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Psychiatric, Demographic and Brain Morphological Predictors of Relapse after Treatment for an Alcohol Use Disorder

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Abstract

Background—Relapse in alcohol use disorders (AUD) is related to a complex interplay among multiple biological, psychiatric, psychological and psychosocial factors, which may change dynamically during and after treatment. At treatment entry for AUD, morphological abnormalities in anterior frontal regions and the insula have been observed in those who ultimately relapse following treatment. The goal of this study was to determine if measures anterior frontal and insula measures of regional brain thickness, surface area and volume *predict* post-treatment drinking status (i.e., relapser or abstainer) over an extended period after outpatient treatment for AUD, while concurrently considering common psychiatric, psychological and psychosocial factors previously associated with relapse.

Methods—Alcohol dependent individuals (n = 129) were followed for 18 months after treatment to determine post-treatment drinking status [Abstainers (n = 47) or Relapsers (n = 82)]. Brain morphometrics were derived from FreeSurfer. Receiver operator characteristic (ROC) curve analysis was used to identify the regional brain thickness, surface area and volume (all scaled to intracranial volume), demographic, psychiatric, other substance use (e.g., cigarette smoking) and alcohol consumption variables, obtained at entry into treatment, that best predicted post-treatment drinking status. Survival analyses determined variables that were related to duration of abstinence after treatment.

Results—ROC analyses indicated that mood disorders, education, and volumes of the right caudal ACC, right rostral ACC and total right frontal gray matter were significant predictors of post-treatment drinking status. Among Relapsers, survival analyses showed smokers and individuals with a comorbid medical condition relapsed earlier after treatment. Additionally, a greater frequency of smokers relapsed within 6 months of treatment.

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The Authors have no conflicts to declare.

Conclusions—Results reinforce that relapse in AUD is a function of multiple biological, psychiatric, psychological and psychosocial factors. Effective treatment of depressive disorders and cigarette smoking concurrent with AUD-focused interventions may promote better treatment outcomes.

Keywords

Relapse; alcohol use disorders; magnetic resonance imaging; mood disorders; cigarette smoking

INTRODUCTION

Many individuals with an alcohol use disorder (AUD) experience a chronically relapsing-remitting course over lifetime (Witkiewitz and Marlatt, 2007). Irrespective of the type of intervention employed, at least 60% of those treated for an AUD will relapse to a period of hazardous alcohol consumption, typically within 6 months of treatment (Meyerhoff and Durazzo, 2010, Witkiewitz, 2011, Kirshenbaum et al., 2009). Resumption of hazardous alcohol consumption levels within 6 months of treatment is associated with extended periods of relapse and clinically significant impairments of psychosocial functioning (e.g., unemployment, relationship/marital discord, legal entanglements) over the ensuing 1–3 years (Durazzo et al., 2008, Maisto et al., 2006, Maisto et al., 2007). Conversely, sustained abstinence during the first 6–12 months following treatment is related to significant neurobiological and neurocognitive recovery and adaptive psychosocial functioning (Maisto et al., 2006, Durazzo et al., 2015, Durazzo et al., 2014, Durazzo et al., 2008).

Various neuroimaging methods have been utilized to identify potential biomarkers of increased relapse risk after treatment for AUD with the aim to better understand neurobiological mechanisms of relapse (Seo and Sinha, 2015, Seo and Sinha, 2014, Meyerhoff et al., 2013, Meyerhoff and Durazzo, 2010). With respect to brain morphology, magnetic resonance imaging (MRI) studies reported that individuals who relapse after treatment, compared to those who maintain abstinence for at least 3 months, have thinner cortices as well as smaller surface areas and volumes in multiple brain regions at treatment entry; these differences were most consistently observed in anterior frontal regions (i.e., orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex) implicated in the development and persistence of alcohol and substance use disorders (Durazzo et al., 2011b, Rando et al., 2011, Seo et al., 2015, Beck et al., 2012, Cardenas et al., 2011). The morphology of the cerebral cortex demonstrates a modular/columnar cellular organization that is oriented perpendicular to the cortical surface in neocortical and several paralimbic regions (Innocenti and Vercelli, 2010). Cortical thickness is related to the number or density of cells in a column, while cortical surface area is reflects the number and/or width of columns (Rakic, 1988). Cortical thickness appears to be genetically and phenotypically distinct from cortical surface area [see (Durazzo et al., 2011a, Eyler et al., 2012) and references therein]. Therefore, comparisons between abstainers and relapsers on all three metrics may provide more specific information on the macrostructural measure that best identifies those at risk for relapse after treatment. In treatment-seeking AUD at 1 week of abstinence, we previously reported that those who were classified as relapsers within 1 year of treatment, compared to those who remained abstinent over 1 year, showed significantly

smaller regional brain volumes and surface areas, but not thinner cortex, predominantly in anterior frontal brain regions (Durazzo et al., 2011b). In that study, our primary outcome measure was mean differences between relapsers and abstainers in brain morphometrics at 1 week of abstinence. Such group differences would gain greater clinical relevance if they were predictive of drinking status (i.e., relapser or abstainer) over an extended period after treatment (Seo et al., 2015).

The chronic relapse-remit cycle in AUD is clearly related to a complex interplay among multiple biological, psychiatric, psychological and psychosocial factors (Meyerhoff and Durazzo, 2010, Witkiewitz and Marlatt, 2007). While magnetic resonance neuroimaging modalities (e.g., structural, perfusion, diffusion tensor imaging, resting and task-based BOLD) can provide valuable information on neurobiological correlates of relapse, co-occurring psychiatric conditions (e.g., mood disorders, other substance use disorders) in those seeking treatment for AUD are also robustly associated with increased risk for relapse after treatment (Durazzo et al., 2008, Meyerhoff et al., 2013, Seo and Sinha, 2014, Hobbs et al., 2011). Unipolar depressive disorders and chronic smoking are among the most prevalent co-occurring conditions in those with AUD (Durazzo and Meyerhoff, 2007, Moss et al., 2015, Grant et al., 2015), and individuals with a history of co-occurring AUD and depressive disorders show markedly greater risk of relapse following treatment [see (Durazzo et al., 2008, Hobbs et al., 2011, Suter et al., 2011) and references therein]. Additionally, those with remitted AUD, who are cigarette smokers, demonstrate significantly increased relapse risk (Satre et al., 2007, Weinberger et al., 2015), and smoking cessation is associated with decreased risk of meeting diagnostic criteria for an AUD in those with a history of AUD (Cavazos-Rehg et al., 2014).

The goal of this study was to expand upon our previous research (Durazzo et al., 2011b), with a significantly larger sample and longer follow-up period, to determine if anterior frontal and insula gray matter (GM) measures of thickness, surface area and volume at entry into treatment *predict* post-treatment drinking status (i.e., Relapser or Abstainer) over an extended period after outpatient treatment for AUD. Additionally, demographic, behavioral and psychiatric variables (e.g., education, alcohol consumption level, frequency of mood disorders) that were associated with relapse in previous reports from our group and others (Durazzo et al., 2008, Greenfield et al., 2003, Witkiewitz, 2011) were also concurrently examined as predictors to determine their association with post-treatment drinking status. Finally, in Relapsers, we determined the variables associated with duration of abstinence before relapse onset.

MATERIALS AND METHODS

Participants

Alcohol dependent individuals (n = 129) were recruited from the San Francisco VA Medical Center (SFVAMC) Substance Abuse Day Hospital and the San Francisco Kaiser Permanente Chemical Dependence Recovery outpatient treatment clinics. All AUD participants were actively in treatment at the time of study, and treatment duration typically ranged from 14–35 days [for additional information on the treatment program characteristics see (Durazzo et al., 2008)]. The predominantly male Veteran participants were between 28 and 71 years of

age and all met DSM-IV criteria for alcohol dependence. All participants in Durazzo et al., 2011b were included in the current study, but the present sample contains 54 new participants. All participants provided written informed consent prior to study. Study procedures were approved by the University of California San Francisco and the SFVAMC and were in accordance with the ethical standards of the Declaration of Helsinki.

Inclusion/exclusion criteria

Primary inclusion criteria for the alcohol dependent participants were fluency in English, DSM-IV diagnosis of alcohol dependence or abuse at baseline (all met criteria for alcohol dependence), consumption of greater than 150 standard alcohol-containing drinks (i.e., 13.6 grams of pure ethanol) per month for at least 8 years prior to enrollment for males, and greater than 80 drinks per month for at least 6 years prior to enrollment for females. See Table 1 for group demographic data. Exclusion criteria for alcohol dependent participants were history of the following: dependence on any substance other than alcohol or nicotine in the 5 years immediately prior to enrollment, any intravenous drug use in the 5 years prior to baseline study, opioid agonist/replacement therapy, intrinsic cerebral masses, HIV/AIDS, cerebrovascular accident, cerebral aneurysm, arteriovenous malformations, myocardial infarction, medically uncontrolled chronic hypertension (systolic > 180 and/or diastolic > 120 mmHg), type-I diabetes, chronic obstructive pulmonary disease, non-alcohol related seizures, significant exposure to established neurotoxins, demyelinating and neurodegenerative diseases, Wernicke-Korsakoff syndrome, delirium, penetrating head injury, and closed head injury resulting in loss of consciousness > 10 minutes. Psychiatric exclusion criteria were history of schizophrenia-spectrum disorders, bipolar disorder, cyclothymia, PTSD, obsessive-compulsive disorder and panic disorder. Hepatitis C, type-2 diabetes, hypertension, unipolar mood disorders (i.e., major depression, substance-induced mood disorder) were allowed, given their high prevalence in those with an AUD (Grant et al., 2015, Mertens et al., 2005). No participant who was seropositive for hepatitis C was taking interferon or other medications to manage active symptomatology. Participants were breathalyzed and urine-tested for illicit substances before assessment and no participant tested positive for substances at any assessment.

Clinical Measures

At baseline, participants completed the Clinical Interview for DSM-IV Axis I Disorders, Version 2.0 (SCID-I/P) and semi-structured interviews for lifetime alcohol consumption (Lifetime Drinking History) and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use). From the Lifetime Drinking History, average number of alcoholic drinks/month over 1 year prior to enrollment, months heavy drinking (cumulative number of months of consumption of ≥ 100 drinks/month), and average number of drinks/month over lifetime were calculated. All participants also completed standardized questionnaires assessing depressive (Beck Depression Inventory, BDI) and anxiety symptomatology (State-Trait Anxiety Inventory, Trait form Y-2, STAI), as well as nicotine dependence via the Fagerstrom Tolerance Test for Nicotine Dependence (FTND). See (Pennington et al., 2013) for corresponding references to the above measures.

Magnetic Resonance Acquisition and Processing

At baseline, a volumetric magnetization-prepared rapid gradient echo (MPRAGE) was acquired with TR/TE/TI = 9.7/4/300ms, 15° flip angle, 1×1 mm^2 in-plane resolution, and 1.5-mm-thick coronal partitions oriented perpendicular to the main long axes of bilateral hippocampi as seen on sagittal scouts. See Gazdzinski and colleagues (Gazdzinski et al., 2005) for detailed information on these 1.5T MR acquisition methods. The publically available FreeSurfer (v4.5) volumetric segmentation and cortical surface reconstruction methods were used to obtain regional measures of cortical volumes (mm^3), surface area (mm^2), and thickness (mm). Spatial normalization to the template cortical surface allowed automatic parcellation of the surface into 34 anatomical regions of interest per cortical hemisphere (Fischl et al., 2004). Average cortical thickness, surface area, and volume were obtained for all 34 bilateral cortical regions, but analyses were confined to anterior frontal regions and the insula (see Table 2). A bilateral frontal cortical gray (GM) composite region was formed for each morphological measure. All morphometrics for each participant were scaled to their individual intracranial volume (ICV). See Durazzo and colleagues (Durazzo et al., 2011b, Durazzo et al., 2011a) for FreeSurfer image processing details.

Baseline and Follow-up Assessments

Baseline Assessment

Participants completed a 1.5 T magnetic resonance imaging (MRI) study 16 ± 13 days (minimum = 1, maximum = 38) after last alcohol consumption, and clinical measures were typically obtained within two days of the baseline MRI study.

Follow-up Assessments

Participants were monitored up to 18 months following baseline, with up to three follow-up assessments. Follow-up 1 (in person, telephone and/or collateral source interview, and/or medical record review) took place approximately 6–8 months after baseline assessment. At this time, 79 of the 129 alcohol dependent participants studied at baseline were re-evaluated with the MRI scans, psychiatric and behavioral measures initially administered at baseline as well as the Time Line Follow-Back (Sobell et al., 1985, Sobell et al., 1988) to specifically assess alcohol consumption patterns during relapse. For the remaining 50 participants, follow-up assessment involved in-person and/or telephone interview (n = 29), review of available medical records (n = 18), or telephone interview of collateral sources (i.e., family or friends; n = 3), where only relapse status (i.e., any alcohol consumption) or date of relapse onset was obtained. Follow-up 2 and 3: All individuals who were abstinent at Follow-up 1 were interviewed again, in-person or via telephone, approximately 12 (Follow-up 2) and 18 (Follow-up 3) months after the initial follow-up to determine if they maintained continuous sobriety since Follow-up 1. Review of available medical records were conducted, when possible, to confirm self-report of post treatment drinking status.

Definition of Abstainers and Relapsers

Abstainers

Participants were designated as Abstainers (n = 47) if they met all the following criteria: a) self-reported no alcohol consumption between baseline and follow-up assessments (see below); b) no report of alcohol consumption between the baseline and follow-up assessments in available medical records; and c) available laboratory indicators of alcohol consumption (e.g., gamma glutamyltransferase; GGT) were within normal limits at follow-up.

Relapsers

Participants were designated as Relapsers (n = 82) if they met any of the following criteria: a) self-report of any alcohol consumption after treatment on follow-up assessments via in-person or telephone interview; b) alcohol consumption or relapse was indicated in medical records; c) report of participant alcohol use by a relative or close friend via telephone contact. In our previous studies, any level of alcohol consumption following treatment was associated with poorer psychosocial functioning (Durazzo et al., 2008). In 84% of the Relapsers (69 of 82), specific information was obtained on post-treatment days of abstinence until first relapse. Detailed information on alcohol use during relapse was obtained on 35 participants via in-person or phone interview (see Table 4).

Statistical Analyses

Demographic, clinical, medical and psychiatric variables

Abstainers and Relapsers were compared on baseline demographic (age, education, sex), clinical (BDI, STAI, FTND, alcohol consumption, frequency of antidepressant and anti-craving medications, disulfiram use), medical (frequency of comorbid medical conditions) and psychiatric (frequency of mood, anxiety, substance use including smoking, and other psychiatric disorders) variables. Group comparisons were conducted with independent sample t-tests or Fisher's Exact Test when indicated, and $p < .05$ was considered statistically significant for these analyses.

Prediction of post-treatment drinking status

Receiver operator characteristic (ROC) curve analysis was conducted to identify which anterior frontal and insula morphological (scaled to intracranial volume), psychiatric, clinical and demographic variables (see Table 2) provided optimal sensitivity and specificity for prediction post-treatment drinking status (i.e., Abstainer vs. Relapser). The ROC method employed is an exploratory procedure and results are not penalized for inclusion of multiple predictors (Kraemer, 1992). ROC was performed using publically available software [ROC version 5.07; (Yesavage and Kraemer, 2007)]. The ROC procedure simultaneously considered morphological, demographic, psychiatric and clinical predictors and determined those that best discriminated the Abstainers and Relapsers. Optimal cutpoints for each statistically significant predictor ($p < .01$) were then ranked according to Cohen's kappa, a measure of inter-rater agreement (Kraemer, 1992). ROC findings are reported as kappa

values, sensitivity and specificity, and p-values. Bootstrapping (n=1000 iterations) was used to establish confidence intervals for each ROC parameter estimate.

Associations of smoking status, clinical variables, and brain morphological variables with relapse characteristics

For Relapsers, the association between smoking status, comorbid medical conditions, alcohol consumption, and anterior frontal and insula volumes and the duration of abstinence following treatment were examined. Smoking status, comorbid medical conditions, alcohol consumption were also simultaneously included as predictors because they were associated with post-treatment drinking status and/or duration of abstinence following treatment for AUD (Durazzo et al., 2011b, Pfefferbaum et al., 2004, Weinberger et al., 2015, Durazzo et al., 2008). The associations were assessed with Cox regression and $p < .05$ was considered statistically significant for individual predictors.

RESULTS

Demographic, clinical and psychiatric measures

Relapsers had fewer years of education ($p = .015$) and a trend for higher lifetime average drinks/month ($p = .053$). Relapsers had higher frequencies of psychiatric conditions and unipolar mood disorders (both $p = .005$). A unipolar mood disorder was the most common psychiatric condition among Relapsers. The majority of participants with a unipolar mood disorder met criteria for major depressive disorder (MDD), recurrent, with an active episode at baseline. No other significant group differences on demographic, clinical and psychiatric measures were observed (**see** Table 1). Seventy-five percent (75%) of those who relapsed resumed drinking within 6 months of treatment.

Prediction of post-treatment drinking status over 18 months

ROC analyses showed that mood disorders, education, and volumes of the right caudal ACC, right rostral ACC and total right frontal GM were significant predictors of post-treatment drinking status (see Table 3). The optimal cutpoint for mood disorder was 1 (0 = negative for mood disorder, 1 = positive for mood disorder), and indicated that 78% were Relapsers among those with a mood disorder. The optimal cutpoint for years of education was 15; 70% of participants who had less than 15 years of education were Relapsers. Optimal cutpoints for right caudal ACC, right rostral ACC, and right frontal GM volumes were 0.14%, 0.12% and 5.58% of ICV, respectively. Seventy-three percent (73%) of the sample with right caudal ACC volume below 0.14%, 70% of the sample with right rostral volume below 0.12%, and 84% of the sample with a right frontal GM volume below 5.58% were Relapsers. Participants with and without a comorbid mood disorder did not differ significantly on volume, surface area or thickness in any region of interest (all $p > .20$); however, individuals with a comorbid mood disorder had higher BDI and STAI-trait scores (both $p < .01$). Therefore, the ROC was repeated with BDI and STAI-trait scores, and these variables were not significant predictors (all $p > .05$). Use of psychiatric comorbidity frequency as a predictor, instead of mood disorders frequency, yielded virtually identical results as those reported above (data not shown).

Associations of smoking status, clinical variables, and brain morphological variables with relapse characteristics

In Relapsers, Cox regression showed that smoking status (smoker vs. non-smoker) and medical comorbidity (present or absent) were associated with the number of post-treatment days of abstinence until relapse [χ^2 (2) = 12.1, p = .002]. Smokers [β = −.877, p = .002, Exp (β) = .406 (95% C.I. = .241 – .719)] and individuals with a medical comorbidity [β = −.618, p = .017, Exp (β) = .598 (95% C.I. = .363 – .987)] showed significantly increased probability for earlier relapse. There were no significant interactions among predictors (all p > .15). Smokers relapsed earlier (at a median of 102 post-treatment days of abstinence) than non-smokers (median of 168 days), and individuals with a comorbid medical condition relapsed earlier (median of 86 days) than those without a comorbid medical condition (median of 147 days (see Figures 1a and 1b). Correspondingly, a significantly greater number of smokers (87%) compared to non-smokers (52%) relapsed within 6 months of treatment ([χ^2 (1) = 10.0, p = .003]). Years of education, frequencies of mood and psychiatric disorders, and volumes of the right rostral and caudal ACC and total frontal GM, which were predictors of relapse status (i.e., Abstainer or Relapser), were not related to the number of post-treatment days of abstinence until relapse (all p > .40). See Table 4 for summary of alcohol use during relapse.

Within the Relapsers group, smokers and non-smokers and individuals with and without a comorbid medical condition were also compared on other demographic, clinical and morphological measures to determine if group differences on such variables were related to earlier relapse. Smokers had significantly higher lifetime average drinks/month, larger volumes in the left medial orbitofrontal cortex, and lower BMI than non-smokers (all p < .05). Accordingly, each of the foregoing variables was individually considered as a predictor with smoking status and medical comorbidity; they were not significant predictors, there were no interactions, and they did not improve model fit (all p > .06). Relapsers with a comorbid medical condition had a lower frequency of anti-craving/relapse medications and a smaller right lateral orbitofrontal cortex volume than Relapsers without a comorbid medical condition (all p < .05). Each of these variables was individually entered as a predictor with smoking status, and medical comorbidity, but they were not significant predictors, there were no interactions, and they did not improve model fit (all p > .33).

DISCUSSION

The main findings from this group of predominately Caucasian, male Veterans seeking treatment for an AUD were: 1) At entry into treatment, the frequency of a unipolar mood disorder, years of education, right rostral and caudal ACC volume, and total right frontal GM volume were significant predictors of post-treatment drinking status over 18 months. 2) Among Relapsers, 75% relapsed within 6 months of treatment. Smokers and individuals with a comorbid medical condition relapsed significantly earlier after treatment, and a greater frequency of smokers relapsed within 6 months of treatment. Taken together, these results reinforce that relapse in AUD is a function of multiple biological, psychiatric, psychological and psychosocial factors, which may change dynamically during and after

treatment (Witkiewitz, 2011, Witkiewitz and Marlatt, 2007, Meyerhoff and Durazzo, 2010, Durazzo et al., 2016).

The frequency of a unipolar mood disorder at baseline was significantly higher in Relapsers and predicted post-treatment drinking status. Distinctions have been made between alcohol-induced unipolar depressive disorders and independent major depressive disorders with regard to onset, course, persistence of symptoms following detoxification, and etiology (Kahler et al., 2002, Raimo and Schuckit, 1998, Verheul et al., 2000). The majority of Relapsers with a unipolar mood disorder were diagnosed with a recurrent MDD, which is often a chronic relapsing-remitting neuropsychiatric disorder. Conversely, the majority of Abstainers were diagnosed with an alcohol-induced mood disorder and this condition is suggested to be transient and remits with abstinence (Raimo and Schuckit, 1998). The level of self-reported depressive symptomatology (i.e., BDI), was not different between Abstainers and Relapsers and was not a significant predictor of post-treatment drinking status. The BDI reflects the magnitude of depressive symptomatology over 1 week, which can be strongly influenced by recent life events and environmental circumstances (Richter et al., 1998), including substance abuse treatment. In multiple studies, a diagnosis of a unipolar mood disorder was associated with relapse in AUD treatment [see (Durazzo et al., 2008, Hobbs et al., 2011, Suter et al., 2011, Greenfield et al., 1998, Rounsaville et al., 1987)], while level of self-reported depressive symptomatology was not related to relapse in others (Soyka and Schmidt, 2009, Durazzo et al., 2008, Bradizza et al., 2006, Greenfield et al., 1998). Comorbid recurrent MDD may be associated with greater probability of relapse for a number of reasons: Individuals with AUD and comorbid MDD demonstrate greater maladaptive coping skills, dysfunctional emotional regulation, and abnormal functioning of the hypothalamic-pituitary-adrenal cortex axis (Kahler et al., 2002, Compare et al., 2014, Moses and Barlow, 2006), which are associated with increased risk of relapse (Moos and Moos, 2007, Seo and Sinha, 2014, Berking et al., 2011); those with AUD and comorbid MDD may resume alcohol consumption to ameliorate the core symptoms of recurrent MDD (Hesselbrock et al., 1986, Pettinati et al., 2013). It is noteworthy that only 20% of Relapsers who met criteria for MDD were taking an antidepressant at the time of study. Collectively, the above suggests that individuals with AUD and comorbid unipolar mood disorders may be at increased risk for relapse to hazardous alcohol consumption in order to attenuate negative mood and/or subjectively enhance mood (Glockner-Rist et al., 2013).

Educational level below 15 years was associated with relapse. Lower education was significantly related to greater lifetime average drinks/month, cumulative months of heavy drinking (i.e., ≥ 100 drinks/month) and age of onset of heavy drinking in this sample (data not shown). The potential assorted biopsychosocial consequences of earlier onset and/or more severe alcohol dependence may have interfered with the level of educational attainment (Greenfield et al., 2003). Additionally, lower formal education in those with AUD may be linked to less adaptive coping skills, placing them at greater risk for relapse (Moos and Moos, 2006).

Right rostral and caudal ACC volumes below 0.12% and 0.14% of ICV, respectively, were associated with relapse. The rostral/perigenual division of the ACC is indicated to subserve processing of affective or emotional stimuli or contexts (Bush et al., 2000, Mohanty et al.,

2007). The caudal/dorsal region of the ACC and interconnectivity with the insula and amygdala complex are proposed as critical components in the salience network, which is implicated in conflict monitoring, interoceptive-autonomic, and reward-processing (Seeley et al., 2007, Williams, 2016). Therefore, macrostructural integrity of both major divisions of the ACC may be related to the ability of the salience network to facilitate appropriate cognitive control in response to external and interoceptive stimuli that has affective and/or emotionally laden content. A large scale meta-analysis of voxel-based morphometry across six diverse diagnostic groups (addictive, schizophrenia, bipolar disorder, depression, obsessive-compulsive disorder, and anxiety disorders) reported that GM loss converged across diagnoses in the caudal/dorsal ACC (as well as the bilateral insula) (Goodkind et al., 2015). This suggests that the decreased volume of the caudal/dorsal ACC represents a common biomarker of compromised structural integrity across a wide variety of neuropsychiatric conditions (Goodkind et al., 2015). Total right frontal GM volume below 5.58% of ICV was also associated with relapse. The findings for the total right frontal GM volume in this study are congruent with our report that used a different tissue quantitation method in a very similar patient cohort (Durazzo et al., 2016); in that study, we observed Relapsers had smaller bilateral total frontal GM volume than Abstainers at both 1 week and 1 month of sobriety that was most pronounced for right total frontal GM volume. Taken together, decreased macrostructural integrity (as evidenced by volume deficits) of the right rostral and caudal ACC and total right frontal GM may serve as endophenotypic markers of increased relapse risk following AUD treatment. Notably, in the current study, measures of cortical surface area and thickness were not predictive of post-treatment relapse status.

In Relapsers, smokers and those with a comorbid medical condition relapsed significantly earlier after treatment (most within 6 months). There are multiple potential explanations for earlier relapse in smokers: In rodents, nicotine consumption is associated with increased alcohol self-administration and reinstatement of extinguished alcohol-seeking behavior. In treatment-seeking alcohol dependent individuals, smoking was associated with increased alcohol use urges, and alcohol relapse was related to high urges to use cigarettes. Chronic co-occurring alcohol and tobacco use can lead to one substance serving as conditioned stimulus for the other, and human and animal studies indicate cross-substance craving [see (McKee and Weinberger, 2013) for review]. In the current study, smokers consumed significantly more average drinks/month lifetime than non-smokers (data not shown); this suggests a greater severity of alcohol dependence, which was associated with earlier relapse onset in some studies [see (Meyerhoff and Durazzo, 2010) for review]. Taken together, continued smoking following treatment for AUD appears to place individuals at increased risk for relapse, or earlier relapse (as apparent in the current study), by classical and operant conditioning mechanisms, greater pretreatment alcohol use disorder severity, as well as by other potential smoking-related neurocognitive and neurobiological deficits (Weinberger et al., 2015, Roche et al., 2016). In addition to smokers, individuals with a medical comorbidity (predominately hypertension or seropositivity for hepatitis C) relapsed earlier than those without these conditions. Twenty-one Relapsers with hypertension (77%) used an antihypertensive, and no participant who was seropositive for hepatitis C took interferon or other medications to manage active hepatitis symptomatology. Furthermore, variables that differed between Relapsers with and without a comorbid medical condition did not account

for the earlier relapse onset. Therefore, the association of a comorbid medical condition with earlier relapse likely represents a proxy for genetic, biomedical, lifestyle and/or psychosocial variables related to duration of abstinence that were not assessed in this study.

Aspects of this study include that may limit the generalizability of the findings include a sample that comprised largely of US Armed Services Veterans, and the primary reliance on self-report for the determination of post-treatment drinking status. Our operationalization of relapse (i.e., any alcohol consumption) may not generalize to other studies; however, in our previous research, any level of alcohol consumption following treatment was associated with poorer psychosocial functioning (Durazzo et al., 2008). Given the consistent finding of anterior frontal and insula neurobiological abnormalities in relapse in AUD, we confined our analyses to anterior frontal GM and insula morphological variables; however, it is possible that there may be additional cortical or subcortical regions associated with relapse in this sample. We were not able to examine for sex effects due to the small number of female participants. We were also unable to assess if the relapse risk or duration associated with substance-induced depressive disorders was different from that related to recurrent major depression due to the small sample sizes when further dividing the Relapsers into these subcategories. Similarly, the subsample size of Relapsers with and without hypertension, hepatitis C and hyperlipidemia were not sufficient to evaluate their individual relationships with duration of abstinence following treatment. It is important to acknowledge that the sensitivity (i.e., correct classification of Relapsers) was marginally above chance for mood disorders, and specificity (i.e., correct classification of Abstainers) was marginal for education and right caudal ACC and frontal GM volumes. We did not include measures of coping skills, stress, emotional regulation, self-efficacy, social support, marital status, and personality disorders, which have been shown to predict drinking behavior after treatment (Witkiewitz, 2011; Witkiewitz and Marlatt, 2007) . It is also probable that the drinking behavior subsequent to treatment in our participants was influenced by genetic factors not assessed in this report.

In this study of predominately middle-aged Caucasian male Veterans, 64% of the sample total relapsed after treatment, which is consistent with previous research conducted over the past three decades (Meyerhoff and Durazzo, 2010). The variables that predicted post-treatment drinking status (i.e., unipolar mood disorder, education and volumes of the right rostral and caudal ACC and total frontal GM) were not the same as those associated with number of post-treatment days of abstinence until relapse [i.e., smoking status, comorbid medical condition (predominately hypertension, hepatitis C and hyperlipidemia)]. This indicates different mechanisms influenced the ability to maintain sustained sobriety over 18 months versus how quickly a Relapser resumed alcohol consumption after treatment. These mechanisms may incorporate multiple tonic (i.e., stable) and phasic (i.e. transient) as well as proximal and distal variables related to treatment outcome (see above limitations) that were not obtained in this study (Witkiewitz and Marlatt, 2007). Overall, the findings suggest effective treatment of mood disorder and cigarette smoking in conjunction with AUD-focused interventions may promote better long-term treatment outcomes (Cavazos-Rehg et al., 2014, Suter et al., 2011, McKee and Weinberger, 2013, Pettinati et al., 2013, Hobbs et al., 2011) and assist in breaking the relapse-remit cycle that afflicts so many individuals with AUD. Larger scale studies are necessary to determine the relative associations of

hypertension, hepatitis C and hyperlipidemia with AUD treatment outcome. The majority (75%) of those who relapsed did so within 6 months of treatment. This is consistent with previous research (Durazzo et al., 2008, Maisto et al., 2006, Maisto et al., 2007, Kirshenbaum et al., 2009) and suggests maintenance of abstinence for a 6 month period post-treatment represents a critical bench mark that is associated with a subsequent period of extended abstinence and adaptive psychosocial functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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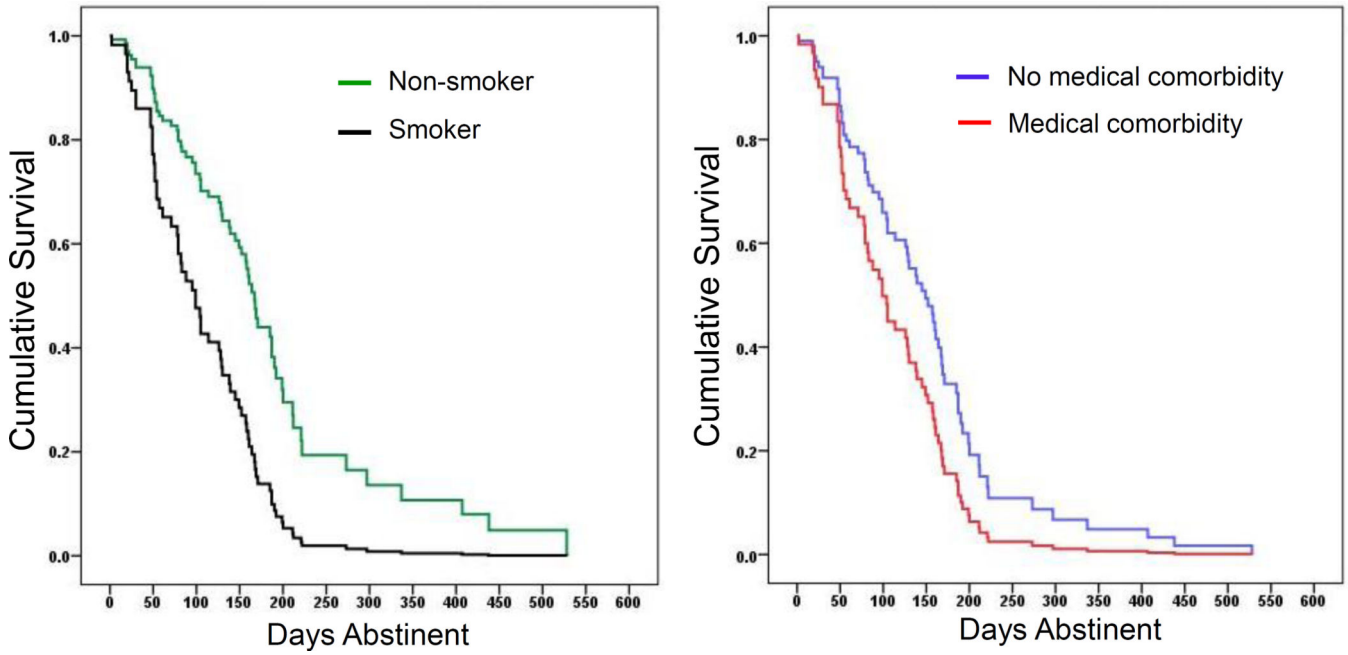

Figure 1.

a. Association between smoking status and post-treatment days of abstinence in Relapsers

b. Association between concurrent medical comorbidity and post-treatment days of abstinence in Relapsers

Table 1

Group Demographics, Alcohol and Cigarette Use Histories, Self-Report Questionnaires and Comorbidity Frequency

Measure	Abstainers (n = 47)	Relapsers (n = 82)	Group differences*
Age (years)	52 (12)	50 (8)	
Education (years)	14.4 (2.2)	13.5 (1.9)	Abstainers > Relapsers
Caucasian (%)	79	71	
Male (%)	92	94	
Days abstinent at baseline	17 (12)	15 (14)	
Days until relapse	NA	141 (79)	
Relapse within 6 months (%)	NA	75	
1-yr average drinks/month	374 (209)	431 (236)	
Lifetime average drinks/month	194 (116)	240 (135)	Abstainers < Relapsers
Months heavy drinking	248 (111)	267 (126)	
Medical comorbidity (%)	49	55	
Hypertension (%)	28	35	
Hepatitis C+ (%)	15	21	
Hyperlipidemia (%)	13	7	
Antihypertensive medication use (%)	21	27	
Substance use disorder comorbidity (%)	26	16	
Psychiatric comorbidity (%)	23	50	Abstainers < Relapsers
Major Depressive Disorder (%)	13	45	Abstainers < Relapsers
Substance-induced Mood Disorder (%)	11	5	
Anxiety Disorder (%)	2	7	
Multiple psychiatric comorbidities (%)	9	22	
Antidepressant use (%)	9	20	
Anti-craving medication use (%)	11	13	
Smokers (%)	57	65	
FTND	5 (2)	5 (2)	
Pack years	26 (17)	26 (18)	
Smoking duration (years)	27 (12)	26 (12)	
BDI	12 (8)	14 (9)	
STAI-Trait	45 (10)	47 (13)	
Body mass index	27 (5)	27 (5)	
Intracranial volume (cc)	1599 (125)	1567 (138)	

Note. BDI: Beck Depression Inventory. CON: Controls. FTND: Fagerstrom Tolerance Test for Nicotine Dependence. NA: not applicable. STAI: State -trait Anxiety Inventory – Trait.

*All listed group differences p < .05. Mean (SD).

Table 2

Variables Included in Primary Receiver Operating Characteristics Analysis

Variable
Frequency of mood disorders
Level of education
Lifetime average drinks per month
Bilateral volume, surface area, and thickness:
Rostral and caudal anterior cingulate cortex
Rostral and caudal middle frontal gyrus
Pars opercularis, orbitalis and triagularis of inferior frontal gyrus
Superior frontal gyrus
Medial and lateral orbitofrontal cortex
Frontal pole
Insula

Table 3

Results of the Receiver Operating Characteristics analyses for Prediction of Post-treatment Drinking Status

Measure	Sensitivity	Specificity	Kappa	X^2	P
Right Rostral ACC Volume	69%	75%	0.42	7.88	<.01
95% CI	(48–82)	(58–89)	(0.30–0.56)		
Mood Disorder (frequency)	55%	76%	0.39	8.05	<.01
95% CI	(39–69)	(57–88)	(0.22–0.47)		
Right Frontal GM Volume	79%	59%	0.37	10.95	<.001
95% CI	(62–89)	(41–75)	(0.23–0.46)		
Right Caudal ACC Volume	74%	52%	0.26	8.84	<.01
95% CI	(56–86)	(35–66)	(0.19 – 0.37)		
Education (years)	79%	35%	0.21	7.21	<.01
95% CI	(61–90)	(20–57)	(0.14–0.39)		

Note. ACC: anterior cingulate cortex; CI: confidence interval; GM: gray matter

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Table 4

Post-treatment Alcohol Consumption Characteristics in Relapsers

Relapse duration (days)					Average drinks per drinking day during relapse					Total drinks during relapse				
mean	median	SD	min	max	mean	median	SD	min	max	mean	median	SD	min	max
78	66	104	2	540	13	10	7	3	30	857	573	980	9	4320

Note. n = 35; min: minimum; max: maximum; SD: standard deviation

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