with significantly increased risk of Alzheimer's disease (Rusanen et al., 2010). The aforementioned mortality and morbidity data, combined with the findings for asALC and fsALC in this study, and those from our previous longitudinal neurocognitive and neuroimaging research (Durazzo et al., 2007b; Gazdzinski et al., 2008; Mon et al., 2009: Pennington et al., 2013) strongly support smoking cessation interventions for those seeking treatment for alcohol and substance use disorders (Kalman et al., 2010).

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This cross-sectional study 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 alcohol use disorders [(Durazzo et al., 2010a) and references therein]. Results may have also been influenced by factors not assessed in this study, such as subclinical biomedical conditions (e.g., hypertension, atherosclerosis, COPD), as well as diet, exercise and exposure to environmental cigarette smoke or genetic factors [see (Durazzo et al., 2012a)]. No cogent statements can be made about the potential factors contributing to the performance of fsALC given the cross-sectional design of this study. Longitudinal studies, that employ pre-and-post measurement of the effects of smoking cessation, are required to delineate the neurocognitive consequences of former chronic smoking in alcohol use disorders. Finally, the majority of participants were males from the San Francisco VA Medical Center, which did not allow for the examination of the potential effects of sex on neurocognition.

In conclusion, the overall findings indicated that smoking status (i.e., never, former and active) may contribute to the substantial heterogeneity in neurocognitive dysfunction demonstrated by treatment seeking alcohol dependent individuals during early sobriety. We also observed an overall low frequency of clinically significant impairment, and weak associations of alcohol consumption variables and common comorbidities with neurocognition in these 1-month-abstinent ALC. Longitudinal research addressing the potential effects of never, former and active smoking status may promote a better understanding the factors affecting neurocognitive recovery during extended abstinence in those with alcohol use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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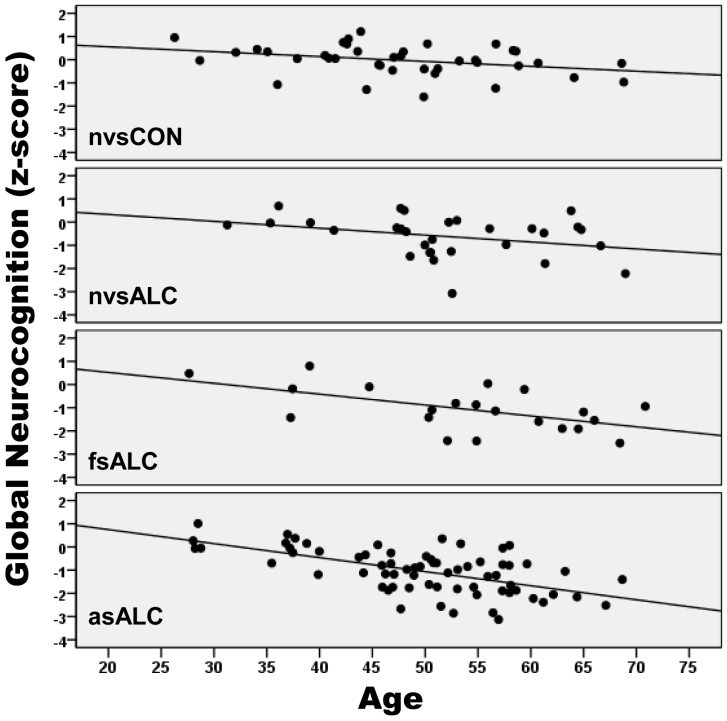

Figure 1.

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Table 1

Group demographics and clinical variables

Variable	nvsCOM n = 39	nvsALC n = 30	fsALC n = 21	asALC n = 68	Group comparison
Age [years]	48 (8) min = 26 max = 69	52 (10) min = 31 max = 69	54 (12) min = 28 max = 71	50 (9) min = 28 max = 69	fsALC > nvsCOM (p = .03)
% Male	85	87	81	97	asALC > fsALC (p =.05)^
% Caucasian	77	73	86	71	NS^
Education [years]	15.7 (1.9)	14.4 (2.2)	14.5 (2.0)	13.4 (1.9)	nvsCOM > nvsALC = fsALC = asALC (p < .02) nvsALC > asALC (p = .03)
AMNART	120 (7)	113 (10)	116 (7)	113 (9)	nvsCOM > nvsALC = asALC (p < .02)
Duration of Abstinence [days]	NA	33 (8)	34 (8)	32 (9)	NS
BDI	4 (2)	10 (2)	9 (2)	10 (2)	nvsALC, fsALC, asALC > nvsCOM (p < .01)
STAI Y-2	33 (2)	45 (2)	42 (2)	43 (2)	nvsALC, fsALC, asALC > nvsCOM (p < .01)
1-yr average drinks/month	15 (16)	366 (223)	253 (154)	445 (247)	nvsALC, fsALC, asALC > nvsCOM (p < .01) nvsALC & asALC > fsALC (p < .05)
Lifetime average drinks/month	17 (14)	185 (122)	130 (81)	260 (113)	nvsALC, fsALC, asALC > nvsCOM (p < .01) nvsALC & asALC > fsALC (p < .05) asALC > nvsALC (p < .01)
Months of heavy drinking	NA	232 (124)	207 (124)	281 (115)	NS
% with any psychiatric comorbidity % with history of unipolar mood disorder % history of anxiety disorder	NA	47 47 0	48 48 0	31 23 8	NS^
% with any substance comorbidity % with history of psychostimulant abuse or dependence % with history of cannabis abuse or dependence % with history of other substance use or dependence	NA	23 20 3 0	21 14 7 0	27 15 9 3	NS^
% with any medical comorbidity % with hypertension % with hepatitis C % with other medical	NA	43 26 13 4	67 33 0 34	52 21 16 15	NS^

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Variable	nvsCOM n = 39	nvsALC n = 30	fsALC n = 21	asALC n = 68	Group comparison
conditions					

mean (standard deviation)

^ Fishers Exact Test;

Mann-Whitney U Test; 1-yr average = number of alcoholic drinks per month over 1-year prior to study; 3 yr average = number of alcoholic drinks per month over 3-years prior to study; Lifetime average = number of alcoholic drinks per month over lifetime; AMNART = American National Adult Reading Test; asALC: actively-smoking alcohol dependent participants; BDI = Beck Depression Inventory; fsALC: former-smoking alcohol dependent participants; Months heavy drinking = number of months > 100 alcoholic drinks consumed/month; NA = not applicable, NS = no significant group differences; nvsALC: never-smoking alcohol dependent participants; nvsCOM: never-smoking healthy comparison participants; STAI Y-2 = State -trait Anxiety Inventory – State.

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Table 2

Parameter estimates for age-related effects in neurocognitive domains for the ALC cohorts

Domain	nvsALC n = 30 slope (SE); p-value	fsALC n = 21 slope (SE); p-value	asALC n = 68 slope (SE); p-value
Auditory-verbal Learning	0.013 (0.031); 0.68	−0.013 (0.031); 0.38	−0.024 (0.025); 0.34
Auditory-verbal Memory	−0.018 (0.027); 0.50	−0.034 (0.027); 0.21	−0.041 (0.022); 0.049
Cognitive efficiency	−0.020 (0.016); 0.22	−0.022 (0.016); 0.21	−0.030 (0.013); 0.029
Executive functions	−0.016 (0.024); 0.22	−0.018 (0.024); 0.47	−0.043 (0.020); 0.025
Fine motor skills	−0.026 (0.036); 0.34	−0.017 (0.035); 0.64	−0.066 (0.030); 0.014
General intelligence	−0.010 (0.013); 0.79	−0.008 (0.014); 0.72	−0.015 (0.010); 0.15
Processing speed	−0.021 (0.017); 0.24	−0.023 (0.017); 0.20	−0.030 (0.014); 0.043
Visuospatial learning	−0.021 (0.028); 0.46	−0.016 (0.028); 0.58	−0.049 (0.023); 0.035
Visuospatial memory	−0.014 (0.032); 0.65	−0.016 (0.032); 0.62	−0.047 (0.026); 0.072
Visuospatial functions	−0.015 (0.032); 0.38	−0.001 (0.018); 0.98	−0.023 (0.015); 0.12
Working memory	−0.012 (0.020); 0.60	−0.005 (0.020); 0.80	−0.009 (0.016); 0.57
Global neurocognition	−0.011 (0.016); 0.47	−0.016 (0.016); 0.32	−0.031 (0.013); 0.014

Note: asALC: actively-smoking alcohol dependent participants; fsALC: former-smoking alcohol dependent participants; nvsALC: never-smoking alcohol dependent participants; SE: standard error of the estimate.

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Alcohol Clin Exp Res. Author manuscript; available in PMC 2014 October 01.

Table 3

Group domain z-scores based on normative data

Cognitive Measure and % ≥ 1.5 STD below mean	nvsCOM n = 39	nvsALC n = 30	fsALC n = 21	asALC n = 68	All ALC n = 119	Effect Size (Cohen's *d*)					
						nvsCOM vs. nvsALC	nvsCOM vs. fsALC	nvsCOM vs. asALC	nvsALC vs. fsALC	nvsALC vs. asALC	fsALC vs. asALC
Auditory-verbal learning	1.01 (0.82) 0%	0.99 (0.81) 0%	0.27 (0.88) 0%	0.20 (0.88) 3%	0.49 (0.85) < 1%	0.03	0.87#	0.94#	0.85#	0.92#	0.07
Auditory-verbal memory	0.72 (0.93) 0%	0.71 (0.90) 3%	0.08 (0.89) 10%	0.02 (0.91) 6%	0.27 (0.86) 6%	0.01	0.71#	0.76#	0.71#	0.76#	0.06
Cognitive efficiency	0.14 (0.53) 0%	0.08 (0.51) 0%	−0.23 (0.50) 0%	−0.24 (0.51) 3%	−0.13 (0.48) < 1%	0.12	0.71#	0.73#	0.60	0.62#	0.02
Executive functions	0.13 (0.62) 0%	−0.06 (0.59) 3%	−0.19 (0.59) 0%	−0.29 (0.54) 4%	−0.18 (0.52) 3%	0.31	0.53	0.69#	0.22	0.39	0.17
Fine motor skills	−0.10 (1.04) 3%	−0.49 (1.01) 24%	−0.88 (1.02) 30%	−0.82 (1.04) 27%	−0.73 (1.01) 26%	0.38	0.77#	0.70#	0.39	0.33	0.06
General intelligence	0.69 (0.58) 0%	0.73 (0.60) 3%	0.09 (0.60) 0%	0.27 (0.57) 4%	0.36 (0.55) 3%	0.08	1.05#	0.73#	1.16#	0.83#	0.32
Processing speed	0.07 (0.56) 0%	0.12 (0.54) 0%	−0.16 (0.54) 0%	−0.29 (0.55) 2%	−0.25 (0.53) < 1%	0.07	0.42	0.65#	0.50	0.74#	0.24
Visuospatial learning	−0.13 (1.07) 13%	−0.22 (1.04) 10%	−0.89 (1.03) 29%	−0.71 (1.04) 29%	−0.61 (1.02) 24%	0.09	0.73#	0.55#	0.64#	0.47#	0.17
Visuospatial memory	0.12 (1.14) 8%	−0.17 (1.10) 23%	−0.99 (1.10) 33%	−0.56 (1.11) 28%	−0.25 (1.08) 28%	0.25	0.98#	0.60#	0.74#	0.35	0.39
Visuospatial functions	0.26 (0.79) 0%	−0.17 (0.77) 7%	−0.40 (0.76) 5%	−0.19 (0.76) 4%	−0.13 (0.74) 5%	0.54	0.85#	0.65#	0.31	0.02	0.28
Working memory	0.36 (0.69) 0%	0.24 (0.66) 3%	−0.13 (0.66) 0%	0.17 (0.69) 7%	0.09 (0.65) 5%	0.17	0.72#	0.28	0.56	0.11	0.45
Global neurocognition	0.36 (0.55) 0%	0.22 (0.53) < 1%	−0.26 (0.56) 0%	−0.17 (0.69) 4%	−0.14 (0.61) 3%	0.21	1.11#	0.92#	0.92#	0.72#	0.19

Mean (standard deviation);

p ≤ .019 for pairwise t-tests (two-tailed); % ≥ 1.5 STD below mean: percent of participants scoring ≥ 1.5 standard deviations below the z-score mean; asALC: actively-smoking alcohol dependent participants; fsALC: former-smoking alcohol dependent participants; nvsALC: never-smoking alcohol dependent participants; nvsCOM: never-smoking healthy comparison participants.

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Table 4

Correlations (semi-partial coefficients) of Lifetime Number of Years of Smoking, and Lifetime Average Drinks per Month with Neurocognitive and Fine Motor skills Domains in asALC (n = 68).

Domain	Lifetime Number of Years of Smoking@	Lifetime Average Drinks per Month&
Auditory-verbal learning	−0.23	−0.09
Auditory-verbal memory	−0.26*	−0.10
Cognitive efficiency	−0.30*	−0.07
Executive functions	−0.31*	−0.14
Fine Motor skills	−0.14	−0.02
General intelligence	−0.28*	−0.23
Processing speed	−0.32*	−0.08
Visuospatial learning	−0.38*	0.05
Visuospatial memory	−0.34*	0.03
Visuospatial functions	−0.36*	−0.08
Working memory	−0.21	−0.26*

@Note: Controlled for Lifetime Average Drinks per Month;

&Controlled for Lifetime Number of Years of Smoking;

*p < .05; asALC: actively smoking alcohol dependent participants.