THE NEUROBIOLOGICAL AND NEUROCOGNITIVE CONSEQUENCES OF CHRONIC CIGARETTE SMOKING IN ALCOHOL USE DISORDERS

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Abstract — A vast body of research attests to the adverse effects of chronic smoking on cardiac, pulmonary, and vascular function as well as the increased risk for various forms of cancer. However, comparatively little is known about the effects of chronic smoking on human brain function. Although smoking rates have decreased in the developed world, they remain high in individuals with alcohol use disorders. Despite the high prevalence of comorbid chronic smoking in alcohol use disorders, very few studies have attempted to characterize the neurobiological or neurocognitive effects of chronic smoking in alcohol use disorders. Here, we briefly review the existing literature on the neurobiological and neurocognitive consequences of chronic cigarette smoking and summarize our neuroimaging and neurocognitive studies on the effects of comorbid chronic excessive alcohol consumption and cigarette smoking in treatment-seeking and treatment-naïve populations. Our research suggests comorbid chronic cigarette smoking modulates magnetic resonance-detectable brain injury and neurocognition in alcohol use disorders and that neurobiological recovery in our abstinent alcoholics is adversely affected by chronic smoking. Consideration of the potential separate effects and interactions of chronic smoking and alcohol consumption may foster a better understanding of specific mechanisms and neurocognitive consequences of brain injury in alcoholism and of brain recovery during sustained abstinence from alcohol. The material presented also contributes to ongoing discussions about treatment strategies for comorbid alcoholism and cigarette smoking and will hopefully stimulate further research into the neurobiological and neurocognitive consequences of chronic smoking in alcoholism and other substance use disorders.

INTRODUCTION

An extensive body of research indicates that chronic alcohol use disorders (i.e. alcohol abuse and dependence) are associated with abnormalities in brain morphology, cerebrovascular function, cortical glucose and amino acid metabolism, monoaminergic and cholinergic transmitter systems, cellular structure and function, regional cerebral blood flow and neurocognition (Oscar-Berman, 2000; Rourke and Loborg, 1996; Sullivan, 2000). In alcohol use disorders, the concurrent misuse of other substances (e.g. psychostimulants, cannabinoids) is well documented (Bjork et al., 2003; Degenhardt and Hall, 2003; Kampman et al., 2004). Therefore, it is possible that the neurobiological and neurocognitive abnormalities in alcohol use disorders may be, at least in part, due to, or compounded by, the concurrent use of other substances. The most frequently used substances among individuals with alcohol use disorders are tobacco products. Approximately 80% of alcohol-dependent individuals in North America are regular smokers (Hurt et al., 1994; Pomerleau et al., 1997; Romberger and Grant, 2004) and an estimated 50–90% of individuals seeking treatment for alcoholism are heavy smokers (Room, 2004). Several theories attempt to explain the concurrent heavy use of alcohol and tobacco products. It has been postulated that nicotine and alcohol potentiate each other’s rewarding properties (Narahashi et al., 2001; Rose et al., 2003; Barrett et al., 2006), which is supported by human and animal research demonstrating that nicotine increases voluntary alcohol intake (Le et al., 2003; Barrett et al., 2006). Others suggest that nicotine may counteract the adverse effects of alcohol on cognition and motor incoordination (Prendergast et al., 2002), or that paired use of nicotine and alcohol produce a conditioned cue reactivity, leading to cravings for both substances (Drobes, 2002). A genetic susceptibility for concurrent cigarette smoking and alcoholism has also been proposed (Madden and Heath, 2002; Wilhelmsen et al., 2005; Le et al., 2006).

In the United States, the mortality rate associated with cigarette smoking has been reported to be substantially greater than in alcohol-induced diseases (Hurt et al., 1996). Epidemiological research has indicated that mortality associated with chronic cigarette smoking is related to its adverse effects on cardiac and pulmonary function, central and peripheral vascular systems, as well as its carcinogenic properties (see Feeman, 1999; Bartal, 2001). Furthermore, a growing body of research suggests chronic smoking is associated with abnormalities in brain morphology, cerebral blood flow, neurochemistry, and neurocognition. Yet, the vast majority of previous research on alcohol use disorders did not consider the potential contribution of chronic smoking to the neurobiological and neurocognitive abnormalities reported. Consequently, it is presently unclear if chronic smoking influences the neurobiological and neurocognitive abnormalities typically reported for individuals afflicted with alcohol use disorders.

In early analyses of our neuroimaging and neurocognitive studies of alcohol-dependent individuals, primarily composed of US Armed Services Veterans in treatment, we consistently observed significant differences between smokers and non-smokers on many of our neuroimaging and neurocognitive measures. As chronic cigarette smoking is very common in this population, we postulated that the neurobiological and neurocognitive abnormalities observed in alcoholics might be, at least partially, attributable to the concurrent chronic smoking. Here, after a brief literature overview of the biological...
and neurocognitive consequences of chronic cigarette smoking, we review our neuroimaging and neurocognitive evidence of the adverse effects of chronic smoking on human brain neurobiology and function in our treatment-seeking and treatment-naive alcoholic samples.

NEUROBIOLOGICAL AND NEUROCOGNITIVE CONSEQUENCES OF CHRONIC SMOKING—LITERATURE REVIEW

Chronic smoking, independent of alcohol use disorders, has been linked to abnormalities in brain morphology, neurochemistry, cerebral blood flow as well as neurocognition. Chronic smokers compared to non-smokers demonstrated lower cortical gray matter volumes and densities in the prefrontal cortex, smaller left anterior cingulate volume, and lower gray matter densities in the right cerebellum (Brody et al., 2004), as well as increased generalized brain atrophy with advancing age (Hayee et al., 2003). Nicotine and/or cigarette smoking modulates brain gamma aminobutyric acid (GABA) concentrations in animals and humans (Zhu and Chiappinelli, 1999; Epperson et al., 2005). Proton magnetic resonance spectroscopy indicated cortical GABA concentrations were lower in female chronic smokers (and modulated by menstrual cycle phase), but GABA levels were not different in a small sample of male smokers relative to non-smokers (Epperson et al., 2005). Chronic smokers showed lower global cerebral blood flow and limbic system blood flow than non-smokers (Zubieta et al., 2001; Rose et al., 2003; Domino et al., 2004). Additionally, electrophysiological studies indicated that current and former smokers demonstrated diminished P300 amplitudes and hypoactivation of the anterior cingulate, orbital frontal and prefrontal cortices, compared to never smokers (Neuhaus et al., 2006).

While acute nicotine administration has been found to transiently improve some areas of cognition, most prominently on measures of sustained attention in healthy non-smokers (Sacco et al., 2004), a growing body of evidence suggests chronic cigarette smoking adversely affects both neurocognition and postural stability. Specific dysfunction among active chronic smokers has been reported in auditory-verbal learning and memory (Hill et al., 2003; Schinka et al., 2003), prospective memory (Heffernan et al., 2005), working memory (Spillich et al., 1992; Ernst et al., 2001), executive functions (Razani et al., 2004; Paul et al., 2006), visual search speeds (Richards et al., 2003), processing speed and cognitive flexibility (Kalnins et al., 2002), general intellectual abilities (Deary et al., 2003), and postural stability (Iki et al., 1994). In addition, adolescent daily smokers showed deficits in accuracy of working memory, with individuals who began smoking at a younger age demonstrating a greater level of impairment (Jacobsen et al., 2005). Furthermore, prospective longitudinal research with non-demented adults suggests that chronic cigarette smoking is associated with abnormal rates of decline of verbal memory in middle age (Richards et al., 2003) and general cognitive functioning in the elderly (Ott et al., 2004). Chronic smoking is also linked to increased risk for various forms of dementia, most notably Alzheimer’s disease (Ott et al., 1998; Launer et al., 1999; Merchant et al., 1999). It is apparent that the patterns of brain structural (Fein et al., 1990; Tivis et al., 1995; Oscar-Berman, 2000; Sullivan et al., 2000a; Sullivan et al., 2000b; Sullivan et al., 2003), brain perfusion (Nicolas et al., 1993; Mampunza et al., 1995; Demir et al., 2002) and neurocognitive (Fein et al., 1990; Tivis et al., 1995; Oscar-Berman, 2000) abnormalities reported for alcohol use disorders are very similar to those reported in chronic cigarette smokers (as described above).

Taken together, it appears that chronic cigarette smoking has similar effects on human brain morphology and neurocognition as chronic alcohol use disorders. Nevertheless, the neurobiological effects of chronic smoking were rarely considered in past neuroimaging or neurocognitive studies of individuals with alcohol use disorders. Thus, it is uncertain if the full extent of the neurobiological abnormalities reported in neuroimaging studies of alcohol use disorders are solely related to chronic, excessive alcohol consumption, or if concurrent chronic cigarette smoking contributes to the aberrations observed.

NEUROBIOLOGICAL AND NEUROCOGNITIVE CONSEQUENCES OF CHRONIC SMOKING IN ALCOHOL USE DISORDERS—A REVIEW OF OUR RESEARCH (see Table 1)

Characterization of alcohol use disorders cohorts

Treatment-seeking alcoholics. One-week abstinent alcoholics in treatment were retrospectively divided into chronic smokers and non-smokers based on self-report of smoking history at enrollment. In these cross-sectional studies, the smoking histories and non-smoking alcoholics groups were largely composed of Caucasian male, Armed Services Veterans, who were 50 ± 9 years of age, with 14 ± 2 years of education, and generally unemployed at the time of enrollment. Non-smoking and smoking light drinking control participants were recruited from the community. Inclusion criteria for treatment-seeking alcoholics required consumption of more than 150 alcoholic drinks per month (one standard alcohol containing drink equivalent = 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor, all corresponding to 13.6 grams pure alcohol) for at least 8 years prior to enrollment for men, and consumption of greater than 80 drinks per month for at least 6 years prior to enrollment for women. All treatment-seeking alcoholics met diagnostic and statistical manual for mental disorders, fourth edition (DSM-IV) criteria for alcohol dependence with physiological dependence. Primary exclusion criteria are fully detailed in Durazzo et al. (2004). In summary, all participants were free of general medical, neurological, and neuropsychiatric conditions known or suspected to influence neurocognition, except hepatitis C, hypertension and unipolar mood disorders. Current or past unipolar mood disorders (e.g. dysthymia, major depression, substance-induced unipolar mood disorder) were not exclusionary, given the reported high comorbidity with both alcoholism (Gilman and Abraham, 2001) and chronic cigarette smoking (Fergusson et al., 2003). Overall, both the smoking and non-smoking alcoholics groups manifested a similar frequency of concurrent unipolar mood disorders. No subject met criteria for substance
dependence in the 5 years prior to enrollment. With the exception of one participant who met DSM-IV criteria for current cannabis abuse, no other alcoholics met criteria for substance abuse in the 5 years prior to enrollment. Non-smoking alcoholics consumed approximately 200 drinks per month over lifetime, while smoking alcoholics consumed approximately 45% more drinks per month over lifetime than non-smoking alcoholics. Smoking alcoholics consumed approximately 20 cigarettes per day over about 20 years. All smoking alcoholics were actively smoking at all assessment points and were allowed to smoke ad libitum prior to magnetic resonance studies, and prior to and during neurocognitive assessment.

We quantified brain structure with high-resolution magnetic resonance imaging (MRI) (Gazdzinski et al., 2005), brain metabolite concentrations with proton magnetic resonance spectroscopic imaging (Durazzo et al., 2004), and brain blood flow with perfusion-weighted MRI using with pulsed arterial spin labeling (Gazdzinski et al., 2006). A brief neurocognitive battery, emphasizing processing speed, learning and memory and working memory was administered after approximately 1 month of sustained sobriety, a comprehensive neurocognitive battery

Table 1. Published magnetic resonance and neurocognitive studies of comorbid chronic alcohol use disorders and cigarette smoking from D.J. Meyerhoff lab

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Method</th>
<th>Primary findings</th>
</tr>
</thead>
</table>
| Durazzo et al., 2004 | 10 nsALC; 14 sALC; 19 nsLD; 7 sLD | H MRSI and brief neurocognitive battery at 1 week of abstinence from alcohol | — ALC associated with ↓ frontal NAA and Cho and ↓ parietal and thalamic Cho.  
— Smoking associated with ↓ midbrain NAA and Cho and ↓ cerebellar vermis Cho.  
— sALC vs. nsALC: 10% ↓ NAA in frontal WM; 15% ↓ NAA and 21% ↓ Cho in the midbrain.  
— sALC: greater nicotine dependence and higher # of cigarettes smoked per day negatively correlated with thalamic and lenticular NAA |
| Gazdzinski et al., 2005 | 13 nsALC; 24 sALC; 23 nsLD; 7 sLD | High-resolution 3D MRI and brief neurocognitive battery at 1 week of abstinence from alcohol | — ALC associated with ↓ parietal and temporal GM, and ↓ frontal and parietal WM  
— Smoking associated with ↓ parietal, temporal and occipital GM, and ↑ temporal and frontal WM  
— nsALC: visuospatial learning and memory positively correlated with temporal and occipital WM volumes  
— sALC: no significant structure-function relationships  
— sALC vs. nsLD: perfusion 19% ↓ in frontal GM and 12% ↓ in parietal GM  
— sALC vs. nsALC: perfusion 18% ↓ in frontal GM and 11% ↓ in parietal GM  
— nsALC vs. nsLD: no significant differences in GM perfusion  
— sALC: parietal GM perfusion inversely correlated with θ of cigarettes smoked per day |
| Gazdzinski et al., 2006 | 10 nsALC; 19 sALC; 19 nsLD | MR pulsed arterial spin labeling at 1 week of abstinence from alcohol | — sALC vs. nsLD: perfusion 19% ↓ in frontal GM and 12% ↓ in parietal GM  
— nsALC vs. nsLD: no significant differences in GM perfusion  
— sALC: no significant differences in GM volume differences  
— sALC: parietal GM perfusion inversely correlated with θ of cigarettes smoked per day |
| Durazzo et al., 2007 | 16 nsHD; 17 sHD; 20 nsLD | High-resolution 3D MRI; HD actively drinking at time of study | — sHD vs. nsLD: ↓ frontal, parietal, temporal and total GM  
— sHD vs. nsHD: ↓ temporal and total GM  
— nsHD vs. nsLD: no significant neocortical GM volume differences  
— sALC: parietal GM perfusion inversely correlated with θ of cigarettes smoked per day |
| Durazzo et al., 2006a | 11 nsALC; 14 sALC | Repeat 1H MRSI at 1 week and after 1 month of abstinence from alcohol; brief neurocognitive battery at 1 week of abstinence and comprehensive neurocognitive battery at 1 month of abstinence | — sALC over 1 month of abstinence: ↑ frontal WM NAA; ↑ Cho in frontal, parietal, temporal GM; ↑ Cho in frontal, parietal, temporal, occipital WM  
— sALC: ↑ frontal GM NAA; ↓ parietal and occipital WM NAA; ↑ frontal GM and WM Cho  
— sALC: improving visuospatial learning positively related to increasing frontal and occipital WM NAA; improving visuospatial learning, visuospatial memory and working memory, related to increasing thalamic NAA; improving visuospatial learning related to increasing frontal GM Cho  
— sALC: longer smoking duration related to decreasing frontal WM NAA, frontal WM Cho, and thalamic Cho. |
assessed functions known to be adversely affected by chronic alcoholism (Durazzo et al., 2006b) and proton magnetic resonance spectroscopic imaging procedures were repeated for longitudinal analyses (Durazzo et al., 2006a) at that time.

**Treatment-naïve hazardous drinkers.** Individuals seeking treatment for alcohol use disorders constitute only a small fraction of persons afflicted with chronic alcoholism in the developed world, yet most of what is known about the effects of chronic alcoholism on the human brain has been derived from volunteers recruited from inpatient or outpatient treatment programs. Information from treatment-naïve, actively drinking hazardous drinkers may be more relevant to the general Western population as the vast majority of individuals with alcohol use disorders are not in treatment. Our group observed abnormalities in regional brain metabolites (Meyерhoff et al., 2004), volumes (Cardenas et al., 2005) as well as neurocognition (Rothlind et al., 2005) in treatment-naïve hazardous drinkers. In these studies, the potential effects of chronic cigarette smoking were not considered. Therefore, in retrospective analyses, we divided our hazardous drinking participants into smokers and non-smokers, based on self-report of smoking history at enrollment. Smoking hazardous drinkers reported smoking daily or nearly every day. They were actively smoking at the time of study and allowed to smoke ad libitum prior to magnetic resonance scans and prior to and during neurocognitive assessment. Information regarding number of cigarettes smoked per day was not obtained in these earlier studies. The smoking and non-smoking hazardous drinker groups consisted primarily of Caucasian males, averaging 44 ± 10 years of age, with 14 ± 2 years of formal education. Classification as a hazardous drinker required an average consumption of at least 100 (80 for women) standard alcoholic drinks per month for a minimum of 3 years prior to enrollment and active alcohol consumption at time of study. Non-smoking hazardous drinkers consumed approximately 130 ± 80 drinks per month over lifetime. Smoking hazardous drinkers consumed approximately 45% more drinks per month over lifetime than non-smoking hazardous drinkers, which is consistent with the greater lifetime alcohol consumption we observed in our treatment-seeking, smoking alcoholics. Approximately 90% of hazardous drinkers participants met DSM-IV criteria for alcohol dependence and the remaining hazardous drinkers met criteria for alcohol abuse. Exclusion criteria are fully detailed in Cardenas et al. (2005). In short, all participants were free of general medical, neurological, and psychiatric conditions known or suspected to influence brain morphology. Participants were excluded if they met DSM-IV criteria for dependence on any other substance than alcohol or nicotine in the 6 months prior to enrollment and no hazardous drinker participant met criteria for abuse of other substances at the time of study.

**Cross-sectional quantitative MR studies in alcohol use disorders**

**Quantitative volumetric MRI in 1-week-abstinent, treatment-seeking alcoholics.** High-resolution 3D MRIs were acquired from 13 non-smoking alcoholics, 24 smoking alcoholics, 23 non-smoking light drinkers and light drinkers and 7 smoking light drinkers (Gazdzinski et al., 2005). Quantitative volumetric measures of neocortical gray matter, white matter, subcortical structures and sulcal and ventricular cerebral spinal fluid were derived from high-resolution T1-weighted magnetic resonance images as previously detailed (Cardenas et al., 2005). Regional brain volumes were converted to age-corrected z-scores based on the non-smoking light drinkers control group. Multivariate analysis of variance for all measured regions

### Table 1. (Continued)

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<td>Durazzo et al., 2005</td>
<td>20 nsHD, 13 sHD; 22 nsLD</td>
<td>Comprehensive neurocognitive battery; hazardous drinkers were actively drinking at time of study</td>
<td>—sHD: greater perseverative errors, perseverative responses, and total errors on WCST than both nsHD and nsLD. nsHD and nsLD not significantly different.</td>
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<tr>
<td>Durazzo et al., 2006b</td>
<td>20 nsALC; 22 sALC, from 1 month of abstinence from alcohol</td>
<td>nsALC superior to sALC on measures of auditory-verbal learning and memory, processing speed, cognitive efficiency, and static postural stability.</td>
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Note: ALC, alcohol dependence; Cho, choline-containing compounds; GM, gray matter; NAA, N-acetylaspartate; MR, magnetic resonance; MRI, magnetic resonance imaging; sALC, non-smoking treatment seeking alcoholic; sHD, non-smoking treatment-naïve hazardous drinker; sLD, non-smoking light drinking control; 3H MRSI, proton magnetic resonance spectroscopic imaging; sALC, smoking treatment seeking alcoholic; sHD, smoking treatment-naïve hazardous drinker; sLD, smoking light drinking control; WM, white matter; WCST, Wisconsin Card Sorting Test
yielded main effects for both alcohol dependence and smoking status. Follow-up analyses demonstrated significant alcohol effects for the parietal and temporal gray matter, with less gray matter in treatment-seeking alcoholics than light drinkers. Significant smoking effects were found for parietal, temporal, and occipital gray matter, where smokers demonstrated less gray matter in these regions than non-smokers. These effects remained significant after covarying for the greater lifetime alcohol consumption in smokers. Alcohol effects were also seen for the frontal white matter, and parietal white matter, with smaller white matter in alcoholics compared to light drinkers. Significant smoking effects were observed for the temporal white matter and a trend for frontal white matter were observed, with greater white matter volumes in smokers compared to non-smokers. Follow-up tests revealed that smoking alcoholics had significantly smaller neocortical gray matter volumes than non-smoking light drinkers in all four lobes, but non-smoking alcoholics and non-smoking light drinkers were not significantly different in gray matter volume in any lobe. Consistent with our findings in a treatment-naïve hazardous drinker cohort (see below), we observed strong trends for larger temporal and frontal white matter volume in smoking alcoholics compared to non-smoking alcoholics. These trends were apparent after controlling for the greater lifetime alcohol consumption in smoking alcoholics. For smoking alcoholics, visuospatial learning and memory were positively correlated with temporal white matter and occipital white matter volumes, whereas no significant structure-function relationships were observed for smoking alcoholics. This suggests that chronic smoking in recovering alcoholics may further disrupt alcohol-induced disturbances in functional neurocircuitry (Sullivan and Pfefferbaum, 2005) that subserves such abilities as learning and memory, executive skills and working memory. In this study, both chronic, excessive alcohol consumption and chronic smoking were associated with significant neocortical gray matter loss. The larger white matter volumes in smokers may reflect mild cytotoxic and/or vasogenic swelling secondary to smoking-induced alterations in mitochondrial function (Alonso et al., 2004) and/or vascular endothelial damage (Hawkins et al., 2002).

Quantitative volumetric MRI in treatment-naïve hazardous drinkers. We previously reported in Cardenas et al. (2005) that actively drinking hazardous drinkers demonstrated smaller regional neocortical gray matter volumes compared to light drinking controls; however, the potential effects of chronic cigarette smoking on regional brain volumes were not addressed in that report. From the 49 hazardous drinker participants in Cardenas et al. (2005), we identified 17 smoking hazardous drinkers who reported consistently smoking daily or nearly every day for at least 6 months prior to study enrollment and compared them to 16 non-smoking hazardous drinkers and 20 non-smoking light drinkers from the Cardenas et al. (2005) sample (Durazzo et al., 2007). All subjects were equivalent in age. Multivariate analyses yielded significant group differences for regional neocortical gray matter, and follow-up tests indicated smoking hazardous drinkers demonstrated significantly smaller volumes than non-smoking light drinkers in the frontal, parietal, temporal gray matter and for total neocortical gray matter. Notably, smoking hazardous drinkers had significantly smaller temporal and total gray matter volumes than non-smoking hazardous drinkers, whereas gray matter volumes in non-smoking hazardous drinkers did not differ significantly from those in non-smoking light drinkers. The smaller temporal and total gray matter volumes observed in smoking hazardous drinkers relative to non-smoking hazardous drinkers were apparent after covarying for greater lifetime alcohol consumption in smoking hazardous drinkers. The groups did not differ significantly on lobar white matter, subcortical structure or cerebrospinal fluid volumes; however, we found trends for larger white matter volumes in smoking hazardous drinkers relative to non-smoking hazardous drinkers, which is consistent with the volumetric findings in our treatment-seeking alcoholics (see Section in Quantitative volumetric MRI in 1-week-abstinent, treatment-seeking alcoholics). The absence of cortical gray matter volume differences between the non-smoking hazardous drinkers and non-smoking light drinkers groups in this study is consistent with our volumetric findings in 1-week abstinent non-smoking alcoholics (Gazdzinski et al., 2005). The non-smoking treatment-seeking alcoholics in Gazdzinski et al., 2005 consumed nearly three times as much ethanol (in kilograms) over lifetime than our non-smoking hazardous drinkers and nearly twice as much as smoking hazardous drinkers, yet they still did not show significant neocortical gray matter volume reductions in any lobar region relative to non-smoking light drinkers. 

Quantitative metabolite imaging in1-week-abstinent, treatment-seeking alcoholics. Ten non-smoking alcoholics, 14 smoking alcoholics, 19 non-smoking light drinkers and 7 smoking light drinkers were compared on levels of common brain metabolites in gray matter and white matter of the four neocortical lobes, basal ganglia, midbrain and cerebellar vermis, obtained via short-echo time, multislice proton magnetic resonance spectroscopic imaging (Durazzo et al., 2004). Concentrations of N-acetylaspartate (a surrogate marker of neuronal viability), choline-containing compounds (choline; a marker of cell membrane synthesis/turnover), and other metabolites were derived from spectra measured in three parallel planes through the centrum semiovale, basal ganglia, and cerebellar vermis. Regional atrophy-corrected metabolite concentrations were calculated by combining proton magnetic resonance spectroscopic imaging and segmented MRI data (Meyerhoff et al., 2004). Analysis of covariance, with age as a covariate, indicated that chronic alcohol dependence, independent of smoking, was associated with lower frontal N-acetylaspartate and choline levels, as well as lower parietal and thalamic choline. Chronic cigarette smoking was associated with lower midbrain N-acetylaspartate and choline and with lower cerebellar vermis choline. The smoking alcoholics group compared to the non-smoking alcoholics group demonstrated 10% lower N-acetylaspartate concentrations in the frontal white matter and 15% lower N-acetylaspartate and 21% lower choline in the midbrain. In addition, smoking alcoholics showed trends to lower N-acetylaspartate in the parietal gray matter and lenticular nuclei relative to non-smoking alcoholics. The regional metabolite concentration differences between smoking alcoholics and non-smoking alcoholics remained significant after controlling for the greater lifetime alcohol consumption in smoking alcoholics. Numerically, smoking alcoholics evidenced the lowest N-acetylaspartate and choline levels of all four groups in virtually all regions.
measured. In non-smoking alcoholics, cerebellar vermis \textit{N}-acetylaspartate was positively related to visuospatial learning and visuospatial memory, whereas in smoking alcoholics, cerebellar vermis \textit{N}-acetylaspartate was positively related to visuomotor scanning speed and incidental learning. In smoking alcoholics, higher nicotine dependence and number of cigarettes smoked per day were negatively correlated with thalamic and lenticular \textit{N}-acetylaspartate levels. Thus, chronic smoking in 1-week-abstinent treatment-seeking alcoholics was associated with greater metabolite abnormalities in a 'dose'-dependent manner. Overall, our results suggest that cigarette smoking had independent \textit{and} additive adverse effects on regional brain metabolites, in particular on markers of neuronal viability and cellular membrane turnover/synthesis.

Quantitative brain blood flow in 1-week-abstinent, treatment-seeking alcoholics. Ten non-smoking alcoholics, 19 smoking alcoholics and 19 non-smoking light drinkers, matched on age, were compared on regional neocortical gray matter blood flow (Gazdzinski et al., 2006) using a non-invasive pulsed arterial spin labeling method that imaged primarily the frontal and parietal lobes (Jahng et al., 2003; Gazdzinski et al., 2006). Multivariate analyses indicated significant group differences for perfusion in both frontal and parietal gray matter. Follow up univariate tests indicated frontal gray matter perfusion in smoking alcoholics was 18% lower than non-smoking alcoholics and 19% lower than non-smoking light drinkers. Parietal gray matter perfusion in smoking alcoholics was 11% lower than in non-smoking alcoholics and 12% lower than non-smoking light drinkers. The regional perfusion differences between smoking alcoholics and non-smoking alcoholics remained significant after controlling for the greater lifetime alcohol consumption in smoking alcoholics. Gray matter perfusion was similar in non-smoking alcoholics and non-smoking light smokers. Parietal gray matter perfusion in smoking alcoholics was inversely correlated with the number of cigarettes smoked per day. There was no relationship between the interval of last cigarette smoked and frontal or parietal gray matter perfusion in smoking alcoholics. This suggests that the chronic effects of cigarette smoking, rather than the acute effects of nicotine exposure or withdrawal, modulated brain perfusion in our treatment-seeking alcoholics, which is consistent with results of previous research of heavy smoking alcoholics, without consideration of smoking status, demonstrated poorer performance on measures of working memory, balance, and executive function than non-smoking light drinkers (Rothlind et al., 2005), which is generally consistent with results of previous review of heavy social drinkers (see Parsons 1998; Parsons and Nixon, 1998 for review). However, these previous studies did not assess the potential effects of chronic smoking on neurocognition in this population. Therefore, we compared 20 non-smoking hazardous drinkers, 13 smoking hazardous drinkers, and 22 non-smoking light drinkers from Rothlind et al. (2005) on measures of executive function, processing speed, learning and memory, and working memory (Durazzo et al., 2005). All participants were matched on age and education. Multivariate analyses indicated groups were different on the Wisconsin Card Sorting Test, where both non-smoking light drinkers and non-smoking hazardous drinkers made fewer perseverative errors, perseverative responses, and total errors than smoking hazardous drinkers. Groups also differed on the Fregly Sharpened Romberg (a measure of static postural stability), where non-smoking light drinkers performed better than both smoking hazardous drinkers and non-smoking hazardous drinkers, and non-smoking hazardous drinkers performed better than smoking hazardous drinkers. Group differences between smoking hazardous drinkers and non-smoking hazardous drinkers remained significant after covarying for greater lifetime alcohol consumption in smoking hazardous drinkers. These findings suggest that in hazardous drinkers,
chronic cigarette smoking may account for a significant proportion of the executive dysfunction and balance previously attributed solely to heavy alcohol consumption (e.g. Rothblind et al., 2005). As in our treatment-seeking alcoholic consideration of the effects of smoking on neurocognition and postural stability appears to be warranted in treatment-naïve hazardous drinkers.

EFFECTS OF CHRONIC SMOKING ON NEUROBIOLOGICAL AND NEUROCOGNITIVE RECOVERY DURING ABSTINENCE FROM ALCOHOL

Quantitative morphometric MRI in treatment-seeking alcoholics

Deformation based morphometry is a brain shape analysis method that, in our application, employs robust fluid registration of serial structural MRIs to illuminate and quantitate brain tissue and cerebrospinal fluid changes over time. We applied this method to serial MRIs obtained in 17 treatment-seeking alcoholics, who had sustained approximately 7 months of abstinence from alcohol, compared to eight treatment-seeking alcoholics, who had relapsed before repeat MRI. We observed that tissue volume recovery in alcoholics occurs primarily in the frontal white matter, subcortical nuclei, pons, cerebellum, hippocampi and sections of the corpus callosum (Cardenas et al., 2007). Furthermore, our deformation based morphometry analyses clearly indicated that chronic cigarette smoking influenced the volume recovery during sustained abstinence from alcohol. Specifically, these preliminary analyses indicated that abstinent smoking alcoholics had significantly lower tissue volume recovery rate than abstinent non-smoking alcoholics in the left anterior hippocampus/amygdala region, with trends for lower volume recovery rate in smoking alcoholics in frontal and temporal gray matter. Results also showed that greater nicotine dependence and longer smoking duration in smoking alcoholics were related to slower tissue recovery over 7 months of sobriety in regions of the corpus callosum, basal ganglia and frontal lobe.

Longitudinal metabolite imaging in treatment-seeking alcoholics

Eleven non-smoking alcoholics and 14 smoking alcoholics were studied 6 ± 3 days after consumption of their last drink (as described above) and again at 34 ± 10 days of abstinence from alcohol (Durazzo et al., 2006a). Repeated measures analysis of variance indicated that the non-smoking alcoholics group showed significant increases in frontal white matter N-acetylaspartate (+8%) and choline in the frontal (+14%), parietal (+12%) and temporal (+8%) gray matter over 1 month of abstinence from alcohol. Significant choline increases were also observed for non-smoking alcoholics in the white matter of the frontal (+16%), parietal (+17%), temporal (+7%), and occipital (+13%) lobes. In smoking alcoholics, over 1 month of abstinence from alcohol, N-acetylaspartate concentrations increased only in the frontal gray matter (+5%), while N-acetylaspartate significantly decreased in the parietal white matter and occipital white matter (both — 6%). For smoking alcoholics, choline increased in the frontal gray matter (+8%) and frontal white matter (+11%). Overall, smoking alcoholics demonstrated numerically smaller and fewer regional increases of N-acetylaspartate and choline concentrations over 1 month of abstinence than non-smoking alcoholics. The non-smoking alcoholic group showed many significant relationships between changes of metabolite levels and neurocognition, attesting to the functional relevance of brain metabolite changes. Specifically, in non-smoking alcoholics, improvements in visuospatial learning were related to increases of frontal white matter N-acetylaspartate and occipital white matter N-acetylaspartate; increases of parietal gray matter N-acetylaspartate correlated with improvements of visuomotor scanning speed and incidental learning; increases of thalamic N-acetylaspartate were related to improving visuospatial learning, visuospatial memory and working memory; improving visuospatial learning also correlated with increasing frontal gray matter choline, frontal white matter choline and thalamic choline. For smoking alcoholics, the only significant relationships were between increasing midbrain N-acetylaspartate and improving visuospatial learning, and between increasing caudate N-acetylaspartate and improving visuospatial memory. In smoking alcoholics, longer smoking duration was related to lower longitudinal increases in frontal white matter N-acetylaspartate (see Fig. 2), frontal white matter choline, and thalamic choline.

We also investigated volumetric changes in the hippocampus and changes in medial temporal lobe metabolite concentrations over 1 month of abstinence in 13 smoking alcoholics and 11 non-smoking alcoholics. Over 1 month of sobriety, medial temporal lobe N-acetylaspartate and choline levels in non-smoking alcoholics significantly increased and normalized to non-smoking light drinkers levels. However, in smoking alcoholics, N-acetylaspartate and choline concentrations did not change significantly and remained depressed relative to non-smoking light drinkers. Increased N-acetylaspartate and choline levels in both non-smoking and smoking alcoholics were associated with improvements in visuospatial memory. Hippocampal volumes significantly increased in both groups over 1 month of abstinence from alcohol, but
or metabolism of neural and glial tissue, particularly that with potentially diminished cardiopulmonary function or cerebrovascular integrity, in combination with potentially diminished cardiopulmonary function or cerebrovascular integrity, may adversely affect the morphology or metabolism of neural and glial tissue, particularly that comprising the frontal-striatal-thalamic circuitry. Potentially greater modulation of brain tissue comprising frontal-striatal-thalamic circuitry in smokers is suggested by the pattern of neuroimaging and neurocognitive findings in both alcoholic (Durazzo et al., 2004, 2005, 2006a, 2006b, 2007; Friend et al., 2005; Glass et al., 2006; Gazdzinski et al., 2006) and non-alcoholic (Spilich et al., 1992; Ernst et al., 2001; Kalmijn et al., 2002; Brody et al., 2004; Razani et al., 2004; Brody, 2006; Paul et al., 2006) chronic smokers. Therefore, a combination of chronically increased CO levels, chronic exposure to reactive oxygen species from both ethanol metabolism and cigarette smoke, and potentially compromised vascular and pulmonary function may all contribute to the greater neurobiological abnormalities and lower cognitive performance we observe in our smoking alcoholics and smoking hazardous drinkers cohorts. Furthermore, chronic smoking may influence some aspects of neurocognition through modulation of regional monoaminergic, cholinergic, glutamatergic and GABAergic activity (see Bonvento et al., 2003; Das, 2003; Pitsikas et al., 2003; Brody, 2006).

Thus, it is possible that the functional integrity of frontal-striatal-thalamic neural networks (see Mega and Cummings, 1994) is further altered in smoking alcoholics relative to their non-smoking counterparts. Finally, it is feasible that the brain regions adversely affected in alcohol use disorders (e.g. neocortical gray matter) are rendered more vulnerable to the effects of the potentially noxious compounds found in cigarette smoke (or vice-versa).

Acute effects of nicotine
When investigating chronic cigarette smoking-induced neurobiological and neurocognitive dysfunction, independently or in conjunction with alcohol use disorders and other conditions, it is important to distinguish between the effects of acute nicotine ingestion/intoxication and withdrawal and the consequences of chronic exposure to the multitude of noxious compounds contained in cigarette smoke. Acute nicotine administration has been found to transiently improve some areas of neurocognition, most appreciably on measures of sustained attention, primarily in healthy non-smokers and individuals with attention deficit hyperactivity disorder and schizophrenia-spectrum disorders (see Rezvani and Levin, 2001; Sacco et al., 2004; Brody, 2006 for review). The half-life of nicotine in humans is approximately 2–3 h (Nakajima and Yoko, 2005), and the adverse effects of nicotine withdrawal on aspects of neurocognition may not be apparent for 12 h or longer (for review see Sacco et al., 2004). With respect to our neurocognitive studies, all of our smoking participants were allowed to smoke ad libitum prior to and during the 2–2.5 h neurocognitive assessment; therefore, our findings were not likely a function of nicotine withdrawal. However, the effects of acute nicotine administration on neurocognition in smoking alcoholics and other substance abusers are not clear (see Ceballos et al., 2006).

A few functional MRI studies have investigated the acute effects of nicotine administration on brain activity during task performance in healthy non-smokers (e.g. Kumari et al., 2000).
2003; Thiel et al., 2005). Results suggested that, depending on the nature of the task, acute nicotine administration was associated with increased blood oxygenation level-dependent Blood Oxygenation Level-Dependent (BOLD) brain activity and improved performance (Thiel et al., 2005) or decreased BOLD activity and improved performance (Kumari et al., 2003). The effects of acute cigarette smoking on functional imaging measures (in resting conditions or during task activation) in healthy non-smokers have yet to be reported (Brody, 2006). In chronic smokers deprived of tobacco for more than 2 h, acute cigarette smoking elicits different patterns of relative perfusion responses, with increases of the order of 6–8% in a number of brain regions including prefrontal and cingulate cortices as well as decreases in cerebellum and occipital lobes that were associated with plasma nicotine levels (Rose et al., 2003; Domino et al., 2004; Brody, 2006). With respect to cerebral blood flow and glucose metabolism some studies report a 7–10% decrease in global glucose utilization following acute nicotine administration in chronic smokers deprived from nicotine for 8 h or more (Domino et al., 2000; Stapleton et al., 2003). Thus, the effects of acute nicotine administration and acute cigarette smoking on functional imaging measures and neurocognition appear to depend on the extent of nicotine deprivation, the brain region studied, resting versus activation conditions, and the neurocognitive domain investigated (Brody, 2006).

SUMMARY AND CONCLUSIONS

Although smoking rates in the general population of United States has decreased over the last three decades, smoking prevalence remains high especially among the economically disadvantaged (Jha et al., 2006) and individuals with alcohol, substance use and other neuropsychiatric disorders (e.g. schizophrenia-spectrum disorders, mood disorders) (Ferguson et al., 2003; Dani and Harris, 2005; Esterberg and Compton, 2005; Patkar et al., 2006). Our cross-sectional MR findings suggest that chronic cigarette smoking in alcohol use disorders is associated with regional neocortical gray matter volume loss, and smoking is linked to a significant (and possibly pathological) increase in temporal white matter volume. Chronic smoking in alcohol use disorders is also associated with perfusion abnormalities in the frontal and parietal gray matter and appears to compound alcohol-induced neuronal injury and cell membrane dysfunction in the frontal lobes and midbrain. Taken together, our cross-sectional quantitative volumetric and blood flow studies suggest that chronic excessive alcohol consumption per se was not associated with significant abnormalities in neocortical gray matter morphology and perfusion in our alcohol use disorder cohorts; rather the combination of chronic alcohol misuse and cigarette smoking resulted in significant volume loss and diminished blood flow in the neocortical gray matter relative to non-smoking controls. Similarly, our quantitative proton magnetic resonance spectroscopic imaging results suggest the combination of chronic excessive alcohol consumption and cigarette smoking was associated with the greatest abnormalities in markers of neuronal viability and cell membrane synthesis/turnover. Our longitudinal findings suggest that chronic smoking in alcohol use disorders adversely affected recuperation of regional biochemical markers of neuronal viability and cell membrane synthesis/turnover during short-term abstinence as well as recovery of brain volume with sustained abstinence from alcohol.

The significant relationships between magnetic resonance measures and neurocognitive tests from both cross-sectional and longitudinal MR studies indicate that our magnetic resonance-derived neurobiological measures are robust predictors of brain function. Consistent with the greater neuropsychologic, metabolic and blood flow abnormalities in the neocortex and frontal-subcortical circuits we observed in alcohol use disordered smokers versus non-smokers, the smoking treatment-seeking alcoholics cohort demonstrated inferior performance on measures of auditory-verbal learning and memory, processing speed, cognitive efficiency and static postural stability, and treatment-naïve smoking hazardous drinker exhibited poorer performance on measures of executive function relative to their non-smoking counterparts. Our neurocognitive findings are consistent with those of Glass and colleagues (Glass et al., 2006) who observed that higher smoking and drinking severity was inversely related to measures of general intelligence and cognitive efficiency, but only smoking severity individually predicted both general intelligence and cognitive efficiency. Our results are also consistent with Friend et al. (2005) who reported that the combination of chronic alcoholism and smoking predicted poorer performance on measures of set-shifting and processing speed and observed that non-smoking alcoholics performed superior to smoking alcoholics on tasks measuring set-shifting and processing speed. Our morphological, metabolite and perfusion studies along with the neurocognitive findings of others (i.e. Friend et al., 2005; Glass et al., 2006) suggest that chronic smoking in alcohol use disorders may further compromise alcohol-induced disturbances in frontal-subcortical neurocircuitry (Sullivan and Pfefferbaum, 2005), thereby modulating relationships between magnetic resonance-derived neurobiological measures and neurocognition.

The brain morphological, metabolite, blood flow and neurocognitive abnormalities observed in our smoking alcoholic cohorts may be related to chronic exposure to the numerous sources of oxidative stress and other noxious compounds found in cigarette smoke. Additionally, smoking-induced deficiencies in cardiovascular, pulmonary or cerebrovascular integrity may contribute to our findings, particularly in individuals with a longer history of smoking. Although we attempted to control for factors (e.g. age, drinking severity) that may have influenced our dependent measures, it is possible that the greater neurobiological and neurocognitive abnormalities demonstrated by our alcoholic smokers are at least partially related to potential unrecorded differences in nutrition, exercise, overall physical health, exposure to environmental cigarette smoke or to genetic predispositions/vulnerabilities.

Overall, our studies with treatment-seeking and treatment-naïve cohorts demonstrate converging lines of evidence that suggest chronic cigarette smoking adversely affects both brain neurobiology and neurocognition in alcohol use disorders, thus contributing to the growing body of literature linking chronic smoking to brain injury and dysfunction. Examining alcoholics as a homogeneous group, without...
consideration of smoking status, may obscure the ability of magnetic resonance-derived neurobiological measures to serve as useful surrogate markers of brain function as well as neurocognitive studies to accurately delineate the functional consequences of alcohol use disorders. As most of our results were obtained retrospectively, additional prospective research, with larger groups that include greater numbers of females, is required to confirm our findings and evaluate for sex effects, particularly since it is unclear if males and females manifest the same degree or pattern of alcohol-induced neurobiological and neurocognitive abnormalities (Mann et al., 1992; Parsons, 1998; Rosenbloom et al., 2004). If chronic cigarette smoking does indeed modulate brain neurobiology and neuroognition, it is possible that smoking and non-smoking alcoholics may differ in the nature or extent of their response to pharmacological and/or behavioral interventions designed to promote abstinence from alcohol. Our findings, in conjunction with the known mortality and morbidity associated with chronic smoking, lend support to the growing clinical initiative that encourages chronic smokers entering treatment for substance use disorders to participate in a smoking cessation program (see Romberger and Grant, 2004 for review). At the very least, our preliminary results suggest that the effects of concurrent chronic cigarette smoking should be considered in future studies investigating the consequences of alcohol use disorders on neurobiology and neurocognition and their recoveries during abstinence, as well as in research of other neuropsychiatric conditions in which chronic cigarette smoking is prevalent (e.g. mood and schizophrenia-spectrum disorders).

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