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TREATMENT

Combined Neuroimaging, Neurocognitive and Psychiatric Factors to Predict Alcohol Consumption Following Treatment for Alcohol Dependence

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Abstract — Aims: Resumption of hazardous drinking after treatment is common in alcohol use disorders (AUD). This study examined the ability of multimodality magnetic resonance, neurocognitive, psychiatric and demographic, to predict alcohol consumption after treatment for AUD. **Methods:** Seventy treatment-seeking participants completed 1.5T magnetic resonance studies, yielding regional gray matter (GM) and white matter (WM) surrogate markers of neuronal integrity (*N*-acetylaspartate: NAA) and cell membrane turnover/synthesis (choline: Cho), assessment of major psychiatric disorders and comprehensive neurocognitive assessment after ∼1 month of abstinence. Participants were followed up 6–12 months after treatment and classified as Abstainers (no alcohol consumption; $n = 26$) and Resumers (any alcohol consumption; $n = 44$). Abstainers and Resumers were contrasted on various outcome measures, and those that significantly differed between groups were entered as factors in a logistical regression model to predict drinking status at follow-up. **Results:** The following variables were independent predictors of resumption of drinking: temporal GM NAA, frontal WM NAA, frontal GM Cho, processing speed and comorbid unipolar mood disorder. With each standard deviation unit decrease in temporal GM NAA, frontal WM NAA, frontal GM Cho and processing speed, the odds of resumption of drinking were increased 3.1, 3.3, 6.4 and 14.2 times, respectively. Diagnosis of a unipolar mood disorder was associated with 14.5-fold increased odds of resumed drinking. **Conclusions:** The findings suggest that Resumers, relative to Abstainers, demonstrated greater abnormalities in anterior frontal-subcortical circuits involved in mood and behavioral regulation, and development and maintenance of alcohol use disorders, The magnetic resonance-derived variables used in this study may provide additional information regarding the prediction and neurobiological correlates of resumption of hazardous drinking.

INTRODUCTION

Within ∼12 months of completion of treatment for an alcohol use disorder (AUD) (i.e. alcohol dependence or abuse), ∼50–80% of individuals will resume consuming alcohol at hazardous levels (Monahan and Finney, 1996; Miller *et al.*, 2001). Resumption of alcohol consumption in those with an AUD appears to be mediated by a combination (and possibly an interaction) of biological, neurocognitive, psychological/psychiatric and sociodemographic factors (Parsons *et al.*, 1990; Glenn and Parsons, 1991; Jin *et al.*, 1998; Weiss and Porrino, 2002; Heinz *et al.*, 2003; Adinoff *et al.*, 2005; Bottlender and Soyka, 2005; Bradizza *et al.*, 2006). A considerable amount of research investigating the factors associated with resumed alcohol consumption following treatment has focused on psychological/psychiatric variables (e.g. coping styles, comorbid mood, personality or substance abuse disorders), and sociodemographic (e.g. age, education, marital status) and behavioral (e.g. drinking severity and chronicity, previous treatment attempts) factors. In general, poor coping skills, low self-esteem/self-efficacy, social isolation, comorbid mood or personality disorders, greater severity of drinking history and depressive symptomatology have been associated with relapse [see Parsons *et al.* (1990), Glenn and Parsons (1991), Miller (1991), Miller *et al.* (1996b), Noone *et al.* (1999), Boening *et al.* (2001), Teichner *et al.* (2001), Bradizza *et al.* (2006), Krampe *et al.* (2006), Moos and Moos (2006), Walter *et al.* (2006) and Kodl *et al.* (2008)].

Fewer studies have addressed the neurobiological and neurocognitive correlates of resumption of drinking in adult AUD. In treatment seeking AUD, higher brain activation in the putamen, anterior cingulate and medial prefrontal cortex at ∼2 months of abstinence was associated with the level of alcohol consumption in those who resumed drinking subsequent to treatment (Grusser *et al.*, 2004). Higher levels of brain activation in the thalamus and striatum in response to affectively positive (versus neutral) cues were inversely related to drinking days and overall alcohol intake in those who relapsed after treatment (Heinz *et al.*, 2007). In a group of treated AUD abstinent for ∼18 days, lower frontal cerebral blood flow was observed in individuals who relapsed relative to those who remained abstinent for ∼2 months following treatment (Noel *et al.*, 2002). Greater suppression of the hypothalamus–pituitary–adrenal axis during pharmacological or behavioral challenge has been observed in relapsed versus abstinent alcoholics following treatment (Adinoff *et al.*, 2005). Erythrocyte count, hemoglobin concentration and hematocrit in 1-month-abstinent treatment-seeking alcoholics were higher among participants who maintained sobriety compared to those who relapsed over 2–12 months following treatment (Pfefferbaum *et al.*, 2004).

Studies investigating the utility of neurocognitive variables to predict relapse in adult AUD have yielded mixed findings. At admission to treatment, better performance on the Wechsler Adult Intelligence Scale, Block Design was observed in those who abstained versus those who relapsed within 6 months (Donovan *et al.*, 1984). In short-term abstinent AUD, poorer performance on a global measure of learning and memory, problem solving, abstraction and perceptual motor task following detoxification was associated with relapse (Parsons, 1987; Parsons *et al.*, 1990; Glenn and Parsons, 1991). Poorer performance on a composite measure of auditory–verbal and

visuospatial learning and memory following detoxification tended to predict lower probability of long-term abstinence (Bartels *et al.*, 2007). In treatment-seeking AUD, the interaction of coping skills and neurocognition was predictive of alcohol consumption following treatment. Specifically, those who concurrently demonstrated higher neurocognitive abilities and poor coping responses had a greater percentage of alcohol-drinking days during relapse (Tapert *et al.*, 2004). Other studies have found neurocognitive functioning to have minimal or no value in predicting relapse in adult AUD [see Glenn and Parsons (1991), Miller (1991), Jin *et al.* (1998)].

Overall, the neuroimaging and neurocognitive studies of relapse in AUD suggest dysfunction in spatially overlapping brain systems involved in the initiation and maintenance of AUD/substance use disorders, as well as in decision making, impulse control, judgment, planning and reasoning skills (Koob, 2003; Lubman *et al.*, 2004; Bowirrat and Oscar-Berman, 2005; Baler and Volkow, 2006). This is consistent with the vast number of neuroimaging and neurocognitive studies that indicate AUD is associated with abnormalities in the GM and WM of the frontal, temporal and parietal lobes, as well as subcortical nuclei (Oscar-Berman, 2000; Pfefferbaum and Sullivan, 2005; Durazzo and Meyerhoff, 2007).

To the best of our knowledge, no reports have simultaneously examined the ability of proton magnetic resonance (MR)-derived measures of brain metabolites and morphology, as well as neurocognitive, psychiatric, demographic and behavioral factors to predict resumption of alcohol consumption after treatment for adult AUD. Thus, the primary goal of the current work was to determine the extent to which our quantitative neuroimaging, neurocognitive, clinical laboratory and psychiatric/behavioral outcome measures obtained in treatment-seeking adult alcoholics with ~1 month of abstinence predict drinking status 6–12 months subsequent to outpatient treatment for AUD. We hypothesized that individuals who resumed drinking after treatment demonstrate lower levels of markers of neuronal integrity and cell membrane turnover/synthesis in the frontal, parietal and temporal lobes, poorer executive skills, and greater anxiety and depressive symptomatology relative to those who remained abstinent.

METHODS

Participants and measures

Seventy outpatient participants (three females) were recruited from the VA Medical Center Substance Abuse Day Hospital ($n = 62$) and the Kaiser Permanente Chemical Dependence Recovery Program ($n = 8$) in San Francisco for a longitudinal study on the effects of abstinence from alcohol on neurobiology and neurocognition. Outpatient treatment ranged from 14 to 30 days. All participants were between the ages of 28 and 66 years and met DSM-IV criteria for alcohol dependence at study enrollment. Primary inclusion criteria were fluency in English, DSM-IV diagnosis of alcohol dependence or alcohol abuse at the time of enrollment (all met the criteria for alcohol dependence with physiological dependence), consumption of >150 standard alcoholic drinks (i.e. 13.6 g of ethanol) per month for at least 8 years prior to enrollment for men, or consumption of <80 drinks per month for at least 6 years prior to enrollment for women. See Table 1 for demographic data.

Table 1. Demographic, alcohol and cigarette consumption, mood and anxiety measures, and clinical laboratory variables

Variable	Abstainers ($n = 26$)	Resumers ($n = 44$)
Age	50.1 (6.8)	51.2 (11.4)
Education	14.4 (2.5)	13.6 (1.8)
AMNART	113 (10)	112 (9)
1-year average drinks/month	395 (239)	452 (202)
3-year average drinks/month	374 (241)	408 (182)
8-year average drinks/month	337 (240)	348 (137)
Lifetime average drinks/month	210 (124)	256 (127)
Lifetime years	35 (11)	34 (9)
Months of heavy drinking	255 (119)	272 (112)
Smokers (%)	48	60
FTND total	6.3 (1.5)	5.6 (1.9)
Smoking duration	29 (12)	28 (15)
Cigarette pack years	29 (19)	28 (21)
Beck Depression Inventory	6.5 (5.7)	9.9 (8.5)
STAI-trait	40.3 (9.6)	44.8 (12.5)
Comorbid unipolar mood disorder (%)	15.0	46.0[a]
Comorbid medical condition (%)	41.0	38.0
History of substance abuse disorder (%)	17.5	10.0
Body mass index	25.8 (4.5)	26.7 (5.0)
Gamma glutamyltransferase	45 (40)	52 (52)
Aspartate aminotransferase	34 (19)	33 (18)
Alanine aminotransferase	37 (27)	35 (24)
Red blood cell count	4.6 (.42)	4.4 (.31)
Hemoglobin	16 (6.2)	14 (1.0)
Hematocrit	46 (2.8)	43 (2.9)
White blood cell count	7.3 (1.7)	7.4 (1.8)
Prealbumin	26 (7.3)	26 (6.0)

AMNART: American National Adult Reading Test; FTND: Fagerstrom Test for Nicotine Dependence; STAI: State-Trait Anxiety Inventory.
[a] Abstainers < Resumers, $P \leq 0.05$ after modified Bonferroni correction [mean (SD)].

Medical exclusion criteria were history of the following: intrinsic cerebral masses, HIV/AIDS, cerebrovascular accident, brain aneurysm, arteriovenous malformations, peripheral vascular disease, myocardial infarction, uncontrolled chronic hypertension (systolic >180 mmHg and/or diastolic >120 mmHg), type I diabetes, moderate or severe chronic obstructive pulmonary disease, nonalcohol-related seizures, significant exposure to known neurotoxins (e.g. toluene, carbon tetrachloride), demyelinating and neurodegenerative diseases, Wernicke–Korsakoff syndrome, alcohol-induced persisting dementia, penetrating head trauma and closed head injury resulting in loss of consciousness for >10 min. Psychiatric exclusion criteria were history of schizophrenia or other thought disorders, bipolar disorder, dissociative disorders, posttraumatic stress disorder, obsessive compulsive disorder, panic disorder (with or without agoraphobia), major depression with mood-incongruent psychotic symptoms, dependence on any substance other than alcohol or nicotine in the 5 years immediately prior to enrollment, intravenous drug use in the 5 years immediately prior to enrollment in the study and current opioid agonist therapy.

At the time of enrollment (7 ± 3 days of sobriety), participants completed the Clinical Interview for DSM-IV Axis I Disorders, Version 2.0 (SCID-I/P) (First *et al.*, 1998) and semi-structured interviews for lifetime alcohol consumption (Lifetime Drinking History; Sobell *et al.*, 1988; Sobell and Sobell, 1992) and substance use (in-house questionnaire

assessing substance type, and quantity and frequency of use). From the Lifetime Drinking History, we derived average number of alcoholic drinks per month over 1, 3 and 8 years prior to enrollment, average number of drinks per month over lifetime, lifetime years of regular drinking (i.e. years in which the participant consumed at least one alcoholic drink per month), age of onset and duration of heavy drinking (defined as drinking more than 100 drinks per month in males and 80 drinks per month in females). After 34 ± 8 days of abstinence and near or following conclusion of outpatient treatment, participants completed proton MR studies at 1.5 Tesla magnetic field strength that yielded regional brain volumes and surrogate markers of neuronal integrity (*N*-acetylaspartate: NAA) and cell membrane turnover/synthesis (choline-containing compounds: Cho). In the morphological MR studies, regional white matter (WM), gray matter (GM) and cerebral spinal fluid (CSF) volumes were obtained via automated probabilistic segmentation and combined with automated atlas-based labeling of the major lobes, cerebellum and subcortical structures. All volumes were corrected for intracranial volume. Multislice proton magnetic resonance spectroscopic imaging (^{1}H MRSI) yielded regional absolute concentrations for NAA, Cho and other metabolites, which were derived from region-averaged metabolite spectra obtained in three parallel planes through the centrum semiovale, basal ganglia and cerebellar vermis. For details on the acquisition and processing of MR data, see Meyerhoff *et al.* (2004) and Cardenas *et al.* (2005).

Within ∼1 day of the MR studies, participants completed comprehensive neuropsychological and motor/ataxia assessment (∼2.5 h), 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). 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 (Kongs *et al*., 2000) nonperseverative errors, perseverative errors, and perseverative responses. *Fine motor skills:* Grooved Peg Board [Lafayette Instrument (1989), Lafayette, IN, USA). *General intelligence:* Ward-7 Full Scale IQ [(Axelrod *et al*., 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. The Cognitive efficiency domain 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 nonverbal tasks. The cognitive efficiency domain is an approximation of the concept of cognitive efficiency described by Glen and Parsons (1992) and Nixon and colleagues (1995, 1998). Premorbid verbal intelligence was estimated with the American National Adult Reading Test (Grober and Sliwinski, 1991). Participants also completed standardized questionnaires assessing 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 via the Fagerstrom Tolerance Test for Nicotine Dependence (FTND) (Fagerstrom *et al.*, 1991). All smoking participants were allowed to smoke *ad libitum* at the time of all assessments. The total number of cigarettes smoked per day and the number of years of smoking at the current level were recorded and pack years calculated. Follow-up for all participants occurred 6–12 months following the 1-month assessment. Participants were urine-tested for illicit substances immediately before all assessments (i.e. cannabinoids, opiates, phencyclidine, cocaine and amphetamines).

Fifty-two of 70 participants were revaluated 227 ± 71 days after the 1-month assessment with all MR, neurocognitive and psychiatric outcome measures administered at the 1-month assessment. Alcohol consumption during this interval was evaluated with the Timeline Follow-Back Interview (Sobell and Sobell, 1992), and any other substance use was recorded. The disposition of the remaining 18 participants was obtained via brief face-to-face or telephone interview with the participants ($n = 5$), medical records (confined to entries from mental health professionals providing outpatient substance abuse treatment for the participant; $n = 8$) or telephone interview of collateral sources (i.e. family or friends; $n = 5$).

Participants were designated as Abstainers ($n = 26$) if (a) they self-reported no alcohol consumption between the 1-month assessment and follow-up; (b) there was no report of alcohol consumption between the 1-month assessment and follow-up in medical records; (c) laboratory indicators of recent alcohol consumption (e.g. gamma glutamyltransferase: GGT) were within normal limits at follow-up. Participants were designated as resumers of alcohol consumption (Resumers; $n = 44$) if (a) they self-reported any alcohol consumption at any time between the 1-month assessment and follow-up via telephone or in-person interview; (b) the use of alcohol was indicated in medical records by mental health professionals providing outpatient substance abuse treatment for the participant or other medical professionals; (c) they report of alcohol use by a relative or close friend of the participant via telephone or in-person interview.

To assist in characterizing the severity of the drinking episode(s) in Resumers, we identified the number of participants who met the Project MATCH criteria for an alcohol relapse (i.e. males: ≥3 consecutive days of consumption of ≥6 drinks per day; females: ≥3 consecutive days of consumption of ≥4 drinks per day). These criteria were applied only to those Resumers who had specific quantity/frequency information regarding their drinking episodes after the 1-month assessment.

Table 2. Outcome variables and constituent measures

Grouping variable	Constituent measures
Demographic	Age
	Education
Alcohol consumption	1-year average drinks/month
	3-year average drinks/month
	8-year average drinks/month
	Lifetime average drinks/month
	Lifetime years of regular drinking
	Months of heavy drinking
Cigarette consumption	Smokers (%)
	Fagerstrom total
	Smoking duration
	Cigarette pack years
Psychiatric	Beck Depression Inventory
	State-Trait Anxiety Inventory—Trait
	Comorbid unipolar mood disorder (%)
	History of substance abuse disorder (%)
Clinical laboratory/behavioral	Body mass index
	Gamma glutamyltransferase
	Aspartate aminotransferase
	Alanine aminotransferase
	Red blood cell count
	Hemoglobin
	Hematocrit
	White blood cell count
	Prealbumin
MRI volumes	Gray and white matter of frontal, temporal, parietal, occipital lobes
^{1}H MRSI	Gray matter of frontal, temporal, parietal lobes
	White matter frontal, temporal, parietal, occipital lobes
Neurocognitive	Cognitive efficiency
	Executive skills
	Fine motor and postural stability
	General intelligence
	Learning and memory
	Processing speed
	Visuospatial skills
	Working memory

The 26 Abstainers were initially reassessed 183 ± 73 days and the 44 Resumers 268 ± 66 days after the 1-month assessment. Of 26 Abstainers, 24 were again successfully interviewed later in person or via telephone, at different intervals, to obtain self-reports on drinking status. At this second follow-up, 24/26 Abstainers self-reported 764 ± 433 days (minimum = 165, maximum = 2004) of continuous sobriety following their 1-month assessment. Two Abstainers were lost to this second follow-up. All participants gave written informed consent, which was approved by review boards of the University of California, San Francisco, and the San Francisco VA Medical Center.

Data analyses

Volumetric and metabolite concentration data were converted to *z*-scores based on a group of 35 age-equivalent controls. Neurocognitive data were converted to *z*-scores from age- or age and education-corrected test norms. Outcome measures were grouped according to demographic, alcohol consumption, cigarette consumption, psychiatric variables, clinical laboratories, neurocognitive, regional MRI volumetric and ^{1}H MRSI variables (see Table 2). Abstainers and Resumers were contrasted on these grouped variables using *t*-tests or nonparametric tests. A modified Bonferroni procedure was employed to adjust alpha levels ($P = 0.05$, two-tailed) for multiple comparisons. This procedure corrected the alpha level according to the intercorrelations among measures and number of measures in each group of outcome variables (Sankoh *et al*., 1997). Six individual measures were found to be significantly different after correction for multiple comparisons (see Table 3). These six predictors were simultaneously entered into a binary logistic regression, with future drinking status as the dependent measure. The alpha level for the omnibus binary logistic regression was adjusted for the six significant predictors entered into the model ($P = 0.008$), and an alpha level of 0.05 was considered statistically significant for each of the individual predictors. All analyses were completed with SPSS v15.

Table 3. Outcome measures significantly different between Abstainers and Resumers at the 1-month assessment

Variable	Abstainers ($n = 26$)	Resumers ($n = 44$)
Frontal GM NAA	0.44 (1.2)	−0.52 (1.4)[a]
Temporal GM NAA	0.14 (1.1)	−0.87 (1.0)[a]
Frontal WM NAA	0.17 (0.98)	−0.51 (1.1)[a]
Frontal GM Cho	1.0 (1.0)	0.25 (0.99)[a]
Processing speed	0.04 (0.57)	−0.49 (0.55)[a]
Comorbid unipolar mood disorder (%)	15.0	46.0[b]

[a]Abstainers > Resumers (*z*-scores), $P \leq 0.05$ after modified Bonferroni correction.
[b]Abstainers < Resumers, $P \leq 0.05$ after modified Bonferroni correction [mean (SD)].

Table 4. Drinking characteristic of Resumers between the 1-month assessment and follow-up

Variable	Mean (SD)	Minimum	Maximum
Duration of abstinence from 1 month			
Assessment to follow-up (days)	137 (88)	22	353
Duration of drinking episode(s) (days)	69 (65)	3	138
Drinks per day during drinking episode(s)	13.6 (7.7)	3	24
Total drinks during drinking episode(s)	675 (821)	9	3024
Percent drinking ≥6 drinks per day	79		
Percent meeting Project Match relapse criteria	73		

Duration of abstinence: number of consecutive abstinent days from 1-month assessment to first drink. Duration of drinking episode(s): total number of days where at least one alcoholic beverage was consumed.

RESULTS

Demographic, alcohol and cigarette consumption variables

Of the 70 participants, 26 (37%) were Abstainers and 44 (63%) were Resumers. Thirty-two of 44 Resumers (73%) met the Project MATCH criteria for an alcohol relapse. Table 4 provides alcohol use characteristics for Resumers over the interval between the 1-month assessment and follow-up. In the total sample, 76% were Caucasian, 12% African American, 7% Latino and 5% Native American/Aleutian. Abstainers and Resumers were equivalent on age, education, predicted premorbid verbal intelligence and body mass index (see Table 1).

Table 5. Employment, educational and treatment status for Abstainers and Resumers at the 1-month assessment and follow-up

	Abstainers (%)		Resumers (%)	
Status	1 month	Follow-up	1 month	Follow-up
Gainfully employed	18	46	10	12
Unemployed and not in treatment	82	0	87	63
Attending school and gainfully employed	4	15	3	3
Engaged in long-term treatment and unemployed	NA	39	NA	0
Retired	0	8	5	7

1 month: 1-month assessment.

Abstainers and Resumers were also equivalent on average number of drinks per month over 1, 3 and 8 years prior to enrollment and number of months of heavy drinking. Resumers tended to consume more drinks per month over lifetime than Abstainers ($P = 0.13$). Sixty percent of Resumers and 48% of Abstainers were chronic smokers; the frequency of smokers was not significantly different between groups ($P = 0.22$), and smokers in both groups were equivalent on measures of smoking severity (see Table 1). As shown in Table 5, Abstainers demonstrated a significantly higher level of psychosocial functioning than Resumers at follow-up. There were no significant differences in indexes of psychosocial functioning (e.g. socioeconomic status, percent gainfully employed) between Abstainers and Resumers at study entry.

Comorbid psychiatric disorders, medical and substance use

At enrollment, a significantly greater proportion of Resumers (20 of 44; 46%) met current DSM-IV criteria for a unipolar mood disorder (i.e. major depression, or substance-induced mood disorderwith depressive features) compared to Abstainers (4 of 26; 15%) ($P = 0.01$). Among those who met the criteria for a unipolar mood disorder, 40% were diagnosed with recurrent major depression and 60% with a substance-induced (alcohol) mood disorder with depressive features. At the 1-month assessment, 30% of participants diagnosed with a unipolar mood disorder took an antidepressant medication. There was no difference between Resumers and Abstainers in the frequency of use of antidepressant medication. At the 1-month assessment, 40% of Resumers and 36% of Abstainers had a comorbid medical condition ($P = 0.85$); for both groups, the most common condition was hypertension, followed by hepatitis C. The frequency of these conditions was equally distributed across groups. In both the Resumer and Abstainer groups, ~70% of participants with hypertension took antihypertensive medications. Seven Resumers (16%) had a previous history of substance abuse or dependence, but in each case, the substance use disorder was in sustained full remission at enrollment. Two Abstainers (8%) met the criteria for current substance abuse at the time of enrollment.

Predictors of drinking status at follow-up

The binary logistic regression model was significant [χ^2 (6) = 38.0, $P < 0.001$, r^2 (Nagelkerke) = 0.72] with the following predictors: temporal GM NAA [$\beta = -1.13$, $P = 0.047$, Exp(β) = 0.322 (95% CI = 0.170–0.938)], frontal WM NAA [$\beta = -1.81$, $P = 0.049$, Exp(β) = 0.302 (95% CI = 0.080–0.923)], frontal GM Cho [$\beta = -1.85$, $P = 0.024$, Exp(β) = 0.157 (95% CI = 0.032–0.780)], processing speed [$\beta = -4.30$, $P = 0.003$, Exp(β) = 0.070 (95% CI = 0.023–0.232)] and comorbid unipolar mood disorder [$\beta = -4.51$, $P = 0.004$, Exp(β) = 0.069 (95% CI = 0.007–0.158)]. The model accurately classified 83% of Abstainers and 90% of Resumers into their respective groups and accounted for 72% of the variance in drinking status at follow-up. With each standard deviation unit decrease in temporal GM NAA, frontal WM NAA, frontal GM Cho and processing speed, the odds of resumption of drinking were increased 3.1, 3.3, 6.4 and 14.2 times, respectively. Diagnosis of a unipolar mood disorder at enrollment was associated with a 14.5-fold increase of the odds of resumption of drinking. Colinearity diagnostics indicated that each of the five predictors accounted for a unique portion of the variance in drinking status at follow-up. Removal of females from the analysis did not appreciably alter the foregoing findings.

In Resumers, lower frontal WM NAA ($r = -0.30$), temporal GM NAA ($r = -0.37$) and processing speed ($r = -0.39$) at the 1-month assessment were related to a greater number of drinking days at follow-up; however, these associations were not statistically significant after correction for multiple comparisons.

The trend differences for higher BDI score ($P = 0.10$) and average drinks/month over lifetime ($P = 0.13$) in Resumers prompted us to conduct a second logistic regression in which these variables were entered together with the five significant predictors described above. Additionally, comorbid medical conditions (e.g. hypertension, hepatitis C), smoking history and substance abuse history (all categorical variables) were also individually entered with the five predictors. None of these additional factors were significant predictors, and each decreased the classification accuracy of the original model.

Neurocognitive and psychiatric evaluations are far more commonplace than MR assessment in treatment settings. Therefore, we examined the added value of using our MR outcome variables in the prediction of resumption of drinking in our cohort by entering processing speed and unipolar depression as the sole predictors into the logistical regression model to predict future drinking status. These two predictors explained only 26% of the variance and accurately classified 62% of Abstainers and 80% of Resumers.

DISCUSSION

In this sample of predominately male Caucasian veterans, a combination of neurocognitive, psychiatric and MR-derived neurobiological variables were found to predict, with high accuracy, those who resumed alcohol consumption and those who maintained abstinence following completion of outpatient treatment for AUD. At ~1 month of abstinence from alcohol, decreasing levels of temporal GM NAA, frontal WM NAA, frontal GM Cho and processing speed, together with the presence of comorbid unipolar depression (at study entry), were significant predictors of resumed alcohol consumption. Combined, these predictors accurately classified 83% of Abstainers and 90% of Resumers into their respective groups, accounting for 72% of the variance in drinking status at follow-up. Taken together, the data suggest that the combination of these

variables are robust predictors of drinking status over 12 or more months after outpatient treatment in this cohort.

The clinical relevance of participant drinking status at follow-up is apparent in the higher psychosocial functioning in Abstainers compared to Resumers, as evidenced by the greater percentages of Abstainers who were gainfully employed, in long-term treatment and/or attending school at follow-up (see Table 5). Abstainers also reported an average of 764 days of continuous sobriety following outpatient treatment at the second follow-up (24 of 26 Abstainers who were successfully contacted). For the vast majority of Resumers, the magnitude and duration of their drinking episode(s) were more than a simple 'slip' and commensurate with their overall psychosocial functioning.

Long-term alcohol and substance use disorders promote enduring abnormalities in brain morphology, metabolism and biochemistry, most prominently in the midbrain, basal forebrain, basal ganglia, diencephalon, limbic system, and the frontal and mesial temporal lobes (Pfefferbaum *et al.*, 1998; Sullivan, 2000; Cami and Farre, 2003; Koob, 2003; Crews *et al.*, 2005; Kalivas and Volkow, 2005). These structures/regions are components of the reward circuit implicated in the development and maintenance of alcohol/substance use disorders [see Kalivas and Volkow (2005)]. Baler and Volkow (2006) suggest that chronic alcohol/substance abuse leads to prolonged plastic modifications in the functional connectivity of the reward circuit, which alters the ability of anterior dorsolateral and dorsomedial frontal regions to regulate other frontal and limbic structures/regions involved in motivation, drive and evaluation of stimulus salience. We observed that lower concentrations of temporal GM NAA, frontal WM NAA and frontal GM Cho at 1 month of abstinence were associated with increased risk for resumption of hazardous levels alcohol consumption. The significantly lower temporal GM NAA and frontal WM NAA demonstrated in Resumers relative to Abstainers at 1 month of abstinence may be indicative of morphological abnormalities of axons and neuroglia (Sullivan, 2000; Crews *et al.*, 2005; Harper *et al.*, 2005) and/or derangements of neurometabolism (De Stefano *et al.*, 1995; Hugg *et al.*, 1996; Moffett *et al.*, 2007). The ^{1}H MRSI Cho signal originates mainly from phosphocholine and glycerophosphocholine. Cho concentrations are thought to reflect cellular membrane turnover and density (Barker *et al.*, 1994; Miller *et al.*, 1996a) and/or myelin catabolism (Ross and Bluml, 2001). The lower frontal GM Cho concentration in Resumers at 1 month of abstinence suggests abnormalities in cell membrane synthesis/turnover of neuronal and/or glial tissue in that region. These regional metabolite findings are congruent with Noel and colleagues (2002), who reported lower frontal lobe cerebral blood flow in relapsers relative to individuals who remained abstinent 2 months after their initial assessment. At least 25–30% of our ^{1}H MRSI voxels covering the frontal lobes are spatially located in the anterior mesial (Brodmann areas 9, 10, 24, 32) and dorsolateral (Brodmann areas 9 and 10) frontal cortex, components of the anterior frontal-subcortical circuits implicated in emotional and behavioral regulation (Baler and Volkow, 2006). Virtually, none of our spectroscopic imaging voxels were spatially localized in mesial temporal (e.g. hippocampal complex) or basal forebrain regions/structures that are implicated in the development and maintenance of addiction. However, >30% of our temporal GM spectroscopic imaging voxels were localized in the insula, a temporal GM region implicated in decision making, assignment of emotional valence and cue-induced alcohol/substance craving (Bechara *et al.*, 1999; Paulus, 2007; Sinha and Li, 2007). Studies have reported morphological abnormalities in the insula of cocaine-dependent individuals (Franklin *et al.*, 2002) and chronic cigarette smokers (Gallinat *et al.*, 2006). Taken together, the lower temporal GM NAA, frontal WM NAA and frontal GM Cho seen in Resumers may reflect dysfunction of circuits involved in the modulation of internal drive states, mood and behavior, which may convey increased risk for resumed drinking.

In this study, participants who met DSM-IV criteria for a unipolar mood disorder at study enrollment (34%) had 14.5 times greater odds for relapse. Participants were either diagnosed with recurrent major depression or substance-induced (alcohol) mood disorder with depressive features. For each subtype, the depressive symptomatology was generally characterized by multiple episodes over several months to years during the participant's lifetime. There was a trend ($P = 0.10$) for a higher mean BDI in Resumers (9.9 ± 8.5) relative to Abstainers (6.5 ± 5.7) at 1 month of abstinence. However, the mean score of Resumers was just above the clinical cutoff of 9, indicating only a mild level of depressive symptomatology, and the BDI was not a significant predictor of relapse in this cohort. Approximately 30% of participants diagnosed with a unipolar mood disorder in both groups took an antidepressant at the time of the 1-month assessment. Outpatient substance abuse treatment, antidepressants, and any neurobiological and neurocognitive recovery during early recovery may have contributed to the low BDI scores at 1 month of abstinence in both the groups. Previous studies with treatment-seeking alcoholics indicated that higher BDI scores (Parsons *et al.*, 1990; Glenn and Parsons, 1991; Miller *et al.*, 1996b; Bottlender and Soyka, 2005; Kodl *et al.*, 2008), negative affect (Zywiak *et al.*, 2006) and endorsement of depressed mood (Strowig, 2000) were associated with greater risk for relapse. In this cohort, a diagnosis of a unipolar mood disorder at study entry predicted relapse, whereas the self-reported level of depressive symptomatology (via the BDI) at 1 month of abstinence was not a significant predictor. This finding may be related to a diagnosis of unipolar depression reflecting a chronic and recurrent neuropsychiatric condition in our participants, while the BDI represents the magnitude of depressive symptomatology over a 7-day period, which can be strongly influenced by recent life circumstances (Richter *et al.*, 1998). Both unipolar mood disorders and addiction evidence morphological, metabolic and neurotransmitter/neuromodulator abnormalities in similar brain regions (e.g. orbitofrontal, dorsolateral and ventromedial frontal lobes, anterior cingulate gyrus), as well as their WM connectivity with other cortical and subcortical regions/structures (e.g. basal ganglia, thalamus) (Drevets, 1999; Benes and Berretta, 2001; Deicken *et al.*, 2001; Wang *et al.*, 2001; Sheline, 2003; Kanner, 2004; Seminowicz *et al.*, 2004; Kalivas and Volkow, 2005; Baler and Volkow, 2006; Campbell and MacQueen, 2006; Yildiz-Yesiloglu and Ankerst, 2006; Hasler *et al.*, 2007). This is particularly apparent for circuits involved in affective expression/regulation and behavioral regulation. Enduring disturbances in these frontal GM regions, their WM connectivity and/or corresponding neurotransmitters may

decrease the ability to respond adaptively to common or significant psychosocial stressors, suppress alcohol cravings and/or attain/maintain a euthymic mood, thereby increasing the risk for relapse. Distinctions have been made between alcohol-induced unipolar depressive disorders and independent major depressive disorders with regard to onset, course, and persistence of symptoms following detoxification (Raimo and Schuckit, 1998; Verheul *et al.*, 2000; Kahler *et al.*, 2002). The small size of the subgroups with substance-induced and recurrent major depression, however, precluded their use as factors in our study models.

Lower processing speed at 1 month of abstinence was associated with a 14 times greater risk for relapse in this sample. Measures comprising the processing speed domain were Symbol Search and Digit Symbol from the WAIS-III, Color & Word trials of the Stroop Test and Trail Making Test-A. These measures involve visuomotor scanning, cognitive flexibility and incidental learning, where rapid and accurate responses lead to better performance. While frontal-subcortical circuitry likely contributes to the execution of these tasks (Cummings, 1998), multiple primary and heteromodal neocortical regions, subcortical nuclei, the cerebellum, and the WM interconnecting these regions/structures all contribute to the processing speed domain. Tapert and colleagues (2004) observed that the interactions of Trails A and Digit Symbol (measures of processing speed), with coping styles, predicted number of days of alcohol consumption following treatment. Previous studies found that worse performance on a composite measure of learning and memory, problem solving, abstraction and perceptual motor function was associated with relapse (Parsons *et al.*, 1990; Glenn and Parsons, 1991); however, in these studies depressive symptomatology, as measured by the BDI, was a stronger predictor of relapse than neurocognitive measures. In the present report, both lower processing speed and comorbid unipolar mood disorder were independent predictors of drinking status and both were associated with nearly the same increase of odds for relapse at follow-up. There were trends for Abstainers to have better executive skills ($P = 0.07$) and cognitive efficiency ($P = 0.10$) than Resumers at the 1-month assessment. Subtle deficiencies in these domains, in addition to processing speed, may interfere with the integration and/or practical application of skills presented in the participant's early recovery outpatient programs (Bates *et al.*, 2002; Tapert *et al.*, 2004).

Limitations of this study include the reliance on self-report and/or medical records for the determination of drinking status in some participants and the inability to examine sex effects due to the small number of female participants. We did not obtain measures of coping skills, self-esteem/self-efficacy, social support and personality disorders, which have been shown to predict drinking behavior after treatment. We were also unable to assess if the relapse risk associated with substance-induced depressive disorders is different from that imposed by recurrent major depression. It is also possible that the drinking behavior subsequent to treatment in this cohort was influenced by genetic or environmental factors not assessed in this report.

In summary, at the 1-month assessment, Resumers relative to Abstainers demonstrated lower metabolite concentrations in the frontal lobe and temporal GM, as well as lower processing speed, and a higher frequency of comorbid unipolar depression. Overall, this suggests that Resumers experienced abnormalities in anterior frontal-subcortical circuits that are involved in the development and maintenance of AUD, emotional processing, mood and behavioral regulation, and fast and flexible cognitive processes. Altered integrity of these circuits may have increased the risk of resumed alcohol consumption through a combination of factors, such as diminished coping skills, increased sensitivity to cue-induced cravings, deficient cognitive flexibility, decreased impulse control and chronically dysphoric mood. It is noteworthy that our Abstainers demonstrated a markedly higher level of psychosocial functioning than Resumers (which were comparable at enrollment), as evidenced by the considerably higher percentages of Abstainers who were gainfully employed, in long-term treatment and/or school at follow-up (see Table 5). Additionally, Abstainers reported >2 years of continuous sobriety following outpatient treatment at the second follow-up. This may be related to overall better neurobiological, neurocognitive and psychiatric functioning in our Abstainers relative to Resumers, as suggested by the pattern of group differences on these measures observed at 1 month of abstinence from alcohol. Our findings highlight the benefit of including MR-derived neurobiological measures in addition to the more conventional neurocognitive and psychiatric factors in the prediction of relapse following treatment. Given the indications from this and other studies that relapse in AUD may preferentially involve abnormalities in frontal- and temporal-subcortical circuitry implicated in the development and maintenance of substance use disorders [see Baler and Volkow (2006)], future neuroimaging research may wish to investigate separately those regions of the anterior frontal and mesial temporal regions, and their WM connectivity.

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