Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism

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1. ABSTRACT

Chronic cigarette smoking is associated with adverse effects on cardiac, pulmonary, and vascular function as well as the increased risk for various forms of cancer. However, 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 (AUD) and other neuropsychiatric conditions. Despite the high prevalence of chronic smoking in AUD, few studies have addressed the potential neurobiological or neurocognitive consequences of chronic smoking in alcohol use disorders. Here, we review the the neurobiological and neurocognitive findings in both AUD and chronic cigarette smoking, followed by a review of the effects of comorbid cigarette smoking on neurobiology and neurocognition in AUD. Recent research suggests that comorbid chronic cigarette smoking modulates magnetic resonance-detectable brain injury and neurocognition in alcohol use disorders and adversely affects neurobiological and neurocognitive recovery in abstinent alcoholics.. Consideration of the potential separate and interactive effects of chronic smoking and alcohol use disorders may have significant implications for pharmacological and behavioral treatment interventions.
2. INTRODUCTION

The designation of an alcohol use disorder (AUD) refers to the constellation of symptoms manifested by individuals afflicted with alcohol abuse or dependence. The adverse effects of AUD on human brain morphology, blood flow, metabolism, and neurocognition are well documented in the biomedical literature. In AUD, the concurrent use of other substances, such as psychoactive drugs (e.g., cocaine and methamphetamine) and tobacco, is common, with tobacco products being the most frequently consumed substances in this population. The majority of individuals with AUD smoke regularly and many are nicotine dependent. The separate and combined effects of comorbid psychostimulant and cannabinoid misuse on brain structure, metabolite levels and neurocognition in persons with AUD have been investigated. Chronic cigarette smoking alone is associated with abnormalities in brain structure, brain perfusion and neurocognition that are similar in type and pattern to those reported in AUD. However, despite the high percentage (50-90%) of chronic cigarette smokers in AUD, the combined effects of smoking and chronic and excessive alcohol consumption on central nervous system function have received little attention. Thus, the brain injury and the neurocognitive and/or motor dysfunction seen in AUD may have received little attention. Thus, the brain injury and the neurocognitive and/or motor dysfunction seen in AUD may have received little attention.

2.1. Neuropathological findings

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3. NEUROBIOLOGICAL AND NEUROCOGNITIVE CONSEQUENCES OF CHRONIC ALCOHOL USE DISORDERS

3.1. Neuropathological findings

Post mortem examinations of individuals with uncomplicated AUD indicate neuronal loss occurs primarily in the dorsolateral frontal cortex, hypothalamus and cerebellum, with the hippocampi showing glial rather than neuronal loss (7-10). According to a general model by Harper and Kril (11), alcohol-related cortical brain damage falls in two classes. The first class includes loss of dendritic arbor and shrinkage of neuronal cell body volume. The second class is neuronal death and Wallerian degeneration of myelinated axons, which is irreversible [e.g., (12)] and was observed primarily in frontal lobe. Expansion of the dendritic arbor and increased neuronal soma volume may occur with abstinence lead to increased tissue density, particularly in the neocortical and subcortical gray matter. Dlugos and Pentney (13), for example, showed that the dendritic arbor of rat Purkinje neurons recover with abstinence. Several mechanisms have been proposed to explain how chronic and excessive alcohol consumption promotes injury to brain tissue and neurocognitive dysfunction. They include (but are not limited to): glutamate and homocysteine-induced excitotoxicity, reduced levels of neurotrophic factors (e.g., brain derived neurotrophic factor), increased oxidative stress, thiamine and other nutritional deficiencies, increased acetaldehyde and aldehydes levels, and hepatic dysfunction (14-20). Excitotoxicity has been suggested to be most prominent during withdrawal from alcohol (21-23). These potential mechanisms may work independently or concert to compromise various cellular structures or organelles, membrane phospholipids, myelin, DNA, gene expression, protein synthesis and cellular respiration (14-17, 24).

3.2. Neuroimaging findings

3.2.1. Structural neuroimaging: computerized tomography, magnetic resonance imaging and diffusion tensor imaging

Computerized tomography (CT) and magnetic resonance imaging (MRI) studies of AUD have consistently demonstrated widespread morphological abnormalities involving increased sulcal cerebrospinal fluid (CSF) volume (25, 26) and brain tissue loss in neocortical gray matter (GM) (3, 27-30) and white matter (WM) (31-33). These morphological abnormalities are generally most pronounced in the frontal lobes (3, 34-36), medial temporal structures (37-39), corpus callosum (35, 40-42), and the cerebellum (43-46). Volume reductions in the mammillary body, basal ganglia nuclei and nucleus accumbens are also reported (47-49). The morphological abnormalities observed in AUD neuroimaging studies are generally consistent with post-mortem neuropathological findings (11, 28, 52). Abstinence from alcohol has been associated with decreases of ventricular and sulcal CSF volume (53-55) and increases of neocortical GM (47), WM (56) and whole brain volumes (57, 58) over approximately 1 to 3 months of abstinence. With long-term sustained abstinence (greater than 12 months), significant decreases in sulcal and subcortical CSF volumes (59, 60), and increases in regional WM and neocortical GM volumes are reported (61). Regional volume recovery may be most rapid in the first 1 to 3 months of abstinence (50, 53, 55, 58), and relapse appears to arrest volumetric recovery or may promote further regional volumetric loss (55, 57, 62). In AUD with variable lengths of sobriety, regional lobar WM and 3rd ventricle volumes were associated with learning and memory (50, 62), regional cerebellar volumes predicted non-motor functions such as learning and executive functions (51), and striatal and forebrain nuclei volumes were related to working memory (47). Age effects should be considered in cross-sectional and longitudinal structural neuroimaging studies of AUD samples, as regional brain morphological derangements observed in AUD are compounded by increasing age (26, 42, 63). It is noteworthy that greater than normal brain atrophy (irrespective of etiology) is associated with greater risk for cognitive decline and memory impairment with increasing age (64, 65).
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Diffusion Tensor Imaging (DTI) assesses the random motion of water within and between cells and yields measures of the magnitude (via mean diffusivity, MD) and predominant orientation (via fractional anisotropy, FA) of this motion within WM tracts. In the absence of frank macrostructural abnormalities, DTI is thought to be sensitive to microstructural (or ultrastructural) abnormalities in WM such as Wallerian degeneration (axonal deterioration), myelin loss, and enlargement of microtubules, gliosis, and degeneration of membranes (66-69). DTI has been applied to the examination of neocortical and subcortical nuclei GM, but the ability to this approach to assess the integrity of GM is still developing (Thus, DTI measures may reflect axonal and myelin integrity, particularly of association, projection and callosal pathways that are components of functional neural circuits that subserve various aspects of neurocognition. Disruption of such neural circuitry can result in impaired neurocognitive functioning (27, 66, 70-72). In alcoholics, lower FA, lower fiber coherence, and larger MD were detected in the genu, body, and splenium of the corpus callosum, as well as in the centrum semiovale (73, 74). These microstructural abnormalities may precede CT or MRI detectable brain atrophy (Pfefferbaum and Sullivan, 2002). In AUD DTI measures were related to performance on measures of attention and working memory (75), as well as interhemispheric transfer (74), and callosal FA correlated with processing speed in young adults with fetal alcohol syndrome (76). Animal studies showed that DTI may differentiate demyelination from axonal loss (68, 77, 78); demyelination is associated with larger diffusion perpendicular to fibers with no differences in parallel diffusivity, suggesting that radial diffusivity is sensitive to remyelination, whereas changes in axial diffusivity reflect primarily axonal injury. Finally, most publications so far reported region of interest analyses of DTI data, but the use of tractography (79, 80) in alcoholism to probe neural connections is being explored.

3.2.2. Magnetic resonance spectroscopy and spectroscopic imaging

Magnetic resonance spectroscopy (MRS) enables the measurement of aspects of alcohol-induced brain injury that may accompany or precede alcohol-induced morphological changes. Proton MRS (1H MRS) allows non-invasive and concurrent quantitation of several brain metabolites from most brain regions. N-acetylaspartate (NAA) is an amino acid that is found in high concentrations in axons and dendrites of neurons, particularly in pyramidal neurons (81, 82) and is virtually absent in mature glial cells (81). MRS derived NAA concentration is thought to reflect neuronal viability (83) with decreased levels reflecting neuronal loss, atrophied dendrites and/or axons, or demagengements of neurometabolism (84-86). The 1H MRS signal from choline-containing metabolites (Cho), which includes choline, phosphocholine and glycerophosphocholine, reflects compounds primarily involved in cell membrane breakdown and/or synthesis (87) and may reflect cellular membrane turnover and density (88), and/or catabolism of myelin (89). In its bioactive form, myo-inositol (mI) is a constituent of phosphatidylinositol, an important component of the phospholipid bilayer that constitutes all eukaryotic cell membranes. mI is also suggested to be an astrocyte marker (90) and/or an osmolyte (91). The signal from creatine-containing metabolites (Cr) corresponds to the sum of concentrations of intracellular creatine and phosphocreatine (PCr), both of which are involved in the bioenergetics of neuronal and glial tissue (92).

The first cross-sectional 1H MRS study to suggest residual neuronal injury in the frontal cortex of abstinent alcoholics employed spectroscopic imaging (1H MRSI), a method allowing the simultaneous acquisition of spectra from many voxels within a selected brain region (93). Subsequent research in actively drinking AUD found lower frontal WM and parietal GM NAA levels and elevated Cr in the parietal GM (94). Lower NAA concentrations in AUD were associated with poorer performances on measures of executive skills and working memory as well as lower frontal P300b amplitudes. Single-volume 1H MRS studies measured metabolites primarily in the frontal lobes and cerebellum of recovering alcoholics after 3 to 40 days of sobriety. These studies reported depressed NAA in the frontal lobes (95, 96), thalamus (96), and cerebellum (97, 98) of AUD suggesting neuronal injury, atrophied dendeites and/or axons, or derangement of metabolism. Other studies reported lower cerebellar Cho (85, 87) and elevated thalamic mI (91) relative to light-drinking controls. Lower concentrations of NAA in frontal white matter and of NAA, Cho, and mI in the cerebellum correlated with lower neurocognitive and motor functioning [e.g., (95, 97)].

Longitudinal 1H MRS studies investigating the recovery of brain tissue metabolites in short-term abstinent alcoholics focused primarily on the frontal lobes and cerebellum. Martin and colleagues (99) observed an increase of Cho/NAA in the cerebellar vermis over 3-4 weeks of abstinence from alcohol. Bendszus et al. (95) reported increases in both frontal and cerebellar lobar NAA/CRE3 (Cr) and cerebellar lobar Cho/Cr ratios after approximately 5 weeks of abstinence. After that interval, a higher frontal NAA/Cr ratio was related to better auditory-verbal memory while increased cerebellar NAA/Cr ratio positively correlated with attention/concentration. Parks and associates (97) observed vermian NAA levels increased after 3 months of abstinence from alcohol, which was related to improving auditory-verbal learning. In contrast to the group’s earlier study (99), vermian Cho levels did not recover after 3 months, and the authors suggested this might indicate continued compromise of cerebellar vermis tissue, which is consistent with neuropathologic findings (28). Higher mI was observed in the anterior cingulate gyrus, thalamus, frontal and parietal WM of 1-month-abstinent alcoholics but not in 6-year-abstinent alcoholics (91, 100), suggesting reversible membrane breakdown or osmolytic changes with abstinence from alcohol. Bartsch et al. (101) reported significant increases of cerebellar Cho and mesial frontal NAA over approximately one month of abstinence from alcohol. Increasing mesial frontal NAA was positively related to improving attention. Of note, the authors included only smoking alcoholics who consumed less than 10 cigarettes per day. In a longitudinal 1H MRSI study, Ende
et al. (102) observed increasing Cho concentrations in the frontal WM, dorsolateral prefrontal cortex, superior frontal gyrus and cerebellar GM, vermis and dentate nucleus over 3 months of abstinence. No further metabolite recovery was observed between 3 and 6 months of abstinence.

Modulation and adaptation of reciprocal glutamatergic and GABAergic projections among the prefrontal frontal regions, basal forebrain and midbrain are suggested to contribute to the neural basis of substance dependence (103). Pharmacotherapies have become increasingly important in treating both AUD and other substance abuse disorders, and have centered on medications modulating common neurotransmitters such as serotonin, dopamine, glutamate (Glu), and gamma aminobutyric acid (GABA). Therefore, a better understanding of the specific effects of AUD on brain GABA and Glu may further advance the development and efficacy of pharmacological drug treatment. Frontal Glu transmission has been associated with drug seeking. Thus, behavior has been intricately linked to basal cerebral concentrations of specific neurotransmitters. Modulation of the inhibitory GABA system by alcohol is implicated in the development of alcohol tolerance, dependence, and withdrawal. In humans, some studies report plasma and CSF GABA are decreased at 1 month of abstinence from alcohol and normalize by 6 months of sobriety (104, 105). \(^1\)H MRS studies of GABA and Glu in humans have been facilitated by the advent of high-field magnets (>2 Tesla) that permit the detection of the relatively weak in vivo GABA and Glu signals via increased sensitivity and greater spectral dispersion (e.g., (106). Although the MR detectable amino acid levels represent the metabolically available brain pools (which are much larger than the respective neurotransmitter pools), they are in tight equilibrium with synaptic levels (107). MRS derived GABA and Glu concentrations provide valuable information on the role and functional significance of these neurotransmitter systems in a variety of medical conditions. Consistent with plasma and CSF GABA levels, brain tissue GABA levels measured by \(^1\)H MRS in occipital cortex of a small sample of recently detoxified alcoholics were 30% lower than in non-alcoholic controls (5). More detailed studies, however, showed that GABA levels were elevated in 1-week abstinence alcoholics and lower at 4 weeks (108). Excitatory amino acid transmitters (e.g., Glu) are endogenous agonists of N-methyl-D-aspartate (NMDA) receptors and increased NMDA activity (postsynaptic receptors) may produce neurotoxicity presumably through dysregulation of Ca\(^{2+}\) influx [see (18, 23)]. Glu levels are increased during alcohol withdrawal in animal models [see (18) for review], but little is known about brain Glu concentrations in human alcoholism or recovery thereof. An early in vivo \(^1\)H MRS study suggests that Glx (the sum of Glu and glutamine) in healthy controls is lower relative to placebo 20 min after infusion of acamprosate (which shows effects in modulating drinking behavior), consistent with microdialysis results in alcohol dependent rats treated with acamprosate (109). For excellent reviews on the effects of AUD on other brain amino acid transmitters/modulators, monoaminergic and cholinergic systems and receptor function see (110-112).

### 3.2.3. Functional neuroimaging

Global and regional decreases in metabolism or cerebral blood flow (CBF) have been identified in AUD with positron emission tomography (PET) and single photon emission computerized tomography (SPECT) (113-117). Glucose utilization (i.e., glucose metabolic demand) and cerebral blood flow (CBF) are tightly coupled and both show mild to moderate decreases, especially in the frontal lobes of chronic alcoholics (41, 113, 116, 118-120), independent of the level of brain atrophy (121, 122). As with brain morphology, age effects should be considered when investigating the consequences of AUD on brain CBF (123-125). Lower CBF, as measured by PET and SPECT is related to poorer performance on measures of executive skills in AUD (113, 115, 126-128). Frontal hypoperfusion observed following acute detoxification shows variable recovery after approximately 2 months of abstinence (115, 125, 129). Perfusion deficits may be related to compromised cerebrovasculature that may improve with sustained sobriety. White matter perfusion was associated with measures of CT density (130), suggesting re-perfusion as possible contributing factors for the rapid structural improvements and increase of WM density with abstinence (58) and for recovery of WM Cho during abstinence from alcohol (131). In non-alcoholic subjects, acute alcohol administration promotes increased dopamine (DA) in the ventral striatum (132). Reduced availability of striatal dopamine DA\(_{23}\) receptors is observed in alcoholism (133, 134) (135). Detoxification from alcohol results in a rapid decrease of DA release (123-125); however, the sensitivity and availability of central DA\(_{23}\) increases over the first week of sobriety (136, 137).

### 3.3. Neurocognition

AUD-induced neurobiological abnormalities have been associated with dysfunction in several domains of neurocognitive functioning. Although the nature and level of impairment varies across individuals, studies have consistently reported that AUD is associated with dysfunction of cognitive efficiency (138-142) executive skills (143-146), learning and memory (36, 147-153), processing speed (262), visuospatial skills (146, 150, 151), working memory (36) and gait and postural stability (51, 146, 154). In those who manifest neurocognitive dysfunction, some disturbances show considerable recovery with short-term (e.g., 1-3 months) and long-term (e.g., greater than 12 months) abstinence from alcohol (62, 147, 151, 155, 156), whereas dysfunction in some areas may persist after short or long-term abstinence (157, 158). Although numerous studies report significant deficits in multiple areas of neurocognition after approximately one month of abstinence from alcohol relative to controls [see (159)], alcoholics may also show average performance on multiple measures when scores are based on standardized test norms [e.g., (160)]. Additionally, it is estimated that only 50 percent of alcoholics demonstrate detectable neurocognitive dysfunction after 2 to 3 weeks of abstinence (299), which emphasizes the considerable individual variability of effects of chronic alcoholism on neurocognition. Factors such as level of alcohol consumption, age, nutritional status, family history of alcoholism and comorbid psychiatric and other substance...
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abuse disorders may affect the magnitude of neurocognitive dysfunction manifested following detoxification as well as the level of recovery demonstrated with abstinence (4, 147, 149, 151, 159, 161).

3.4. Treatment-seeking versus treatment-naïve alcohol use disorders

The vast majority of what is known about the neurobiological and neurocognitive effects of AUD is derived from individuals engaged in substance abuse treatment programs. Treatment-seeking individuals, however, constitute only a small fraction of persons with AUD, with the majority representing treatment-naïve individuals with AUD. Treatment-seeking alcoholics differ from treatment-naïve alcoholics with regard to alcohol use histories, and prevalence of psychiatric comorbidities and the extent of brain injury manifested. Fein and colleagues (162) demonstrated that male and female treatment-seeking alcoholics had more than 50% higher alcohol consumption and more periods of abstinence than their treatment naïve counterparts, despite similar drinking patterns earlier in life. In comparison to their treatment-naïve counterparts, treatment-seeking alcoholics have higher prevalence of psychiatric comorbidities such as major depressive disorder, post-traumatic stress disorder, schizophrenia spectrum disorders, and antisocial personality disorder (29). Furthermore, treatment-seeking alcoholics demonstrate lower magnitudes of alcohol-induced cerebral morphological abnormalities (163). Therefore, research findings obtained in treatment-seeking alcoholics may not necessarily generalize to the substantially larger population of treatment-naïve alcoholics.

It should be noted that the neuropsychiatric conditions that show a high prevalence of comorbidity with AUD, most notably anxiety disorders (164), attention deficit/hyperactivity disorder (165), substance use disorders (164, 166), mood disorders (167-169), and schizophrenia (170), may independently influence brain morphology, biochemistry and neurocognition. Therefore, evaluation for the comorbid occurrence of these neuropsychiatric factors in the examination of the neurobiological and neurocognitive consequences of AUD is always indicated.

4. NEUROBIOLOGICAL AND NEUROCOGNITIVE CONSEQUENCES OF CHRONIC CIGARETTE SMOKING

Among the 64.5 million active smokers in the USA, smoking-attributed disease results in approximately 440,000 preventable annual deaths. Worldwide, the death toll from smoking is at 4 million a year and climbing. Although smoking rates in the general U.S. population have decreased over the last three decades, smoking prevalence remains especially high, in the economically disadvantaged (171) and among individuals with AUD, substance use disorders, and other neuropsychiatric conditions (e.g., attention deficit disorders, anxiety disorders, mood disorders schizophrenia-spectrum disorders) (165, 172-177). Epidemiological and animal research has indicated the mortality associated with chronic cigarette smoking related to its adverse effects on cardiac and pulmonary function, central and peripheral vascular systems, as well as its carcinogenic properties (178-180). Cigarette smoke contains more than 4000 compounds (178, 181), many of them bioactive, which act locally in the oral cavity and the upper and lower respiratory tracts, and distally via the systemic circulation. The many potentially cytotoxic compounds in cigarette smoke (e.g., carbon monoxide, aldehydes, nitrosamines, dihydroxybenzenes) (182), or their metabolites, may directly compromise neuronal and cellular membrane function of cerebral tissue. In humans, chronic cigarette smoking is associated with increased risk for atherosclerosis, ischemic and hemorrhagic stroke, cerebral white matter disease, and lipid peroxidation secondary to production of oxygen-derived free radicals (183-186).

4.1 Neuroimaging and electrophysiological findings

4.1.1. Structural neuroimaging: CT and MRI

CT studies have shown that chronic smoking is associated with an abnormal increase of brain atrophy with advancing age (187-189). A recent MRI study found smaller volumes and lower tissue densities in the prefrontal and anterior cingulate cortices and the cerebellum of otherwise healthy adult smokers (190); prefrontal cortical tissue density was inversely related to pack-years of smoking (an index reflecting daily cigarette use frequency and lifetime duration). Additionally, cigarette smoking has been linked to the severity of regional lobar white matter signal hyperintensities on MRI (186, 191). The brain regions primarily affected by chronic cigarette smoking overlap with those showing abnormalities in neuroimaging and neuropathological studies of alcohol-dependent individuals (2, 3), namely the frontal-parietal and temporal lobes, corpus callosum, cerebellum, hippocampi and subcortical regions.

4.1.2. Magnetic resonance spectroscopy

Chronic smoking has also been shown to alter brain neurochemistry. Specifically, chronic smokers demonstrated lower NAA concentration in the left hippocampus relative to non-smokers, and anterior cingulate Cho level was positively related to greater pack years (192). Nicotine and/or cigarette smoking modulates brain GABA concentrations in animals and humans (193, 194). In animals, non-specific increases in brain GABA levels are directly associated with reward and nicotine self-administration, and higher than normal intracellular Glu in rats was associated with stronger cocaine seeking behavior (103). In the sole 1H MRS study investigating GABA levels in chronic smokers, cortical GABA concentrations were lower in female smokers (and modulated by menstrual cycle phase), but GABA levels were not different in a small sample of male smokers relative to non-smokers (193).

4.1.3. Functional neuroimaging and electrophysiology

Most research on chronic smoking using brain perfusion measures has investigated the effects of acute nicotine exposure, rather than the consequences of chronic cigarette smoking (195). The few published studies of chronic smokers indicate globally decreased brain perfusion, as measured by 133Xe inhalation (196, 197) and SPECT (198), with perfusion inversely related to cigarette pack-years (198). DA turnover is reduced in both the
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caudate and putamen of in elderly smokers relative to non-smokers, but DA levels in both the caudate and putamen were significantly elevated. The density of high-affinity nicotine binding was higher in smokers in the hippocampus, entorhinal cortex and cerebellum in post-mortem examinations (199). Chronic nicotine and passive smoke exposure in rats has been shown to modulate DA activity in the ventral tegmental area and nucleus accumbens and GABA_A receptor expression in the prefrontal cortex (200). In general, available functional imaging and pharmacological research suggests chronic exposure to nicotine/cigarette smoke exposure results in decreased monoamine oxidase (MAO) A and B activity in the basal ganglia and a reduction in αβ2 nicotinic acetylcholine receptor availability in the thalamus and putamen [see (195, 201) and references therein]. For comprehensive information of the effects of chronic cigarette smoking and nicotine exposure on brain monoaminergic, cholinergic systems and receptors see (195, 199, 202). Electrophysiological studies indicated that current and former smokers demonstrated diminished P300 amplitudes and hypoactivation of the anterior cingulate, orbitofrontal and prefrontal cortices, compared to never smokers (203).

4.2. Neurocognition

A growing body of evidence suggests chronic cigarette smoking adversely affects both neurocognition and motor function in humans ranging from adolescents to older adults. Specific dysfunction among active chronic smokers has been reported for auditory-verbal learning and memory (204, 205, 294), prospective memory (206), working memory (207, 208), executive functions (209), visual search speeds (210), psychomotor speed and cognitive flexibility (211, 294), general intellectual abilities (212), and postural stability (213). Additionally, 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 (214). In young adults, aged 17-21, those who regular cigarette smokers performed significantly worse than age-matched non-smokers on measures of receptive and expressive vocabulary, oral arithmetic and auditory memory (215). Prospective longitudinal research with non-demented elderly subjects suggests that cigarette smoking promotes an abnormal decline in cognitive functioning (216), and significantly increases the risk for various forms of dementia, in particular Alzheimer’s Disease (217-219). However, in some large community-based samples, chronic smoking showed little or no relationship to neurocognition (205, 220). The underlying mechanisms of smoking-induced neurocognitive deficits have yet to be established as the few studies employing neurological measures (e.g., brain volumetrics, evoked potentials) have not related them to cognition. However, findings by (190, 192, 198, 203) suggest there are biological underpinnings to the neurocognitive dysfunction observed in chronic smokers.

As is apparent in AUD, there are other conditions that show a high prevalence of comorbidity with chronic cigarette smoking that may independently influence brain morphology, biochemistry and neurocognition. They include: anxiety disorders (221) attention deficit/hyperactivity disorder (165) substance use disorders (165, 222), mood disorders (175, 176), and schizophrenia (177, 223). Therefore, evaluation for the comorbid occurrence of these neuropsychiatric factors in the examination of the neurobiological and neurocognitive consequences of chronic smoking is warranted.

5. NEUROBIOLOGICAL AND NEUROCOGNITIVE CONSEQUENCES OF COMORBID CHRONIC ALCOHOL USE DISORDERS AND CIGARETTE SMOKING

In North America, approximately 80% of alcohol-dependent individuals are regular smokers (224-226) and an estimated 50-90% of individuals seeking treatment for alcoholism in North America are heavy smokers (160, 227). The neurobiological and neurocognitive consequences of comorbid psychostimulant, cannabinoid abuse/dependence and AUD have been investigated (228-233). However, the potential CNS effects of concurrent chronic cigarette smoking and AUD has received little attention, despite the growing body of research suggests chronic smoking, independent of AUD, is associated with abnormalities in brain morphology, cerebral blood flow, neurochemistry, and neurocognition (see above). Chronic cigarette smoking in AUD is associated with significantly higher quantity and frequency of alcohol consumption (234, 235), particularly compared to non-smoking or former-smoking alcohol-dependent individuals (236, 237). In the US, the mortality rate associated with cigarette smoking has been reported to be substantially greater than the mortality related to alcohol-induced diseases (238). Cigarette smoking in AUD is associated with significantly higher quantity and frequency of alcohol consumption (234), particularly compared to non-smoking or former-smoking alcohol-dependent individuals (236, 237). (Therefore, in the findings from our laboratory described below, all comparisons between smoking and non-smoking AUD groups are statistically corrected for greater drinking severity in the smoking groups). In a US cohort treated for alcoholism, mortality associated with cigarette smoking was at 51%, whereas mortality related to alcohol-induced diseases alone was about 34% (238). 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 (239-241), which is supported by human and animal studies demonstrating that nicotine increases voluntary alcohol intake (241, 242). Nicotine has been suggested to counteract the adverse effects of alcohol on cognition and motor incoordination (243), and that paired use of nicotine and alcohol produce a classical conditioned cue reactivity, leading to cravings for both substances (244). Finally, there is increasing evidence for a genetic susceptibility for concurrent active cigarette smoking and alcohol dependence (245-247).

Given the recent evidence that chronic cigarette smoking alone is associated with abnormalities in human brain morphology, blood flow, neurochemistry and function, it is uncertain if the neurobiological and
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neurocognitive abnormalities in AUD reported previously are solely attributable to alcohol consumption, or if the combination of both chronic alcohol dependence and cigarette smoking promotes greater adverse effects on the human brain than alcohol dependence alone. Since a majority of alcohol dependent individuals in treatment are heavy smokers, with the exact percentage varying geographically, a better understanding of the associated neurobiological and neurocognitive consequences of comorbid AUD and cigarette smoking has important implications for current and future pharmacologic and behavioral interventions aimed at promoting abstinence (Table 1).

5.1. Neuroimaging findings

Our group investigated the effects of concurrent chronic cigarette smoking on regional brain morphology, metabolite concentrations, and blood flow in 1-week-abstinent, treatment-seeking alcoholics (ALC) as well as longitudinal brain metabolite changes during short-term abstinence from alcohol. We also studied the effects of chronic smoking on brain morphology in actively drinking, treatment naïve, hazardous drinkers (HD). Others have addressed the consequences of comorbid chronic smoking and AUD on brain amino acid transmitters/modulators and brain electrophysiology.

5.1.1 Structural neuroimaging: MRI

Using high-resolution MRI (50), we observed that chronic cigarette smokers, irrespective of AUD, demonstrated smaller parietal, temporal and occipital GM volumes and with larger temporal WM volumes, compared to non-smokers. By contrast, 1-week-abstinent, treatment-seeking ALC as a group, demonstrated smaller WM volumes in the frontal and parietal lobes. In non-smoking ALC, visuospatial learning and memory were positively correlated with temporal WM and occipital WM volumes, whereas no significant structure-function relationships were observed for smoking ALC. This suggests that chronic smoking in ALC further disrupts alcohol-induced disturbances in functional neurocircuitry (27) that subserve learning and memory, executive skills and working memory. Thus, in our quantitative MRI studies, both chronic alcohol consumption and chronic smoking were associated with significant neocortical GM loss. Our results suggest that chronic cigarette smoking accounts for some of the variance associated with cortical GM loss in ALC and it may modulate relationships between brain structure and cognition in ALC.

Similarly, in a group of treatment-naive active hazardous drinkers (HD), smoking HD we found significantly smaller volumes than non-smoking controls in the frontal, parietal, temporal GM and for total neocortical GM (248). Furthermore, smoking HD demonstrated significantly smaller temporal and total GM volumes than non-smoking HD, whereas GM volumes in non-smoking HD did not differ significantly from those in controls. We found trends for larger WM volumes in smoking HD relative to non-smoking HD, which is consistent with our volumetric findings in treatment-seeking ALC. Via pulsed magnetic resonance arterial spin labeling (249), we showed that frontal and parietal GM perfusion in smoking ALC was significantly lower than both non-smoking ALC and non-smoking controls; parietal GM. Of note, frontal and parietal GM perfusion levels were not significantly different between non-smoking ALC and non-smoking light drinkers (LD).

5.1.2. Magnetic resonance spectroscopic imaging

Using 1H MRSI (237), we observed that the 1-week-abstinent, treatment-seeking smoking ALC group, compared to the non-smoking ALC group demonstrated 10% lower NAA concentrations (the marker of neuronal viability) in the frontal WM and 15% lower NAA and 21% lower Cho (marker of cell membrane turnover) in the midbrain. In addition, smoking ALC showed trends to lower NAA in the parietal GM and lenticular nuclei relative to non-smoking ALC. Alcohol dependence, independent of smoking, was associated with lower concentrations of frontal lobe NAA and Cho and lower parietal and thalamic Cho. Among smoking ALC, greater nicotine dependence [as measured by Fagerstrom Test of Nicotine Dependence; (250)] and a higher number of cigarettes smoked per day were negatively correlated with thalamic and lenticular NAA levels. In smoking ALC, lower cerebellar vermis NAA was associated with poorer visuomotor scanning speed, and in non-smoking ALC, lower vermian NAA was related to poorer visuospatial learning and memory. This in vivo 1H MRSI finding suggest that chronic smoking compounds alcohol-induced neuronal injury and cell membrane damage in the frontal lobes of ALC and has independent adverse effects on neuronal viability and cell membrane turnover/synthesis in the vermis and midbrain.

In longitudinal 1H MRSI studies of treatment-seeking ALC, after approximately one month of abstinence from alcohol (131), non-smoking ALC showed increases of NAA in the frontal WM (+8%) and of Cho in the frontal, parietal, and temporal GM (+8 to +14%). Significant Cho increases were also observed in the WM of all four lobes (+7 to +17%). In smoking ALC, NAA concentrations increased only in the frontal GM (+5%) and further significantly decreased in the parietal and occipital WM (both -6%); Cho increased by approximately 10% in the frontal GM and WM. Overall, over one month of abstinence from alcohol, smoking ALC demonstrated numerically smaller and fewer regional increases of NAA and Cho concentrations than non-smoking ALC. In non-smoking ALC, improvements in visuospatial learning were related to increases of frontal and occipital WM NAA; increases of parietal GM NAA correlated with improvements of visuomotor scanning speed and incidental learning; increases of thalamic NAA were related to improving visuospatial learning, visuospatial memory and working memory, whereas improving visuospatial learning also correlated with increasing frontal GM Cho, frontal WM Cho and thalamic Cho. In smoking ALC, the only significant relationships were observed between increases of midbrain NAA and improving visuospatial learning, and between increasing caudate NAA and improving visuospatial memory. Furthermore, in smoking ALC, longer smoking duration was related to smaller longitudinal increases in frontal WM NAA, frontal WM Cho, and thalamic Cho.
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Table 1. Neuroimaging and neurocognitive studies of comorbid chronic cigarette smoking and AUD

<table>
<thead>
<tr>
<th>Participants</th>
<th>Method</th>
<th>Primary Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 nsLD 10 sALC 14 sHLD</td>
<td>High-resolution 3D MRI; brief neuropsychological battery emphasizing learning and memory, working memory and processing speed; subjects had 1 month of abstinence from alcohol</td>
<td>--- sHLD vs. nsHLD: perfusion 15% in parietal GM; --- sHLD vs. sALC: perfusion 14% in parietal GM; --- sHLD vs. nsALC: no significant GM volume differences</td>
<td>247</td>
</tr>
<tr>
<td>11 nsLD 14 sHLD</td>
<td>MR pulsed arterial spin labeling at 1 week of abstinence from alcohol</td>
<td>--- sALC vs. sHLD: perfusion 10% in parietal GM; --- sALC vs. nsALC: perfusion 14% in parietal GM; --- sALC vs. nsHLD: no significant GM volume differences</td>
<td>249</td>
</tr>
<tr>
<td>20 nsLD 16 sHD 17 sHLD</td>
<td>Brief battery assessing general intelligence and cognitive efficiency; approximately 40% of alcoholic participants actively drinking at time of study</td>
<td>--- AUD and smoking severity were inversely related to increasing frontal GM NAA; --- AUD and smoking severity were inversely related to increasing temporal GM NAA; --- AUD and smoking severity were inversely related to increasing parietal GM NAA; --- AUD and smoking severity were inversely related to increasing occipital GM NAA; --- AUD and smoking severity were inversely related to increasing thalamic NAA; --- AUD and smoking severity were inversely related to increasing cerebellar NAA.</td>
<td>254</td>
</tr>
<tr>
<td>295</td>
<td>--- sALC superior to sHLD on measures of set-shifting and processing speed.</td>
<td>--- AUD and smoking severity were inversely related to increasing frontal GM NAA; --- AUD and smoking severity were inversely related to increasing temporal GM NAA; --- AUD and smoking severity were inversely related to increasing parietal GM NAA; --- AUD and smoking severity were inversely related to increasing occipital GM NAA; --- AUD and smoking severity were inversely related to increasing thalamic NAA; --- AUD and smoking severity were inversely related to increasing cerebellar NAA.</td>
<td>255</td>
</tr>
<tr>
<td>26 nsLD 106 sALC 66 sHLD</td>
<td>Comprehensive neurocognitive assessment at 1 month of abstinence from alcohol</td>
<td>--- sALC superior to sHLD on measures of set-shifting and processing speed.</td>
<td>256</td>
</tr>
<tr>
<td>4086</td>
<td>--- Group differences not due to disparities in age, education, estimated premorbid verbal intelligence, alcohol consumption variables</td>
<td>--- sALC superior to sHLD on measures of set-shifting and processing speed.</td>
<td>257</td>
</tr>
<tr>
<td>22 nsLD 14 sHLD</td>
<td>Comprehensive neurocognitive assessment at 1 month and 6-7 months of abstinence from alcohol</td>
<td>--- sALC exhibited a significantly greater magnitude of longitudinal improvement than sHLD on the domains of executive skills, timed-test composite, visuospatial skills, and working memory</td>
<td>295</td>
</tr>
</tbody>
</table>

AUD: alcohol use disorders, Cho: choline-containing compounds, GM: gray matter, NAA: N-acetylaspartate, NMRA: N-acetylaspartate, D-aspartate, MRI: magnetic resonance imaging, nsHLD: non-smoking hazardous drinker, sHLD: smoking hazardous drinker, sLD: smoking light drinking control, WM: white matter, ³¹H MRSI: proton magnetic resonance spectroscopic imaging

In other longitudinal investigations, we also studied the effects of chronic smoking in AUD on changes in hippocampal volumes and on metabolite concentration in the medial temporal lobe over one month of abstinence from alcohol. Over this interval of sobriety, medial temporal lobe NAA and Cho levels in non-smoking ALC significantly increased and normalized to non-smoking ALC levels. However, in smoking ALC, NAA and Cho concentrations did not change significantly and remained depressed relative to non-smoking light drinking controls.
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Increasing NAA and Cho levels in both non-smoking ALC and smoking ALC were associated with improvements in visuospatial memory. Hippocampal volumes significantly increased in both groups over one month of abstinence from alcohol, but increasing volumes correlated with visuospatial learning improvements only in non-smoking ALC.

Via 1H MRS, Mason and colleagues (108) showed that chronic smoking modulated occipital GM GABA concentrations during recovery from alcoholism. At 1 week of abstinence, cortical GABA levels were higher in alcohol dependent nonsmokers than smokers. After approximately three weeks of abstinence, GABA levels were lower than at one week and similar between alcoholic non-smokers and smokers. Higher GABA during early withdrawal may reflect compensation for reduced cortical benzodiazepine-GABAA receptor function thought to contribute to alcohol tolerance and withdrawal. The subsequent decline may reflect “normalization” of GABA receptor function with sobriety.

5.1.3. Perfusion-weighted MRI

We assessed frontal and parietal GM perfusion in 1-week-abstinent, treatment-seeking ALC with a non-invasive MR pulsed arterial spin labeling method (249, 251). Results showed that frontal GM perfusion in smoking ALC was 18% lower than non-smoking ALC and 19% lower than non-smoking LD. Parietal GM perfusion in smoking ALC was 11% lower than in smoking ALC and 12% lower than non-smoking LD. The regional perfusion differences between smoking and non-smoking ALC remained significant after controlling for the greater lifetime alcohol consumption in smoking ALC. GM perfusion was similar in non-smoking ALC and non-smoking LD. Parietal GM perfusion in smoking ALC 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 GM perfusion in smoking ALC. This suggests that the chronic effects of cigarette smoking, rather than the acute effects of nicotine exposure or withdrawal, modulate brain perfusion in ALC, which is consistent with results in non-alcoholic chronic smokers (197, 198).

5.1.4. Functional neuroimaging and electrophysiology

SPECT studies suggest chronic cigarette smoking attenuates GABAA receptor adaptations that are associated with alcohol dependence (252). This may contribute to the co-morbidity between alcoholism and smoking and, more importantly, suggests that benzodiazepines commonly used to treat alcohol withdrawal symptoms may be differentially effective in smoking and non-smoking alcoholics. Interestingly, the lower P300 component of ERP measured in alcohol dependent individuals was strongly associated with smoking and not with alcohol dependence (253), which is consistent with findings in chronic smokers (203).

5.2. Neurocognition

We examined domains of neurocognition typically reported to be adversely affected by AUD in smoking and non-smoking one-month-abstinent ALC (160). Our cross-sectional results indicated that non-smoking ALC were superior to smoking ALC on measures of auditory-verbal learning and memory, processing speed, cognitive efficiency, and static postural stability. These group differences were not a function of group disparities in age, education, estimated premorbid verbal intelligence, lifetime alcohol consumption, or other recorded comorbid psychiatric or medical factors. In smoking ALC, longer smoking duration was negatively correlated with executive skills, visuospatial learning, general cognitive efficiency, and static postural stability. Our findings are consistent those from Glass and colleagues (254), who reported that both chronic AUD (combined group of abstinent and actively drinking subjects) and smoking severity were inversely related to neurocognitive function. Smoking severity (i.e., pack years) alone predicted performance on measures of general intelligence and cognitive proficiency (i.e., an index of both speed and accuracy). The authors proposed that the effects of smoking might be most pronounced on measures that require fast and flexible processing. In a large community-based group of actively drinking alcoholics, Friend et al. (255), found that both chronicity of AUD and cigarette smoking were inversely related to measures of general intellectual functioning, set-shifting and processing speed, and the combination of chronic alcohol and cigarette smoking had an additive adverse effect on neurocognitive functioning. Furthermore, in this study, non-smoking alcoholics were superior to smoking alcoholics on measures of processing speed and set-shifting. Rosenbloom et al., (256) reported that 3-month-abstinent smoking alcoholics performed significantly worse on measures of verbal intelligence compared to age and education equivalent controls, but no differences were apparent on tests of mental status/global cognitive functioning, non-verbal intelligence, learning and memory, processing speed and set-shifting. We also examined recovery of neurocognition in smoking and non-smoking over 6-9 months of abstinence from alcohol (295). Non-smoking ALC exhibited significantly greater magnitudes of longitudinal improvement than smoking ALC on measures of cognitive efficiency, executive skills, visuospatial skills and working memory. Both nsALC and sALC showed equivalent improvement on measures of auditory-verbal learning, auditory-verbal memory, and processing speed. In cross-sectional comparisons in this sample at 6 - 9 months of abstinence, non-smoking ALC were superior to smoking ALC on measures of auditory-verbal learning, auditory-verbal memory, cognitive efficiency, executive skills, processing speed and working memory. The longitudinal and cross-sectional findings for non-smoking and smoking ALC were not a function of group differences in age, education, estimated premorbid intelligence or alcohol consumption. In smoking ALC, greater smoking severity was inversely related to longitudinal improvement on multiple neurocognitive measures. The cross-sectional comparisons of nsALC and sALC after 6-9 months of abstinence in this study are consistent with our previous cross-sectional findings from 1-month-abstinent ALC (160). 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 hour neurocognitive assessment; therefore, our findings
were not likely a function of nicotine withdrawal [the half-life of nicotine in humans is approximately 2 - 3 hours; (257)].

5.3. Potential mechanisms promoting greater neurobiological and neurocognitive abnormalities in chronic smokers with alcohol use disorders

5.3.1. Biological consequences of chronic cigarette smoking

There are several possible mechanisms that may contribute independently, or in concert, to the greater neurobiological and neurocognitive abnormalities in chronic smokers relative to non-smokers with AUD. These mechanisms may affect brain tissue in a direct and/or indirect manner.

5.3.1.1. Direct mechanisms

A significant number of potentially cytotoxic compounds are found in the gas and particulate phases of cigarette smoke [e.g., carbon monoxide, free radicals, free radical precursors, nitrosamines, phenolic compounds, and other polynuclear aromatic compounds (182)], which may be directly cytotoxic, promote oxidative damage or impair the function of brain tissue (258, 259). For example, carbon monoxide (CO) levels are significantly higher in smokers (260), and this elevation is associated with decreased effective hemoglobin concentrations, diminished oxygen carrying capacity of erythrocytes (261), as well as a diminished efficiency of the mitochondrial respiratory chain (262). Chronic smoking has also been equated to a type of repeated acute (mild) CO poisoning (262). Furthermore, cigarette smoke also contains high concentrations of free radical species (e.g., reactive nitrogen species; reactive oxygen species, ROS) known to promote oxidative damage or stress to cellular structures as well as macromolecules including membrane lipids, proteins, carbohydrates, and DNA (263). The radical species in the particulate matter are long-lived (i.e., hours to months) compared to those in the gas phase of cigarette smoke (264) and can adversely affect organs other than the lungs (258, 265). Similarly, chronic and heavy alcohol consumption and ethanol oxidation are associated with generation of ROS and other metabolic products that may lead to oxidative damage to various cellular molecules and structures, including phospholipids and DNA (15) (258, 259).

5.3.1.2. Indirect mechanisms

Chronic exposure to cigarette smoke in rats has been shown to significantly decrease membrane-bound ATPases in brain tissue, which may alter ion homeostasis, and lead to increased intracellular levels of Ca²⁺ and Na⁺ (297), and promote necrotic injury in neurons (296). Chronic cigarette smoke exposure is also associated with decreased concentrations of enzyme-based free radical scavengers (i.e., superoxide dismutase, catalase, glutathione reductase) and non-enzyme-based radical scavengers (i.e., glutathione and vitamins A, C and E) in rat brains (266, 298). This may leave tissue more vulnerable to oxidative damage resulting from radical species generated by cellular metabolism or other exogenous sources. The brain in general is exceedingly susceptible to oxidative damage due to the high levels of unsaturated fatty acids and due to high oxygen consumption (and resultant ROS formation). Additionally, chronic cigarette smoking is also related to nocturnal hypoxia (267) as well as chronic obstructive pulmonary disease and other conditions that may impair lung function (178) and decrease blood oxygen levels. Decreased lung function has been associated with poorer neurocognition and increased subcortical atrophy among community dwelling individuals 60 – 64 years of age (268). Chronic smoking is also related to a significantly increased risk for atherosclerosis (183), as well as abnormalities in vascular endothelial function (269, 270). These processes may impact the functional integrity (e.g., vasomotor reactivity/responsivity) of the cerebrovasculature and contribute to the decreased regional cerebral blood flow (240, 271, 272) and/or white matter disease (191, 273) reported in chronic smokers. Both the neocortex and associated WM are vulnerable to the effects of diffuse ischemia [(274) and references therein]. Finally, it has been suggested that late-myelinating areas such as the frontal and temporal lobes may be particularly vulnerable to increased oxidative stress and cerebral hypoperfusion [(275, 276)] both of which have been described in chronic smokers and AUD.

5.3.1.3. Implications for brain neurobiology and neurocognition

In our neuroimaging studies of alcoholism, we observed significantly greater abnormalities in frontal and temporal lobe morphology (50), in makers of neuronal integrity in the frontal lobe (237), and in frontal lobe perfusion (249) in sALC relative to nsALC after detoxification. sALC also demonstrated significantly lower recovery of frontal markers of neuronal integrity and frontal and temporal markers of cell membrane synthesis/turover over approximately 1 month of abstinence (131). Additionally, we observed smaller frontal GM volumes in actively drinking, treatment naïve alcoholics (248). Our cross-sectional neurocognitive results with 1-month abstinent ALC indicated that non-smoking ALC were superior to smokers ALC on the domains of auditory-verbal learning and memory, cognitive efficiency and processing speed. Our longitudinal neurocognitive findings revealed sALC demonstrated significantly less longitudinal improvement than nsALC on the domains of cognitive efficiency, executive skills, visuospatial skills and working memory over 6-8 months of abstinence from alcohol (295). The domains of functioning where nsALC and sALC differed in our cross-sectional and longitudinal studies are all suggested to be extensively subserved by dorsolateral and medial frontal-striatal-thalamic circuitry (72, 277, 278). Modulation of the morphology, biochemistry and function of tissue comprising frontal-striatal-thalamic circuitry by chronic smoking is suggested by the pattern of neurobiological and neurocognitive findings in non-alcoholic chronic smokers (190, 195, 203, 207, 210, 211, 279, 280). Additionally, chronic smoking may affect some aspects of neurocognition through modulation of monoaminergic, cholinergic, glutamatergic and GABAergic activity (195, 281, 282) particularly in frontal-striatal-thalamic circuitry (195, 279). Therefore, it is conceivable that the functional integrity of frontal-striatal-
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thalamic neural networks is altered in sALC relative to their non-smoking counterparts.

A combination of chronically increased CO levels, chronic exposure to free radicals from both ethanol metabolism and cigarette smoke, decreased cerebral concentrations of free radical scavengers and potentially compromised vascular and pulmonary function may all contribute to the greater neurobiological abnormalities we observe in the chronic smokers in our recently detoxified ALC and HD cohorts. It is also plausible that the brain regions adversely affected in AUD (e.g., neocortical GM) are rendered more vulnerable to the effects of the potentially noxious compounds found in cigarette smoke (or vice-versa). With respect to continued smoking during abstinence from alcohol, we postulate that continued chronic smoking provides a sustained direct source of exogenous free radical species, carbon monoxide and other potentially cytotoxic compounds. These noxious agents, in combination with decreased levels of cerebral radical scavengers and potentially diminished cardiopulmonary function or cerebrovascular integrity, may adversely affect the recovery of the morphology or metabolism of neural and glial tissue, particularly that comprising the frontal-striatal-thalamic circuitry.

Although we controlled for factors (e.g., age and drinking severity) in our studies that may have influenced our dependent measures, it is possible that the greater neurobiological and neurocognitive abnormalities demonstrated by our alcoholic smokers are partially related to potential unrecorded differences in nutrition, exercise, overall physical health, exposure to environmental cigarette smoke or to genetic predispositions.

5.3.2. Neurobiological effects of acute cigarette smoking and nicotine exposure

When investigating chronic cigarette smoking-induced neurobiological and neurocognitive dysfunction, alone, or in conjunction with AUD or 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 [(283, 284)]. However, the effects of acute nicotine administration on neurocognition in smoking and non-smoking alcoholics and other substance abusers are not clear [(285, 286)]. With respect to the effects of acute nicotine administration or withdrawal on functional neuroimaging measures, a few functional MRI studies have investigated the acute effects of nicotine administration on brain activity during task activation in healthy non-smokers [(195, 284, 287)]. Depending on the nature of the task, results suggest acute nicotine administration is associated with increased blood oxygenation level-dependent brain activity and improved performance or decreased blood oxygenation level-dependent activity and improved performance (195, 287).

The effects of acute cigarette smoking on functional imaging measures (in resting conditions or during task activation) in healthy non-smokers have not been studied (195, 287).

In non-alcoholic chronic smokers, the adverse effects of nicotine withdrawal are not typically apparent until 8-12 hours after last nicotine dose [(284, 288, 289)]. This is likely attributable to the maintenance of relatively high levels of plasma nicotine due to repeated dosing of nicotine (via cigarettes) during waking hours (257). In chronic smokers deprived of tobacco for more than 2 hours, 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 (195, 240, 271). 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 hours or more (290, 291). Thus, the effects of acute nicotine administration and acute cigarette smoking on functional imaging measures and neurocognition appear to depend on smoking status, the brain region studied, resting versus activation conditions, and the neurocognitive domain investigated (195).

6. CONCLUSIONS AND PERSPECTIVES

It is clear that chronic, excessive alcohol consumption and chronic cigarette smoking are each associated with adverse neurobiological and cognitive consequences. Very little research, however, has addressed the question if comorbid chronic cigarette smoking attributes to brain injury and neurocognitive deficits in AUD. Recent neuroimaging findings from our group and others suggest that chronic cigarette smoking in healthy controls and AUD is associated with regional neocortical GM volume loss, and we observe smoking is linked to a significant (and perhaps pathological) increase in regional WM volume. Chronic smoking in AUD also appears to modulate brain GABA and Glu levels, is associated with regional neocortical perfusion abnormalities, and appears to compound alcohol-induced neuronal injury and cell membrane dysfunction in the frontal lobes and midbrain. Chronic excessive alcohol consumption per se does not appear to be associated with significant abnormalities in neocortical GM morphology and perfusion in our AUD cohorts; rather, the combination of chronic, excessive drinking and cigarette smoking appears to promote a significant volume loss and diminished blood flow in the neocortex relative to non-smoking controls. Similarly, the combination of chronic excessive alcohol consumption and cigarette smoking appears to be associated with significant abnormalities in markers of neuronal viability and cell membrane synthesis/turover in our AUD cohorts. Furthermore, chronic smoking in our AUD participants is associated with diminished recuperation of regional biochemical markers of neuronal viability and cell membrane synthesis/turover during short-term abstinence as well as recovery of brain volume with sustained
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abstinence from alcohol. The significant relationships between MR measures and neurocognitive test results from both our cross-sectional and longitudinal studies indicate that MR-derived neurobiological measures are robust predictors of neurocognition.

Consistent with the greater morphologic, metabolic, and blood flow abnormalities in the neocortex and frontal-subcortical circuits we observed in AUD smokers versus non-smokers, our smoking ALC cohort demonstrated inferior performance on measures of auditory-verbal learning and memory, processing speed, cognitive efficiency and static postural stability, whereas treatment-naive smoking HD exhibited poorer performance on measures of executive function relative to their non-smoking counterparts. Our longitudinal findings suggested chronic smoking is associated with diminished longitudinal improvement in cognitive efficiency, executive skills, visuospatial skills and working memory with sustained abstinence from alcohol. These findings are in line with other recent research indicating chronic smoking adversely affects neurocognition in AUD (254, 255). In general, our MR findings and the neurocognitive results from our group and others (254, 255 Glass, 2005 #13708) suggest that chronic smoking in AUD may further compromise alcohol-induced disturbances in functional neurocircuitry (27, 72), thereby modulating relationships between MR-derived neurobiologic measures and neurocognition.

This review describes a growing body of research that demonstrates converging lines of evidence that chronic cigarette smoking adversely affects both neurobiology and neurocognition in AUD, thus contributing to the accumulating research linking chronic smoking to brain injury and functional deficiencies. Examining AUD as a homogeneous group without consideration of smoking status may obscure the ability of MR-derived neurobiologic measures to serve as useful surrogate markers of brain function as well as to understand the effects of AUD on neurocognition. Additional prospective research, with larger groups that includes more females is required to 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 (161, 292, 293). If chronic cigarette smoking does indeed modulate brain neurobiology and neurocognition, we may have to entertain the possibility that smoking and non-smoking alcohols may differ in the nature or extent of their response to pharmacological and/or behavioral interventions designed to promote abstinence from alcohol or cigarette smoking. Finally, the reviewed literature, in conjunction with the known mortality and morbidity associated with chronic smoking, lends support to the growing clinical initiative that encourages chronic smokers entering treatment for AUD to participate in a smoking cessation program (224). At the very least, the recent research on comorbid AUD and smoking suggests that the effects of concurrent chronic cigarette smoking should be considered in future studies investigating the consequences of AUD on neurobiology and neurocognition and their recoveries with abstinence from alcohol. More generally, the brain effects of chronic smoking appear to be warranted in research of other neuropsychiatric conditions in which chronic cigarette smoking is prevalent (e.g., attention deficit disorders, mood disorders, and schizophrenia-spectrum disorders).

7. ACKNOWLEDGMENT

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