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# 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 psychostimulants (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 be mediated, in part, by chronic cigarette smoking. In this review, we first separately present the research literature on the neurobiological (emphasizing neuroimaging research) and neurocognitive findings in both AUD and chronic cigarette smoking, and subsequently review the literature on the effects of comorbid cigarette smoking on neurobiology and neurocognition in AUD. This review addresses "uncomplicated" AUD, that is, AUD without a history of Wernike-Korsakoff Syndrome (WKS) or significant chronic hepatic disease, as uncomplicated AUD represents the vast majority of individualswith AUD. The neuropathological, neuroimaging and neurocognitive corollaries of WKS and alcohol-induced hepatic encephalopathy are reviewed elsewhere (1-6).

## 3. NEUROBIOLOGICAL AND NEUROCOGNTIVE CONSEQUENCS 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 excitoneurotoxicity, 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). Excitoneurotoxicity 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 3$^{rd}$ 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).

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 ($^{1}$H 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 derangements of neurometabolism (84-86). The $^{1}$H 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 $^{1}$H MRS study to suggest residual neuronal injury in the frontal cortex of abstinent alcoholics employed spectroscopic imaging ($^{1}$H 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 $^{1}$H 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 dendrites 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 $^{1}$H 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/creatine (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 10 cigarettes per day. In a longitudinal $^{1}$H 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 abstinent 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 (113, 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 $DA_{2/3}$ 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 $DA_{2/3}$ 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 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 NEUROCOGNTIVE CONSEQUENCS 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 $^{1}$H 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 $^{133}$Xe inhalation (196, 197) and SPECT (198), with perfusion inversely related to cigarette pack-years (198). DA turnover is reduced in both the 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 $GABA_B$ 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 $\alpha_4\beta_2$ 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 neurobiological 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 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 subserves 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-naïve 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 $^1$H 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* $^1$H 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 $^1$H 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.

**Table 1.** Neuroimaging and neurocognitive studies of comorbid chronic cigarette smoking and AUD

| Participants | Method | Primary Findings | Reference |
|---|---|---|---|
| **Neuroimaging studies** | | | |
| 19 nsLD<br>7 sLD<br>10 nsALC 14 sALC | $^1$H MRSI; brief neurocognitive battery emphasizing learning and memory, working memory and processing speed; subjects had 1 week of abstinence from alcohol | --- AUD associated with ↓ frontal NAA and Cho and ↓ parietal and thalamic Cho.<br>--- Smoking associated with ↓ midbrain NAA and Cho and ↓ cerebellar vermis Cho.<br>--- sALC vs. nsALC: 10% ↓ NAA in frontal WM;<br>15% ↓ NAA and 21% ↓ Cho in the midbrain<br>--- sALC: greater nicotine dependence and higher # of cigarettes smoked per day negatively correlated with thalamic and lenticular NAA | 237 |
| 23 nsLD<br>7 sLD<br>13 nsALC 24 sALC | High-resolution 3D MRI; brief neurocognitive battery emphasizing learning and memory, working memory and processing speed; subjects had 1 week of abstinence from alcohol | --- AUD associated with ↓ parietal and temporal GM, and ↓ frontal and parietal WM<br>--- Smoking associated with ↓ parietal, temporal and occipital GM, and↑ temporal and frontal WM<br>--- nsALC: visuospatial learning and memory positively correlated with temporal and occipital WM volumes<br>--- sALC: no significant structure-function relationships | 50 |
| 19 nsLD<br>10 nsALC 19 sALC | 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<br>--- sALC vs. nsALC: perfusion 18% ↓ in frontal GM and 11% ↓ in parietal GM<br>--- nsALC vs. nsLD: no significant differences in GM perfusion<br>--- sALC: parietal GM perfusion inversely correlated with # of cigarettes smoked per day | 249 |
| 20 nsLD<br>16 nsHD<br>17 sHD | High-resolution 3D MRI; HD actively drinking at time of study | --- sHD vs. nsLD: ↓ frontal, parietal, temporal and total GM<br>--- sHD vs. nsHD: ↓ temporal and total GM<br>--- nsHD vs. nsLD: no significant GM volume differences | 247 |
| 11 nsALC<br>14 sALC | Serial $^1$H MRSI at 1 week and 1 month of abstinence from alcohol; brief neurocognitive battery at 1 week of abstinence from alcohol and comprehensive neurocognitive battery at 1 month of abstinence from alcohol | --- nsALC over one month of abstinence: ↑ frontal WM NAA; ↑ Cho in frontal, parietal, temporal GM; ↑ Cho in frontal, parietal, temporal, occipital WM.<br>---- sALC: ↑ frontal GM NAA; ↓ parietal and occipital WM NAA; ↑ frontal GM and WM Cho.<br>--- nsALC: improving visuospatial learning positively related to increasing frontal and occipital WM NAA; improving visuomotor scanning speed related to increasing parietal GM NAA; improving visuospatial learning, visuospatial memory and working memory, related to increasing thalamic NAA; improving visuospatial learning related to increasing frontal GM Cho.<br>--- nsALC: longer smoking duration related to decreasing frontal WM NAA, frontal WM Cho, and thalamic Cho. | 131 |
| **Neurocognitive Studies** | | | |
| 74 nsALC<br>84 sALC | Brief battery assessing vocabulary, verbal abstraction, processing speed, and set-shifting; majority of participants actively drinking | --- nsALC superior to sALC on measures of set-shifting and processing speed<br>--- The combination of alcohol use disorders and smoking predicted poorer performance on these tasks in sALC | 255 |
| 56 nsLD<br>13 sLD<br>106 nsALC<br>66 sALC | Brief battery assessing general intelligence and cognitive efficiency; approximately 40% of alcoholic participants actively drinking at time of study | --- AUD and smoking severity were inversely related to<br>--- Smoking severity (i.e., pack years) was a unique predictor of general intelligence and cognitive proficiency, an index of speed and accuracy | 254 |
| 20 nsALC<br>22 sALC | Comprehensive neurocognitive assessment at 1 month of abstinence from alcohol | --- nsALC superior to sALC on measures of auditory-verbal learning and memory, processing speed, cognitive efficiency, and static postural stability<br>--- Group differences not due to disparities in age, education, estimated premorbid verbal intelligence, alcohol consumption variables<br>--- sALC: longer smoking duration negatively correlated with executive skills, visuospatial learning, general cognitive efficiency, and static postural stability. | 160 |
| 22 nsLD<br>14 nsALC<br>66 sALC | Comprehensive neurocognitive assessment at 1 month and 6-7 months of abstinence from alcohol | --- nsALC exhibited a significantly greater magnitude of longitudinal improvement than sALC on the domains of executive skills, timed-test composite, visuospatial skills, and working memory<br>--- After 6 to 9 months of abstinence, nsALC were superior to sALC on the domains of auditory-verbal learning, auditory-verbal memory, cognitive efficiency, executive skills, processing speed, and working memory<br>--- In sALC, greater smoking severity was related to less longitudinal improvement on multiple neurocognitive domains | 295 |

AUD: alcohol use disorders, Cho: choline-containing compounds, GM: gray matter, NAA: N-acetylaspartate, NMDA: N-acetyl-D-aspartate, MRI: magnetic resonance imaging, nsALC: non-smoking recovering alcoholic, nsLD: light drinking control, sALC: smoking recovering alcoholic, sHD: smoking hazardous drinker, sLD: smoking light drinking control, WM: white matter, $^1$H 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.

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 $^{1}$H 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-$GABA_A$ receptor function thought to contribute to alcohol tolerance and withdrawal. The subsequent decline may reflect "normalization" of $GABA_A$ 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 $GABA_A$ 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 $Ca^{2+}$ 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/turnover 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 smoking 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 mesial 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-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/turnover 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/turnover during short-term abstinence as well as recovery of brain volume with sustained 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-naïve 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 alcoholics 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).

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## 8. REFERENCES

1. A. D. Thomson & E. J. Marshall: The natural history and pathophysiology of Wernicke's Encephalopathy and Korsakoff's Psychosis. *Alcohol Alcohol*, 41, 151-8 (2006)
2. C. Harper, G. Dixon, D. Sheedy & T. Garrick: Neuropathological alterations in alcoholic brains. Studies arising from the New South Wales Tissue Resource Centre. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 27, 951-61 (2003)
3. E. V. Sullivan: NIAAA Research Monograph No. 34: Human brain vulnerability to alcoholism: Evidence from neuroimaging studies. In: Review of NIAAA's neuroscience and behavioral research portfolio. Eds: A. Noronha, M. Eckardt & K. Warren. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD (2000)
4. M. Oscar-Berman: NIAAA Research Monograph No. 34: Neuropsychological vulnerabilites in chronic alcoholism. In: Review of NIAAA's Neuroscience and Behavioral Research Portfolio. NIAAA, Bethesda, MD (2000)
5. K. Behar & e. al.: Preliminary evidence of low cortical GABA levels in localized 1H-MR spectra of alcohol-dependent and hepatic encephalopathy patients. *Am J Psychiatry*, 156, 952-4 (1999)
6. A. S. Hazell & R. F. Butterworth: Hepatic encephalopathy: An update of pathophysiologic mechanisms. *Proc Soc Exp Biol Med*, 222, 99-112 (1999)
7. J. J. Kril, A. J. Harding, A. Wong, M. D. Svoboda & G. M. Halliday: Is the hippocampus damaged in alcoholics with memory loss? *Alcohol: Clin Exp Res*, 20, 76A (1996)
8. L. Korbo: Glial cell loss in the hippocampus of alcoholics. *Alcohol Clin Exp Res*, 23, 164-8 (1999)
9. A. J. Harding, A. Wong, M. Svoboda, J. J. Kril & G. M. Halliday: Chronic alcohol consumption does not cause hippocampal neuron loss in humans. *Hippocampus*, 7, 78-87 (1997)
10. J. J. Kril & G. M. Halliday: Brain shrinkage in alcoholics: a decade on and what have we learned? *Prog Neurobiol*, 58, 381-7 (1999)
11. C. Harper & J. Kril: Patterns of neuronal loss in the cerebral cortex in chronic alcoholic patients. *J.Neurol.Sci.*, 92, 81-89 (1989)
12. M. E. Schwab & D. Bartholdi: Degeneration and regeneration of axons in the lesioned spinal cord. *Physiol Rev*, 76, 319-70. (1996)
13. C. A. Dlugos & R. J. Pentney: Morphometric evidence that the total number of synapses on Purkinje neurons of old F344 rats is reduced after long-term ethanol treatment and restored to control levels after recovery. *Alcohol and Alcoholism*, 32, 161-172 (1997)

14. C. Harper & I. Matsumoto: Ethanol and brain damage. *Curr Opin Pharmacol*, 5, 73-8 (2005)
15. P. J. Brooks: Brain atrophy and neuronal loss in alcoholism: a role for DNA damage? *Neurochem Int*, 37, 403-12 (2000)
16. D. Wu & A. I. Cederbaum: Alcohol, oxidative stress, and free radical damage. *Alcohol Res Health*, 27, 277-84 (2003)
17. C. Harper, I. Matsumoto, A. Pfefferbaum, E. Adalsteinsson, E. V. Sullivan, J. Lewohl, P. Dodd, M. Taylor, G. Fein & B. Landman: The pathophysiology of 'brain shrinkage' in alcoholics - structural and molecular changes and clinical implicaitons. *Alc Clin Exp Research*, 29, 1106-15 (2005)
18. S. Bleich, D. Degner, W. Sperling, D. Bonsch, N. Thurauf & J. Kornhuber: Homocysteine as a neurotoxin in chronic alcoholism. *Prog Neuropsychopharmacol Biol Psychiatry*, 28, 453-64 (2004)
19. J. Wilhelm, K. Bayerlein, T. Hillemacher, U. Reulbach, H. Frieling, B. Kromolan, D. Degner, J. Kornhuber & S. Bleich: Short-term cognition deficits during early alcohol withdrawal are associated with elevated plasma homocysteine levels in patients with alcoholism. *J Neural Transm*, 113, 357-63 (2006)
20. S. Bleich, K. Bayerlein, U. Reulbach, T. Hillemacher, D. Bonsch, B. Mugele, J. Kornhuber & W. Sperling: Homocysteine levels in patients classified according to Lesch's typology. *Alcohol Alcohol*, 39, 493-8 (2004)
21. B. R. Harris, D. A. Gibson, M. A. Prendergast, J. A. Blanchard, R. C. Holley, S. R. Hart, R. L. Scotland, T. C. Foster, N. W. Pedigo & J. M. Littleton: The neurotoxicity induced by ethanol withdrawal in mature organotypic hippocampal slices might involve cross-talk between metabotropic glutamate type 5 receptors and N-methyl-D-aspartate receptors. *Alcohol Clin Exp Res*, 27, 1724-35 (2003)
22. M. A. Prendergast, B. R. Harris, S. Mayer & J. M. Littleton: Chronic, but not acute, nicotine exposure attenuates ethanol withdrawal-induced hippocampal damage *in vitro*. *Alcohol Clin Exp Res*, 24, 1583-92 (2000)
23. P. De Witte: Imbalance between neuroexcitatory and neuroinhibitory amino acids causes craving for ethanol. *Addict Behav*, 29, 1325-39 (2004)
24. S. C. Bowden, F. T. Crews, M. E. Bates, W. Fals-Stewart & M. L. Ambrose: Neurotoxicity and neurocognitive impairments with alcohol and drug-use disorders: potential roles in addiction and recovery. *Alcohol Clin Exp Res*, 25, 317-21 (2001)
25. A. Pfefferbaum, M. Rosenbloom, K. Crusan & T. L. Jernigan: Brain CT changes in alcoholics: effects of age and alcohol consumption. *Alcohol Clin Exp Res*, 12, 81-87 (1988)
26. A. Pfefferbaum, E. V. Sullivan, M. J. Rosenbloom, P. K. Shear, D. H. Mathalon & K. O. Lim: Increase in brain cerebrospinal fluid volume is greater in older than in younger alcoholic patients: a replication study and CT/MRI comparison. *Psychiatry Research*, 50, 257-274 (1993)
27. E. V. Sullivan & A. Pfefferbaum: Neurocircuitry in alcoholism: a substrate of disruption and repair. *Psychopharmacology (Berl)*, 180, 583-94 (2005)
28. C. Harper: The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *Journal of Neuropathology and Experimental Neurology*, 57, 101-10 (1998)
29. G. Fein, V. Di Sclafani, V. A. Cardenas, H. Goldmann, M. Tolou-Shams & D. J. Meyerhoff: Cortical gray matter loss in treatment--naive alcohol dependent individuals. *Alcohol Clin Exp Res*, 26, 558-64 (2002)
30. V. A. Cardenas, C. Studholme, D. J. Meyerhoff, E. Song & M. W. Weiner: Chronic active heavy drinking and family history of problem drinking modulate regional brain tissue volumes. *Psychiatry Res*, 138, 115-30 (2005)
31. A. Pfefferbaum, K. O. Lim, R. B. Zipursky, D. H. Mathalon, M. J. Rosenbloom, B. Lane, C. N. Ha & E. V. Sullivan: Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcohol Clin Exp Res*, 16, 1078-1089 (1992)
32. G. M. Ditraglia, D. S. Press, N. Butters, T. L. Jernigan, L. S. Cermak, R. A. Velin, P. K. Shear, M. Irwin & M. Schuckit: Assessment of olfactory deficits in detoxified alcoholics. *Alcohol*, 8, 109-115 (1991)
33. V. A. Cardenas, C. Studholme, S. Gazdzinski, T. C. Durazzo & D. J. Meyerhoff: Deformation based morphometry of brain changes in alcohol dependence and abstinence *Neuroimage*., 34, 879-87 (2007)
34. A. Pfefferbaum, E. V. Sullivan, D. H. Mathalon & K. O. Lim: Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol Clin Exp Res*, 21, 521-9 (1997)
35. K. Mann, I. Agartz, C. Harper, S. Shoaf, R. R. Rawlings, R. Momenan, D. W. Hommer, A. Pfefferbaum, E. V. Sullivan, R. F. Anton, D. J. Drobes, M. S. George, R. Bares, H. J. Machulla, G. Mundle, M. Reimold & A. Heinz: Neuroimaging in alcoholism: ethanol and brain damage. *Alcohol Clin Exp Res*, 25, 104S-109S (2001)
36. M. T. Ratti, D. Soragna, L. Sibilla, A. Giardini, A. Albergati, F. Savoldi & P. Bo: Cognitive impairment and cerebral atrophy in "heavy drinkers". *Prog Neuropsychopharmacol Biol Psychiatry*, 23, 243-58 (1999)
37. I. Agartz, R. Momenan, R. R. Rawlings, M. J. Kerich & D. W. Hommer: Hippocampal volume in patients with alcohol dependence. *Arch Gen Psychiatry*, 56, 356-63 (1999)
38. S. Bleich, W. Sperling, D. Degner, E. Graesel, K. Bleich, J. Wilhelm, U. Havemann-Reinecke, K. Javaheripour & J. Kornhuber: Lack of association between hippocampal volume reduction and first-ons*et al*cohol withdrawal seizure. A volumetric MRI study. *Alcohol Alcohol*, 38, 40-4 (2003)
39. M. P. Laakso, O. Vaurio, L. Savolainen, E. Repo, H. Soininen, H. J. Aronen & J. Tiihonen: A volumetric MRI study of the hippocampus in type 1 and 2 alcoholism. *Behavioural Brain Research*, 109, 177-186 (2000)
40. D. Hommer, R. Momenan, P. Ragan, W. Williams, D. Rio & M. Eckardt: Decreased cross-sectional area of the corpus callosum in young female alcoholics: An MRI study. *Alcoholism: Clinical and Experimental Research*, 19, 95A (1995)
41. M. Oishi, Y. Mochizuki & E. Shikata: Corpus callosum atrophy and cerebral blood flow in chronic alcoholics. *J Neurol Sci*, 162, 51-5 (1999)
42. A. Pfefferbaum, K. O. Lim, J. Desmond & E. V. Sullivan: Thinning of the corpus callosum in older alcoholic men: An MRI study. *Alcoholism: Clinical and Experimental Research*, 20, 752-757 (1996)

43. E. Sullivan, M. J. Rosenbloom, A. Deshmukh, J. E. Desmond & A. Pfefferbaum: Volumetric MRI analysis of cerebellar hemispheres and vermis in chronic alcoholics: Relationship to Ataxis. *24th Annual Meeting of the International Neuropsychological Society, Chicago* (1996)
44. E. V. Sullivan: Compromised pontocerebellar and cerebellothalamocortical systems: speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. *Alcohol Clin Exp Res*, 27, 1409-19 (2003)
45. E. V. Sullivan, A. Deshmukh, J. E. Desmond, K. O. Lim & A. Pfefferbaum: Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: relation to ataxia. *Neuropsychology*, 14, 341-52 (2000)
46. M. D. Davila, P. H. Shear, B. Lane, E. Z. Sullivan & A. Pfefferbaum: Mammillary body and cerebellar shrinkage in chronic alcoholics: An MRI and neuropsychology study. *Neuropsychology*, 8, 433-444 (1994)
47. E. V. Sullivan, A. Deshmukh, E. De Rosa, M. J. Rosenbloom & A. Pfefferbaum: Striatal and forebrain nuclei volumes: contribution to motor function and working memory deficits in alcoholism. *Biol Psychiatry*, 57, 768-76 (2005)
48. E. V. Sullivan, B. Lane, A. Deshmukh, M. J. Rosenbloom, J. E. Desmond, K. O. Lim & A. Pfefferbaum: *In vivo* mammillary body volume deficits in amnesic and nonamnesic alcoholics. *Alcohol Clin Exp Res*, 23, 1629-36 (1999)
49. P. K. Shear, E. V. Sullivan, B. Lane & A. Pfefferbaum: Mammillary body and cerebellar shrinkage in chronic alcoholics with and without amnesia. *Alcohol Clin Exp Res*, 20, 1489-95 (1996)
50. S. Gazdzinski, T. C. Durazzo, C. Studholme, E. Song, P. Banys & D. J. Meyerhoff: Quantitative brain MRI in alcohol dependence: preliminary evidence for effects of concurrent chronic cigarette smoking on regional brain volumes. *Alcohol Clin Exp Res*, 29, 1484-95 (2005)
51. E. Sullivan: Compromised Pontocerebellar and Cerebellothalamocortical Systems: Speculations on Their Contributions to Cognitive and Motor Impairment in Nonamnesic Alcoholism. *Alcohol Clin Exp Res*, 27, 1409-1419 (2003)
52. F. T. Crews, T. Buckley, P. R. Dodd, G. Ende, N. Foley, C. Harper, J. He, D. Innes, W. Loh el, A. Pfefferbaum, J. Zou & E. V. Sullivan: Alcoholic neurobiology: changes in dependence and recovery. *Alcohol Clin Exp Res*, 29, 1504-13 (2005)
53. R. B. Zipursky, K. C. Lim & A. Pfefferbaum: MRI study of brain changes with short-term abstinence from alcohol. *Alcohol Clin Exp Res*, 13, 664-666 (1989)
54. P. K. Shear, T. L. Jernigan & N. Butters: Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics [published erratum appears in Alcohol Clin Exp Res 1994 Jun;18(3):766]. *Alcohol Clin Exp Res*, 18, 172-176 (1994)
55. A. Pfefferbaum, E. V. Sullivan, D. H. Mathalon, P. K. Shear, M. J. Rosenbloom & K. O. Lim: Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcohol Clin Exp Res*, 19, 1177-1191 (1995)
56. I. Agartz, S. Brag, J. Franck, A. Hammarberg, G. Okugawa, K. Svinhufvud & H. Bergman: MR volumetry during acute alcohol withdrawal and abstinence: a descriptive study. *Alcohol Alcohol*, 38, 71-8 (2003)
57. S. Gazdzinski, T. C. Durazzo & D. J. Meyerhoff: Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. *Drug Alcohol Depend*, 78, 263-73 (2005)
58. W. Trabert, T. Betz, M. Niewald & G. Huber: Significant reversibility of alcoholic brain shrinkage within 3 weeks of abstinence. *Acta Psychiatr Scand*, 92, 87-90 (1995)
59. A. Drake, T. Jernigan, N. Butters & e. al: Volumetric changes on magnetic resonance imaging in chronic alcoholics: A one year followup. *22nd annual meeting of the International Neuropsychological Society, Cincinnati*, (1994).
60. A. Pfefferbaum, E. V. Sullivan, M. J. Rosenbloom, D. H. Mathalon & K. O. Lim: A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry*, 55, 905-12 (1998)
61. J. O'Neill, V. A. Cardenas & D. J. Meyerhoff: Effects of abstinence on the brain: quantitative magnetic resonance imaging and magnetic resonance spectroscopic imaging in chronic alcohol abuse. *Alcohol Clin Exp Res*, 25, 1673-82 (2001)
62. E. V. Sullivan, M. J. Rosenbloom, K. O. Lim & A. Pfefferbaum: Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: relationships to changes in brain structure. *Neuropsychology*, 14, 178-88 (2000)
63. E. V. Sullivan, L. Marsh, D. H. Mathalon, K. O. Lim & A. Pfefferbaum: Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiol Aging*, 16, 591-606 (1995)
64. J. S. Meyer, G. M. Rauch, K. Crawford, R. A. Rauch, S. Konno, H. Akiyama, Y. Terayama & A. Haque: Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. *Int J Geriatr Psychiatry*, 14, 1050-61 (1999)
65. P. J. Visser, P. Scheltens, F. R. Verhey, B. Schmand, L. J. Launer, J. Jolles & C. Jonker: Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. *Journal of Neurology*, 246, 477-85 (1999)
66. K. O. Lim & J. A. Helpern: Neuropsychiatric applications of DTI - a review. *NMR Biomed*, 15, 587-93 (2002)
67. M. Moseley: Diffusion tensor imaging and aging - a review. *NMR Biomed*, 15, 553-60 (2002)
68. S. K. Song, S. W. Sun, W. K. Ju, S. J. Lin, A. H. Cross & A. H. Neufeld: Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage*, 20, 1714-22 (2003)
69. E. V. Sullivan & A. Pfefferbaum: Diffusion tensor imaging in normal aging and neuropsychiatric disorders. *Eur J Radiol*, 45, 244-55 (2003)
70. M. Rosenbloom, E. V. Sullivan & A. Pfefferbaum: Using magnetic resonance imaging and diffusion tensor imaging to assess brain damage in alcoholics. *Alcohol Res Health*, 27, 146-52 (2003)
71. M. O'Sullivan, D. K. Jones, P. E. Summers, R. G. Morris, S. C. Williams & H. S. Markus: Evidence for

cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*, 57, 632-8 (2001)
72. M. S. Mega & J. L. Cummings: Frontal-subcortical circuits and neuropsychiatric disorders. *J Neuropsychiatry Clin Neurosci*, 6, 358-70 (1994)
73. A. Pfefferbaum & E. V. Sullivan: Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *Neuroimage*, 15, 708-18 (2002)
74. T. Schulte, E. V. Sullivan, E. M. Muller-Oehring, E. Adalsteinsson & A. Pfefferbaum: Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb Cortex*, 15, 1384-92 (2005)
75. A. Pfefferbaum, E. V. Sullivan, M. Hedehus, E. Adalsteinsson, K. O. Lim & M. Moseley: *In vivo* detection and functional correlates of white matter microstructural disruption in chronic alcoholism. *Alcohol Clin Exp Res*, 24, 1214-21 (2000)
76. X. Ma, C. D. Coles, M. E. Lynch, S. M. Laconte, O. Zurkiya, D. Wang & X. Hu: Evaluation of corpus callosum anisotropy in young adults with fetal alcohol syndrome according to diffusion tensor imaging. *Alcohol Clin Exp Res*, 29, 1214-22 (2005)
77. S. K. Song, S. W. Sun, M. J. Ramsbottom, C. Chang, J. Russell & A. H. Cross: Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*, 17, 1429-36 (2002)
78. S. K. Song, J. Yoshino, T. Q. Le, S. J. Lin, S. W. Sun, A. H. Cross & R. C. Armstrong: Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage*, 26, 132-40 (2005)
79. O. Abe, H. Yamada, Y. Masutani, S. Aoki, A. Kunimatsu, H. Yamasue, R. Fukuda, K. Kasai, N. Hayashi, T. Masumoto, H. Mori, T. Soma & K. Ohtomo: Amyotrophic lateral sclerosis: diffusion tensor tractography and voxel-based analysis. *NMR Biomed*, 17, 411-6 (2004)
80. P. J. Basser, S. Pajevic, C. Pierpaoli, J. Duda & A. Aldroubi: *In vivo* fiber tractography using DT-MRI data. *Magn Reson Med*, 44, 625-32 (2000)
81. J. R. Moffett, M. A. Namboodiri, C. B. Cangro & J. H. Neale: Immunohistochemical localization of N-acetylaspartate in rat brain. *Neuroreport*, 2, 131-134 (1991)
82. M. L. Simmons, C. G. Frondoza & J. T. Coyle: Immunocytochemical localization of N-acetyl-aspartate with monoclonal antibodies. *Neuroscience*, 45, 37-45 (1991)
83. J. Vion-Dury, D. J. Meyerhoff, P. J. Cozzone & M. W. Weiner: What might be the impact on neurology of the analysis of brain metabolism by *in vivo* magnetic resonance spectroscopy? [editorial]. *Journal of Neurology*, 241, 354-371 (1994)
84. N. De Stefano, P. M. Matthews & D. L. Arnold: Reversible decreases in N-acetylaspartate after acute brain injury. *Magnetic Resonance in Medicine*, 34, 721-727 (1995)
85. J. W. Hugg, R. I. Kuzniecky, F. G. Gilliam, R. B. Morawetz, R. E. Faught & H. P. Hetherington: Normalization of contralateral metabolic function following temporal lobectomy demonstrated by h-1 magnetic resonance spectroscopic imaging. *Ann.Neurol.*, V40, 236-239 (1996)
86. N. Schuff, F. Ezekiel, A. Gamst, D. Amend, A. Capizzano, A. A. Maudsley & M. W. Weiner: Region and tissue differences of metabolites in normally aged brain using 1H magnetic resonance spectroscopic imaging. *Magnetic Resonance in Medicine*, 45, 899-907 (2001)
87. P. B. Barker, S. N. Breiter, B. J. Soher, J. C. Chathamn, J. R. Forder, M. A. Samphilipo, C. A. Magee & J. A. Anderson: Quantitative proton spectroscopy of canine brain: *in vivo* and *in vitro* correlations. *Magnetic Resonance in Medicine*, 32, 157-163 (1994)
88. B. L. Miller, L. Chang, R. Booth, T. Ernst, M. Cornford, D. Nikas, D. McBride & D. J. Jenden: *In vivo* 1H MRS choline: correlation with *in vitro* chemistry/histology. *Life Sciences*, 58, 1929-1935 (1996)
89. B. Ross & S. Bluml: Magnetic resonance spectroscopy of the human brain. *Anat Rec*, 265, 54-84 (2001)
90. A. Brand, C. Richter-Landsberg & D. Leibfritz: Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. *Dev.Neurosci.*, 15, 289-298 (1993)
91. B. C. Schweinsburg, M. J. Taylor, J. S. Videen, O. M. Alhassoon, T. L. Patterson & I. Grant: Elevated myo-inositol in gray matter of recently detoxified but not long-term alcoholics: A preliminary MR spectroscopy study. *Alc Clin Exp Res.*, 24, 699-770 (2000)
92. K. J. Ferguson, A. M. MacLullich, I. Marshall, I. J. Deary, J. M. Starr, J. R. Seckl & J. M. Wardlaw: Magnetic resonance spectroscopy and cognitive function in healthy elderly men. *Brain*, 125, 2743-9 (2002)
93. G. Fein, D. J. Meyerhoff, V. Di Sclafani, F. Ezekiel, N. Poole, S. MacKay, W. P. Dillon, J.-M. Constans & M. W. Weiner: 1H magnetic resonance spectroscopic imaging separates neuronal from Glial changes in alcohol-related brain atrophy. *Chapter in NIAAA Research Monograph No. 27/Alcohol and Glial Cells*227-241 (1994)
94. D. Meyerhoff, R. Blumenfeld, D. Truran, J. Lindgren, D. Flenniken, V. Cardenas, L. L. Chao, J. Rothlind, C. Studholme & H. Weiner: Effects of heavy drinking, binge drinking, and family history of alcoholism on regional brain metabolites. *Alcohol Clin Exp Res*, 28, 650-61 (2004)
95. M. Bendszus, H. G. Weijers, G. Wiesbeck, M. Warmuth-Metz, A. J. Bartsch, S. Engels, J. Boning & L. Solymosi: Sequential MR imaging and proton MR spectroscopy in patients who underwent recent detoxification for chronic alcoholism: correlation with clinical and neuropsychological data. *AJNR Am J Neuroradiol*, 22, 1926-32 (2001)
96. N. R. Jagannathan, N. G. Desai & P. Raghunathan: Brain metabolite changes in alcoholism: An *in vivo* proton magnetic resonance spectroscopy (MRS) study. *Magnetic Resonance Imaging*, 14, 553-557 (1996)
97. M. H. Parks, B. M. Dawant, W. R. Riddle, S. L. Hartmann, M. S. Dietrich, M. K. Nickel, R. R. Price & P. R. Martin: Longitudinal brain metabolic characterization of chronic alcoholics with proton magnetic resonance spectroscopy. *Alcohol Clin Exp Res*, 26, 1368-80 (2002)
98. D. Seitz, U. Widmann, U. Seeger, T. Nagele, U. Klose, K. Mann & W. Grodd: Localized proton magnetic resonance spectroscopy of the cerebellum in detoxifying alcoholics. *Alcohol Clin Exp Res*, 23, 158-163 (1999)
99. P. R. Martin, S. J. Gibbs, A. A. Nimmerrichter, W. R. Riddle, L. W. Welch & M. R. Willcott: Brain proton magnetic resonance spectroscopy studies in recently abstinent alcoholics. *Alcohol Clin Exp Res*, 19, 1078-1082 (1995)

100. B. C. Schweinsburg, M. J. Taylor, O. M. Alhassoon, J. S. Videen, G. G. Brown, T. L. Patterson, F. Berger & I. Grant: Chemical pathology in brain white matter of recently detoxified alcoholics: a 1H magnetic resonance spectroscopy investigation of alcohol-associated frontal lobe injury. *Alcohol Clin Exp Res*, 25, 924-34 (2001)
101. A. J. Bartsch, G. Homola, A. Biller, S. M. Smith, H. G. Weijers, G. A. Wiesbeck, M. Jenkinson, N. De Stefano, L. Solymosi & M. Bendszus: Manifestations of early brain recovery associated with abstinence from alcoholism. *Brain*, 130, 36-47 (2007)
102. G. Ende, H. Welzel, S. Walter, W. Weber-Fahr, A. Diehl, D. Hermann, A. Heinz & K. Mann: Monitoring the Effects of Chronic Alcohol Consumption and Abstinence on Brain Metabolism: A Longitudinal Proton Magnetic Resonance Spectroscopy Study. *Biol Psychiatry* (2005)
103. P. W. Kalivas & N. D. Volkow: The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*, 162, 1403-13 (2005)
104. J. A. Coffman & F. Petty: Plasma GABA levels in chronic alcoholics. *Am J Psychiatry*, 142, 1204-5 (1985)
105. B. Adinoff, G. L. Kramer & F. Petty: Levels of gamma-aminobutyric acid in cerebrospinal fluid and plasma during alcohol withdrawal. *Psychiatry Res*, 59, 137-44 (1995)
106. H. P. Hetherington, B. R. Newcomer & J. W. Pan: Measurements of human cerebral GABA at 4.1 T using numerically optimized editing pulses. *Magn Reson Med*, 39, 6-10 (1998)
107. D. L. Rothman, K. L. Behar, F. Hyder & R. G. Shulman: *In vivo* NMR studies of the glutamate neurotransmitter flux and neuroenergetics: implications for brain function. *Annu Rev Physiol*, 65, 401-27 (2003)
108. G. F. Mason, I. L. Petrakis, R. A. de Graaf, R. Gueorguieva, E. Guidone, V. Coric, C. N. Epperson, D. L. Rothman & J. H. Krystal: Cortical gamma-aminobutyric acid levels and the recovery from ethanol dependence: preliminary evidence of modification by cigarette smoking. *Biol Psychiatry*, 59, 85-93 (2006)
109. A. Dahchour, F. Lallemand, R. J. Ward & P. De Witte: Production of reactive oxygen species following acute ethanol or acetaldehyde and its reduction by acamprosate in chronically alcoholized rats. *Eur J Pharmacol*, 520, 51-8 (2005)
110. F. Fadda & Z. L. Rossetti: Chronic ethanol consumption: from neuroadaptation to neurodegeneration. *Prog Neurobiol*, 56, 385-431 (1998)
111. I. Nevo & M. Hamon: Neurotransmitter and neuromodulatory mechanisms involved in alcohol abuse and alcoholism. *Neurochem Int*, 26, 305-36; discussion 337-42 (1995)
112. C. L. Faingold, P. N'Gouemo & A. Riaz: Ethanol and neurotransmitter interactions--from molecular to integrative effects. *Prog Neurobiol*, 55, 509-35 (1998)
113. J. M. Nicolas, A. M. Catafau, R. Estruch, F. J. Lomena, M. Salamero, R. Herranz, R. Monforte, C. Cardenal & A. Urbano-Marquez: Regional cerebral blood flow-SPECT in chronic alcoholism: relation to neuropsychological testing. *J Nucl Med*, 34, 1452-9 (1993)
114. N. D. Volkow, R. Hitzemann, G. J. Wang, J. S. Fowler, G. Burr, K. Pascani, S. L. Dewey & A. P. Wolf: Decreased brain metabolism in neurologically intact healthy alcoholics. *Am J Psychiatry*, 149, 1016-22. (1992)
115. G. J. Wang, N. D. Volkow, C. T. Roque, V. L. Cestaro, R. J. Hitzemann, E. L. Cantos, A. V. Levy & A. P. Dhawan: Functional importance of ventricular enlargement and cortical atrophy in healthy subjects and alcoholics as assessed with PET, MR imaging, and neuropsychologic testing [see comments]. *Radiology*, 186, 59-65 (1993)
116. D. A. Gansler, G. J. Harris, M. Oscar-Berman, C. Streeter, R. F. Lewis, I. Ahmed & D. Achong: Hypoperfusion of inferior frontal brain regions in abstinent alcoholics: a pilot SPECT study. *J Stud Alcohol*, 61, 32-7 (2000)
117. B. Demir, B. Ulug, E. Lay Ergun & B. Erbas: Regional cerebral blood flow and neuropsychological functioning in early and late ons*et al*coholism. *Psychiatry Res*, 115, 115-25 (2002)
118. R. L. Rogers, J. S. Meyer, T. G. Shaw & K. F. Mortel: Reductions in regional cerebral blood flow associated with chronic consumption of alcohol. *J.Am.Geriatr.Soc.*, 31, 540-543 (1983)
119. G. Wik, S. Borg, I. Sjogren, F. A. Wiesel, G. Blomqvist, J. Borg, T. Greitz, H. Nyback, G. Sedvall & S. Stone-Elander: PET determination of regional cerebral glucose metabolism in alcohol-dependent men and healthy controls using 11C-glucose. *Acta Psychiatr.Scand.*, 78, 234-241 (1988)
120. R. M. Dupont, S. B. Rourke, I. Grant, P. P. Lehr, R. J. Reed, K. Challakere, G. Lamoureux & S. Halpern: Single photon emission computed tomography with iodoamphetamine-123 and neuropsychological studies in long-term abstinent alcoholics. *Psychiatry Res*, 67, 99-111 (1996)
121. A. C. Kuruoglu, Z. Arikan, G. Vural, M. Karatas, M. Arac & E. Isik: Single photon emission computerised tomography in chronic alcoholism. Antisocial personality disorder may be associated with decreased frontal perfusion. *Br J Psychiatry*, 169, 348-54 (1996)
122. Y. Samson, J. C. Baron, A. Feline, J. Bories & C. Crouzel: Local cerebral glucose utilisation in chronic alcoholics: a positron tomographic study. *J.Neurol.Neurosurg.Psychiatry*, 49, 1165-1170 (1986)
123. N. Schuff, G.-H. Jahng, X.-P. Zhu, K.-L. Li & M. Weiner: Age-related changes of brain perfusion by aterial spin labeled MRI. *Neurobiology of Aging*, 25, 274 (2004)
124. N. Schuff, A.-T. Du, S. Mueller, G.-H. Jahng, L. Stables, N. Cashdollar & M. W. Weiner: Regional Decline of Brain Cerebral Blood Flow in Healthy Aging by High-Field Arterial Spin Labeling. *AAN*, (2006).
125. M. Berglund, S. Hagstadius, J. Risberg, T. M. Johanson, A. Bliding & Z. Mubrin: Normalization of regional cerebral blood flow in alcoholics during the first 7 weeks of abstinence. *Acta Psychiatr Scand*, 75, 202-8 (1987)
126. K. M. Adams, S. Gilman, R. Koeppe & e. al.: Correlation of neuropsychological function with cerebral metabolic rate in subdivisions of frontal lobes of older alcoholic patients measured with 18F fluorodeoxyglucose and positron emission tomography. *Neuropsychology*, 9, 275-340 (1995)
127. X. Noel, J. Paternot, M. Van der Linden, R. Sferrazza, M. Verhas, C. Hanak, C. Kornreich, P. Martin, J. De Mol, I. Pelc & P. Verbanck: Correlation between inhibition, working memory and delimited frontal area blood flow

measure by 99mTc-Bicisate SPECT in alcohol-dependent patients. *Alcohol Alcohol*, 36, 556-63 (2001)
128. X. Noel, R. Sferrazza, M. Van Der Linden, J. Paternot, M. Verhas, C. Hanak, I. Pelc & P. Verbanck: Contribution of frontal cerebral blood flow measured by (99m)Tc-Bicisate spect and executive function deficits to predicting treatment outcome in alcohol-dependent patients. *Alcohol Alcohol*, 37, 347-54 (2002)
129. A. Tutus, N. Kugu, S. Sofuoglu, M. Nardali, A. Simsek, F. Karaaslan & A. S. Gonul: Transient frontal hypoperfusion in Tc-99m hexamethylpropyleneamineoxime single photon emission computed tomography imaging during alcohol withdrawal. *Biol Psychiatry*, 43, 923-8 (1998)
130. C. A. Gebhardt, M. A. Naeser & N. Butters: Computerized measures of CT scans of alcoholics: thalamic region related to memory. *Alcohol*, 1, 133-40 (1984)
131. T. C. Durazzo, S. Gazdzinski, P. Banys & D. J. Meyerhoff: Brain metabolite concentrations and neurocognition during short-term recovery from alcohol dependence: Preliminary evidence of the effects of concurrent chronic cigarette smoking. *Alc Clin Exp Research*, 30, 539-51 (2006)
132. I. Boileau, J. M. Assaad, R. O. Pihl, C. Benkelfat, M. Leyton, M. Diksic, R. E. Tremblay & A. Dagher: Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse*, 49, 226-31 (2003)
133. J. Hietala, C. West, E. Syvalahti, K. Nagren, P. Lehikoinen, P. Sonninen & U. Ruotsalainen: Striatal D2 dopamine receptor binding characteristics *in vivo* in patients with alcohol dependence. *Psychopharmacology (Berl)*, 116, 285-90 (1994)
134. D. Martinez, R. Gil, M. Slifstein, D. R. Hwang, Y. Huang, A. Perez, L. Kegeles, P. Talbot, S. Evans, J. Krystal, M. Laruelle & A. Abi-Dargham: Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry*, 58, 779-86 (2005)
135. N. D. Volkow, G. J. Wang, J. S. Fowler, J. Logan, R. Hitzemann, Y. S. Ding, N. Pappas, C. Shea & K. Piscani: Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol Clin Exp Res*, 20, 1594-8 (1996)
136. M. Dettling, A. Heinz, P. Dufeu, H. Rommelspacher, K. J. Graf & L. G. Schmidt: Dopaminergic responsivity in alcoholism: trait, state, or residual marker? *Am J Psychiatry*, 152, 1317-21 (1995)
137. A. Heinz, P. Dufeu, S. Kuhn, M. Dettling, K. Graf, I. Kurten, H. Rommelspacher & L. G. Schmidt: Psychopathological and behavioral correlates of dopaminergic sensitivity in alcohol-dependent patients. *Arch Gen Psychiatry*, 53, 1123-8 (1996)
138. S. J. Nixon & O. A. Parsons: Alcohol-related efficiency deficits using an ecologically valid test. *Alcohol Clin Exp Res*, 15, 601-6 (1991)
139. S. J. Nixon, R. Tivis & O. A. Parsons: Behavioral dysfunction and cognitive efficiency in male and female alcoholics. *Alcohol Clin Exp Res*, 19, 577-81 (1995)
140. A. Lawton-Craddock, S. J. Nixon & R. Tivis: Cognitive efficiency in stimulant abusers with and without alcohol dependence. *Alcohol Clin Exp Res*, 27, 457-64 (2003)
141. S. W. Glenn & O. A. Parsons: Impaired efficiency in female alcoholics' neuropsychological performance. *J Clin Exp Neuropsychol*, 13, 895-908 (1991)
142. S. W. Glenn & O. A. Parsons: Neuropsychological efficiency measures in male and female alcoholics. *J Stud Alcohol*, 53, 546-52 (1992)
143. A. Bechara, S. Dolan, N. Denburg, A. Hindes, S. W. Anderson & P. E. Nathan: Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, 39, 376-89 (2001)
144. H. F. Moselhy, G. Georgiou & A. Kahn: Frontal lobe changes in alcoholism: a review of the literature. *Alcohol Alcohol*, 36, 357-68 (2001)
145. H. Ihara, G. E. Berrios & M. London: Group and case study of the dysexecutive syndrome in alcoholism without amnesia. *J Neurol Neurosurg Psychiatry*, 68, 731-7 (2000)
146. E. V. Sullivan, M. J. Rosenbloom & A. Pfefferbaum: Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin Exp Res*, 24, 611-21 (2000)
147. S. B. Rourke & I. Grant: The interactive effects of age and length of abstinence on the recovery of neuropsychological functioning in chronic male alcoholics: a 2-year follow-up study. *J Int Neuropsychol Soc*, 5, 234-46. (1999)
148. J. Brandt, N. Butters, C. Ryan & R. Bayog: Cognitive loss and recovery in long-term alcohol abusers. *Archives of General Psychiatry*, 40, 435-42 (1983)
149. G. Fein, L. Bachman, S. Fisher & L. Davenport: Cognitive impairments in abstinent alcoholics. *The Western Journal of Medicine*, 152, 531-537 (1990)
150. W. W. Beatty, K. A. Hames, C. R. Blanco, S. J. Nixon & L. J. Tivis: Visuospatial perception, construction and memory in alcoholism. *J Stud Alcohol*, 57, 136-43 (1996)
151. C. A. Munro, J. Saxton & M. A. Butters: The neuropsychological consequences of abstinence among older alcoholics: a cross-sectional study. *Alcohol Clin Exp Res*, 24, 1510-6 (2000)
152. V. Di Sclafani, F. Ezekiel, D. J. Meyerhoff, S. MacKay, W. P. Dillon, M. W. Weiner & G. Fein: Brain atrophy and cognitive function in older abstinent alcoholic men. *Alcohol Clin Exp Res*, 19, 1121-1126 (1995)
153. R. Fama, A. Pfefferbaum & E. V. Sullivan: Perceptual learning in detoxified alcoholic men: contributions from explicit memory, executive function, and age. *Alcohol Clin Exp Res*, 28, 1657-65 (2004)
154. E. Sullivan, M. J. Rosenbloom, A. Deshmukh, J. E. Desmond & A. Pfefferbaum: Alcohol and the cerebellum: Effects on balance, coordination, and cognition. *Alcohol Health & Research World*, 19, 138-141 (1995)
155. R. J. Reed, I. Grant & S. B. Rourke: Long-term abstinent alcoholics have normal memory. *Alcohol Clin Exp Res*, 16, 677-83. (1992)
156. K. Mann, A. Gunther, F. Stetter & K. Ackermann: Rapid recovery from cognitive deficits in abstinent alcoholics: a controlled test-retest study. *Alcohol Alcohol*, 34, 567-74 (1999)
157. A. J. Wegner, A. Gunthner & M. Fahle: Visual performance and recovery in recently detoxified alcoholics. *Alcohol Alcohol*, 36, 171-9 (2001)
158. M. E. Bates, S. C. Bowden & D. Barry: Neurocognitive impairment associated with alcohol use

disorders: implications for treatment. *Exp Clin Psychopharmacol*, 10, 193-212 (2002)
159. O. A. Parsons: Neurocognitive deficits in alcoholics and social drinkers: a continuum? *Alcohol Clin Exp Res*, 22, 954-61 (1998)
160. T. C. Durazzo, J. C. Rothlind, S. Gazdzinski, P. Banys & D. J. Meyerhoff: A comparison of neurocognitive function in nonsmoking and chronically smoking short-term abstinent alcoholics. *Alcohol*, 39, 1-11 (2006)
161. O. A. Parsons & S. J. Nixon: Cognitive functioning in sober social drinkers: a review of the research since 1986. *J Stud Alcohol*, 59, 180-90 (1998)
162. G. Fein & B. Landman: Treated and treatment-naive alcoholics come from different populations. *Alcohol*, 35, 19-26 (2005)
163. G. Fein, V. Di Sclafani & D. J. Meyerhoff: Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug Alcohol Depend*, 68, 87-93 (2002)
164. H. R. Kranzler & R. N. Rosenthal: Dual diagnosis: alcoholism and co-morbid psychiatric disorders. *Am J Addict*, 12 Suppl 1, S26-40 (2003)
165. P. Rohde, C. W. Kahler, P. M. Lewinsohn & R. A. Brown: Psychiatric disorders, familial factors, and cigarette smoking: II. Associations with progression to daily smoking. *Nicotine Tob Res*, 6, 119-32 (2004)
166. G. Fein, V. Di Sclafani, P. Finn & D. L. Scheiner: Sub-diagnostic psychiatric comorbidity in alcoholics. *Drug Alcohol Depend* (2006)
167. J. Lukassen & M. P. Beaudet: Alcohol dependence and depression among heavy drinkers in Canada. *Soc Sci Med*, 61, 1658-67 (2005)
168. E. B. Raimo & M. A. Schuckit: Alcohol dependence and mood disorders. *Addict Behav*, 23, 933-46 (1998)
169. S. E. Gilman & H. D. Abraham: A longitudinal study of the order of onset of alcohol dependence and major depression. *Drug Alcohol Depend*, 63, 277-86 (2001)
170. E. V. Sullivan, A. Deshmukh, J. E. Desmond, D. H. Mathalon, M. J. Rosenbloom, K. O. Lim & A. Pfefferbaum: Contribution of alcohol abuse to cerebellar volume deficits in men with schizophrenia. *Arch Gen Psychiatry*, 57, 894-902 (2000)
171. P. Jha, R. Peto, W. Zatonski, J. Boreham, M. J. Jarvis & A. D. Lopez: Social inequalities in male mortality, and in male mortality from smoking: indirect estimation from national death rates in England and Wales, Poland, and North America. *Lancet*, 368, 367-70 (2006)
172. A. A. Patkar, P. Mannelli, K. Peindl, H. W. Murray, B. Meier & F. T. Leone: Changes in tobacco smoking following treatment for cocaine dependence. *Am J Drug Alcohol Abuse*, 32, 135-48 (2006)
173. J. A. Dani & R. A. Harris: Nicotine addiction and comorbidity with alcohol abuse and mental illness. *Nat Neurosci*, 8, 1465-70 (2005)
174. M. L. Esterberg & M. T. Compton: Smoking behavior in persons with a schizophrenia-spectrum disorder: a qualitative investigation of the transtheoretical model. *Soc Sci Med*, 61, 293-303 (2005)
175. D. M. Fergusson, R. D. Goodwin & L. J. Horwood: Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychol Med*, 33, 1357-67 (2003)
176. K. N. Paperwalla, T. T. Levin, J. Weiner & S. M. Saravay: Smoking and depression. *Med Clin North Am*, 88, 1483-94, x-xi (2004)
177. R. C. Smith, A. Singh, M. Infante, A. Khandat & A. Kloos: Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. *Neuropsychopharmacology*, 27, 479-97 (2002)
178. M. Bartal: Health effects of tobacco use and exposure. *Monaldi Arch Chest Dis*, 56, 545-554 (2001)
179. X. Wu, H. Zhao, R. Suk & D. C. Christiani: Genetic susceptibility to tobacco-related cancer. *Oncogene*, 23, 6500-23 (2004)
180. D. M. DeMarini: Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. *Mutat Res*, 567, 447-74 (2004)
181. C. Bates, M. Jarvis & G. Connolly: Tobacco Additives: Cigarette engineering and nicotine addiction. Massachusetts Tobacco Control Program, 1-23 (1999).
182. J. Fowles, M. Bates & D. Noiton: The Chemical Constituents in Cigarettes and Cigarette Smoke: Priorities for Harm Reduction. Epidemiology and Toxicology Group, 1-65 (2000).
183. C. Bolego, A. Poli & R. Paoletti: Smoking and gender. *Cardiovasc Res*, 53, 568-76 (2002)
184. K. W. Garey, M. M. Neuhauser, R. A. Robbins, L. H. Danziger & I. Rubinstein: Markers of inflammation in exhaled breath condensate of young healthy smokers. *Chest*, 125, 22-6 (2004)
185. B. T. Hawkins, R. C. Brown & T. P. Davis: Smoking and ischemic stroke: a role for nicotine. *Trends in Pharmacological Sciences*, 23, 78-82 (2002)
186. Y. Tsushima, Y. Tanizaki, J. Aoki & K. Endo: MR detection of microhemorrhages in neurologically healthy adults. *Neuroradiology*, 44, 31-6 (2002)
187. H. Akiyama, J. S. Meyer, K. F. Mortel, Y. Terayama, J. Thornby & S. Konno: Normal human aging: factors contributing to cerebral atrophy. *Journal of Neurological Sciences*, 152, 39-49 (1997)
188. A. Hayee, A. Haque, A. Anwarullah & M. Rabbani: Smoking enhances age related brain atrophy-a quantitative study with computed tomography. *Bangladesh Med. Res. Counc. Bull.*, 29, 118-124 (2003)
189. K. Kubota, T. Matsuzawa, T. Fujiwara, T. Yamaguchi, K. Ito, H. Watanabe & S. Ono: Age-related brain atrophy enhanced by smoking: a quantitative study with computed tomography. *J. exp. Med*, 153, 303-311 (1987)
190. A. L. Brody, M. A. Mandelkern, M. E. Jarvik, G. S. Lee, E. C. Smith, J. C. Huang, R. G. Bota, G. Bartzokis & E. D. London: Differences between smokers and nonsmokers in regional gray matter volumes and densities. *Biol Psychiatry*, 55, 77-84 (2004)
191. H. Fukuda & M. Kitani: Cigarette smoking is correlated with the periventricular hyperintensity grade of brain magnetic resonance imaging. *Stroke*, 27, 645-9 (1996)
192. J. Gallinat, U. E. Lang, L. K. Jacobsen, M. Bajbouj, P. Kalus, D. von Haebler, F. Seifert & F. Schubert: Abnormal hippocampal neurochemistry in smokers: evidence from proton magnetic resonance spectroscopy at 3 T. *J Clin Psychopharmacol*, 27, 80-4 (2007)

193. C. N. Epperson, S. O'Malley, K. A. Czarkowski, R. Gueorguieva, P. Jatlow, G. Sanacora, D. L. Rothman, J. H. Krystal & G. F. Mason: Sex, GABA, and nicotine: the impact of smoking on cortical GABA levels across the menstrual cycle as measured with proton magnetic resonance spectroscopy. *Biol Psychiatry*, 57, 44-8 (2005)
194. P. J. Zhu & V. A. Chiappinelli: Nicotine modulates evoked GABAergic transmission in the brain. *J Neurophysiol*, 82, 3041-5 (1999)
195. A. L. Brody: Functional brain imaging of tobacco use and dependence. *J Psychiatr Res* (2005)
196. R. L. Rogers, J. S. Meyer, T. G. Shaw, K. F. Mortel, J. P. Hardenberg & R. R. Zaid: Cigarette Smoking Decreases Cerebral Blood Flow Suggesting Increased Risk for Stroke. *JAMA*, 250, 2796-2800 (1983)
197. K. Yamashita, S. Kobayashi, S. Yamaguchi, M. Kitani & T. Tsunematsu: Effect of smoking on regional cerebral blood flow in the normal aged volunteers. *Gerontology*, 34, 199-204 (1988)
198. S. B. Rourke, R. M. Dupont, I. Grant, P. P. Lehr, G. Lamoureux, S. Halpern & D. W. Yeung: Reduction in cortical IMP-SPET tracer uptake with recent cigarette consumption in a young group of healthy males. San Diego HIV Neurobehavioral Research Center. *Eur J Nucl Med*, 24, 422-7 (1997)
199. J. A. Court, S. Lloyd, N. Thomas, M. A. Piggott, E. F. Marshall, C. M. Morris, H. Lamb, R. H. Perry, M. Johnson & E. K. Perry: Dopamine and nicotinic receptor binding and the levels of dopamine and homovanillic acid in human brain related to tobacco use. *Neuroscience*, 87, 63-78 (1998)
200. S. P. Li, M. S. Park, J. Y. Bahk & M. O. Kim: Chronic nicotine and smoking exposure decreases GABA(B1) receptor expression in the rat hippocampus. *Neurosci Lett*, 334, 135-9 (2002)
201. I. Berlin & R. M. Anthenelli: Monoamine oxidases and tobacco smoking. *Int J Neuropsychopharmacol*, 4, 33-42 (2001)
202. Y. Tizabi, R. L. Copeland, Jr., V. A. Louis & R. E. Taylor: Effects of combined systemic alcohol and central nicotine administration into ventral tegmental area on dopamine release in the nucleus accumbens. *Alcohol Clin Exp Res*, 26, 394-9 (2002)
203. A. Neuhaus, M. Bajbouj, T. Kienast, P. Kalus, D. von Haebler, G. Winterer & J. Gallinat: Persistent dysfunctional frontal lobe activation in former smokers. *Psychopharmacology (Berl)*, 186, 191-200 (2006)
204. R. D. Hill, L. G. Nilsson, L. Nyberg & L. Backman: Cigarette smoking and cognitive performance in healthy Swedish adults. *Age Ageing*, 32, 548-50 (2003)
205. J. A. Schinka, H. Belanger, J. A. Mortimer & A. B. Graves: Effects of the use of alcohol and cigarettes on cognition in elderly African American adults. *J Int Neuropsychol Soc*, 9, 690-7 (2003)
206. T. M. Heffernan, J. Ling, A. C. Parrott, T. Buchanan, A. B. Scholey & J. Rodgers: Self-rated everyday and prospective memory abilities of cigarette smokers and non-smokers: a web-based study. *Drug Alcohol Depend*, 78, 235-41 (2005)
207. M. Ernst, S. J. Heishman, L. Spurgeon & E. D. London: Smoking history and nicotine effects on cognitive performance. *Neuropsychopharmacology*, 25, 313-9 (2001)
208. G. J. Spilich L. June, & J. Renner: Cigarette smoking and cognitive performance. *Br J Addict*, 87, 1313-26 (1992)
209. J. Razani, K. Boone, I. Lesser & D. Weiss: Effects of cigarette smoking history on cognitive functioning in healthy older adults. *Am J Geriatr Psychiatry*, 12, 404-11 (2004)
210. M. Richards, M. J. Jarvis, N. Thompson & M. E. Wadsworth: Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. *Am J Public Health*, 93, 994-8 (2003)
211. S. Kalmijn, M. P. van Boxtel, M. W. Verschuren, J. Jolles & L. J. Launer: Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. *Am J Epidemiol*, 156, 936-44 (2002)
212. I. J. Deary, A. Pattie, M. D. Taylor, M. C. Whiteman, J. M. Starr & L. J. Whalley: Smoking and cognitive change from age 11 to age 80. *J Neurol Neurosurg Psychiatry*, 74, 1003-1007 (2003)
213. M. Iki, H. Ishizaki, H. Aalto, J. Starck & I. Pyykko: Smoking habits and postural stability. *Am J Otolaryngol*, 15, 124-8 (1994)
214. L. K. Jacobsen, J. H. Krystal, W. E. Mencl, M. Westerveld, S. J. Frost & K. R. Pugh: Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biol Psychiatry*, 57, 56-66 (2005)
215. P. A. Fried, B. Watkinson & R. Gray: Neurocognitive consequences of cigarette smoking in young adults--a comparison with pre-drug performance. *Neurotoxicol Teratol*, 28, 517-25 (2006)
216. A. Ott, K. Andersen, M. E. Dewey, L. Letenneur, C. Brayne, J. R. Copeland, J. F. Dartigues, P. Kragh-Sorensen, A. Lobo, J. M. Martinez-Lage, T. Stijnen, A. Hofman & L. J. Launer: Effect of smoking on global cognitive function in nondemented elderly. *Neurology*, 62, 920-4 (2004)
217. L. J. Launer, K. Andersen, M. E. Dewey, L. Letenneur, A. Ott, L. A. Amaducci, C. Brayne, J. R. Copeland, J. F. Dartigues, P. Kragh-Sorensen, A. Lobo, J. M. Martinez-Lage, T. Stijnen & A. Hofman: Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. *Neurology*, 52, 78-84 (1999)
218. C. Merchant, M. X. Tang, S. Albert, J. Manly, Y. Stern & R. Mayeux: The influence of smoking on the risk of Alzheimer's disease. *Neurology*, 52, 1408-12 (1999)
219. A. Ott, A. J. Slooter, A. Hofman, F. van Harskamp, J. C. Witteman, C. Van Broeckhoven, C. M. van Duijn & M. M. Breteler: Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet*, 351, 1840-3 (1998)
220. J. A. Schinka, R. D. Vanderploeg, M. Rogish, A. B. Graves, J. A. Mortimer & P. I. Ordoric: Effects of the use of alcohol and cigarettes on cognition in elderly adults. *J Int Neuropsychol Soc*, 8, 811-8 (2002)
221. N. Breslau, S. P. Novak & R. C. Kessler: Psychiatric disorders and stages of smoking. *Biol Psychiatry*, 55, 69-76 (2004)
222. A. Schumann, U. Hapke, C. Meyer, H. J. Rumpf & U. John: Prevalence, characteristics, associated mental disorders and predictors of DSM-IV nicotine dependence. *Eur Addict Res*, 10, 29-34 (2004)

223. S. L. Dolan, K. A. Sacco, A. Termine, A. A. Seyal, M. M. Dudas, J. C. Vessicchio, B. E. Wexler & T. P. George: Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia. *Schizophr Res*, 70, 263-75 (2004)
224. D. J. Romberger & K. Grant: Alcohol consumption and smoking status: the role of smoking cessation. *Biomed Pharmacother*, 58, 77-83 (2004)
225. R. D. Hurt, K. M. Eberman, I. T. Croghan, K. P. Offord, L. J. Davis, Jr., R. M. Morse, M. A. Palmen & B. K. Bruce: Nicotine dependence treatment during inpatient treatment for other addictions: a prospective intervention trial. *Alcohol Clin Exp Res*, 18, 867-72 (1994)
226. C. S. Pomerleau, H. J. Aubin & O. F. Pomerleau: Self-reported alcohol use patterns in a sample of male and female heavy smokers. *J Addict Dis*, 16, 19-24 (1997)
227. R. Room: Smoking and drinking as complementary behaviours. *Biomed Pharmacother*, 58, 111-5 (2004)
228. V. Di Sclafani, H. W. Clark, M. Tolou-Shams, C. W. Bloomer, G. A. Salas, D. Norman & G. Fein: Premorbid brain size is a determinant of functional reserve in abstinent crack-cocaine and crack-cocaine-alcohol-dependent adults. *J Int Neuropsychol Soc*, 4, 559-65 (1998)
229. J. O'Neill, V. A. Cardenas & D. J. Meyerhoff: Separate and interactive effects of cocaine and alcohol dependence on brain structures and metabolites: quantitative MRI and proton MR spectroscopic imaging. *Addiction Biology*, 6, 347-61 (2001)
230. T. Lundqvist: Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav*, 81, 319-30 (2005)
231. S. MacKay, D. J. Meyerhoff, W. P. Dillon, M. W. Weiner & G. Fein: Alteration of brain phospholipid metabolites in cocaine- dependent polysubstance abusers. *Biol.Psychiatry*, 34, 261-264 (1993)
232. D. J. Meyerhoff, C. Bloomer, G. Salas, N. Schuff, Norman.D., M. W. Weiner & Fein.G.: Cortical metabolite in abstinent cocaine and cocaine/alcohol dependent subjects: An *in vivo* proton magnetic resonance spectroscopic imaging study. *Addiction Biology*, 4, 405-419 (1999)
233. V. Di Sclafani, C. Bloomer, H. Clark, D. Norman, D. Hannauer & G. Fein: Abstinent chronic cocaine and cocaine/alcohol abusers evidence normal hippocampal volumes on MRI despite cognitive impairments. *Addiction Biology*, 3, 261-270 (1998)
234. U. John, C. Meyer, H. J. Rumpf, A. Schumann, J. R. Thyrian & U. Hapke: Strength of the relationship between tobacco smoking, nicotine dependence and the severity of alcohol dependence syndrome criteria in a population-based sample. *Alcohol Alcohol*, 38, 606-12 (2003)
235. U. John, C. Meyer, H. J. Rumpf & U. Hapke: Probabilities of alcohol high-risk drinking, abuse or dependence estimated on grounds of tobacco smoking and nicotine dependence. *Addiction*, 98, 805-14 (2003)
236. J. L. York & J. A. Hirsch: Drinking patterns and health status in smoking and nonsmoking alcoholics. *Alcohol Clin Exp Res*, 19, 666-73 (1995)
237. T. C. Durazzo, S. Gazdzinski, P. Banys & D. J. Meyerhoff: Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. *Alcohol Clin Exp Res*, 28, 1849-60 (2004)
238. R. D. Hurt, K. P. Offord, I. T. Croghan, L. Gomez-Dahl, T. E. Kottke, R. M. Morse & L. J. Melton, 3rd: Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *Jama*, 275, 1097-103 (1996)
239. T. Narahashi, B. Soderpalm, M. Ericson, P. Olausson, J. A. Engel, X. Zhang, A. Nordberg, W. Marszalec, G. L. Aistrup, L. G. Schmidt, U. Kalouti, Smolka & L. Hedlund: Mechanisms of alcohol-nicotine interactions: alcoholics versus smokers. *Alcohol Clin Exp Res*, 25, 152S-156S (2001)
240. J. E. Rose, F. M. Behm, E. C. Westman, R. J. Mathew, E. D. London, T. C. Hawk, T. G. Turkington & R. E. Coleman: PET studies of the influences of nicotine on neural systems in cigarette smokers. *Am J Psychiatry*, 160, 323-33 (2003)
241. S. P. Barrett, M. Tichauer, M. Leyton & R. O. Pihl: Nicotine increases alcohol self-administration in non-dependent male smokers. *Drug Alcohol Depend*, 81, 197-204 (2006)
242. A. D. Le, A. Wang, S. Harding, W. Juzytsch & Y. Shaham: Nicotine increases alcohol self-administration and reinstates alcohol seeking in rats. *Psychopharmacology (Berl)*, 168, 216-21 (2003)
243. M. A. Prendergast, D. T. Rogers, S. Barron, M. T. Bardo & J. M. Littleton: Ethanol and nicotine: a pharmacologic balancing act? *Alcohol Clin Exp Res*, 26, 1917-8 (2002)
244. D. J. Drobes: Cue reactivity in alcohol and tobacco dependence. *Alcohol Clin Exp Res*, 26, 1928-9 (2002)
245. P. A. Madden & A. C. Heath: Shared genetic vulnerability in alcohol and cigarette use and dependence. *Alcohol Clin Exp Res*, 26, 1919-21 (2002)
246. A. D. Le, Z. Li, D. Funk, M. Shram, T. K. Li & Y. Shaham: Increased vulnerability to nicotine self-administration and relapse in alcohol-naive offspring of rats selectively bred for high alcohol intake. *J Neurosci*, 26, 1872-9 (2006)
247. K. C. Wilhelmsen, G. E. Swan, L. S. Cheng, C. N. Lessov-Schlaggar, C. I. Amos, H. S. Feiler, K. S. Hudmon, H. Z. Ring, J. A. Andrews, E. Tildesley, N. L. Benowitz & H. Hops: Support for previously identified alcoholism susceptibility Loci in a cohort selected for smoking behavior. *Alcohol Clin Exp Res*, 29, 2108-15 (2005)
248. T. C. Durazzo, V. A. Cardenas, C. Studholme, M. W. Weiner & D. J. Meyerhoff: Non-treatment-seeking heavy drinkers: Effects of chronic cigarette smoking on brain structure. *Drug Alcohol Depend*, 87, 76-82. (2007)
249. S. Gazdzinski, T. C. Durazzo, G.-H. Jahng, F. Ezekiel, P. Banys & D. J. Meyerhoff: Effects of chronic alcohol dependence and chronic cigarette smoking on cerebral perfusion: A preliminary magnetic resonance study. *Alcoholism: Clinical and Experimental Research*, 30, 1-12 (2006)
250. K. O. Fagerstrom, T. F. Heatherton & L. T. Kozlowski: Nicotine addiction and its assessment. *Ear Nose Throat J*, 69, 763-5 (1991)
251. G. H. Jahng, X. P. Zhu, G. B. Matson, M. W. Weiner & N. Schuff: Improved perfusion-weighted MRI by a novel

double inversion with proximal labeling of both tagged and control acquisitions. *Magn Reson Med*, 49, 307-14 (2003)
252. J. K. Staley, C. Gottschalk, I. L. Petrakis, R. Gueorguieva, S. O'Malley, R. Baldwin, P. Jatlow, N. P. Verhoeff, E. Perry, D. Weinzimmer, E. Frohlich, E. Ruff, C. H. van Dyck, J. P. Seibyl, R. B. Innis & J. H. Krystal: Cortical gamma-aminobutyric acid type A-benzodiazepine receptors in recovery from alcohol dependence: relationship to features of alcohol dependence and cigarette smoking. *Arch Gen Psychiatry*, 62, 877-88 (2005)
253. A. P. Anokhin, A. B. Vedeniapin, E. J. Sirevaag, L. O. Bauer, S. J. O'Connor, S. Kuperman, B. Porjesz, T. Reich, H. Begleiter, J. Polich & J. W. Rohrbaugh: The P300 brain potential is reduced in smokers. *Psychopharmacology (Berl)*, 149, 409-13 (2000)
254. J. M. Glass, K. M. Adams, J. T. Nigg, M. M. Wong, L. I. Puttler, A. Buu, J. M. Jester, H. E. Fitzgerald & R. A. Zucker: Smoking is associated with neurocognitive deficits in alcoholism. *Drug Alcohol Depend,* 82, 119-26 (2006)
255. K. B. Friend, P. F. Malloy & H. A. Sindelar: The effects of chronic nicotine and alcohol use on neurocognitive function. *Addict Behav*, 30, 193-202 (2005)
256. M. J. Rosenbloom, A. O'Reilly, S. A. Sassoon, E. V. Sullivan & A. Pfefferbaum: Persistent cognitive deficits in community-treated alcoholic men and women volunteering for research: limited contribution from psychiatric comorbidity. *J Stud Alcohol*, 66, 254-65 (2005)
257. J. Hukkanen, P. Jacob, 3rd & N. L. Benowitz: Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*, 57, 79-115 (2005)
258. E. M. Park, Y. M. Park & Y. S. Gwak: Oxidative damage in tissues of rats exposed to cigarette smoke. *Free Radic Biol Med*, 25, 79-86 (1998)
259. J. E. Muscat, W. Kleinman, S. Colosimo, A. Muir, P. Lazarus, J. Park & J. P. Richie, Jr.: Enhanced protein glutathiolation and oxidative stress in cigarette smokers. *Free Radic Biol Med*, 36, 464-70 (2004)
260. S. Deveci, F. Deveci, Y. Acik & A. Ozan: The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. *Respiratory Medicine*, 98, 551-56 (2004)
261. G. Macdonald, N. Kondor, V. Yousefi, A. Green, F. Wong & C. Aquino-Parsons: Reduction of carboxyhaemoglobin levels in the venous blood of cigarette smokers following the administration of carbogen. *Radiother Oncol*, 73, 367-71 (2004)
262. J. R. Alonso, F. Cardellach, J. Casademont & O. Miro: Reversible inhibition of mitochondrial complex IV activity in PBMC following acute smoking. *Eur Respir J*, 23, 214-8 (2004)
263. S. E. Moriarty, J. H. Shah, M. Lynn, S. Jiang, K. Openo, D. P. Jones & P. Sternberg: Oxidation of glutathione and cysteine in human plasma associated with smoking. *Free Radic Biol Med*, 35, 1582-8 (2003)
264. J. A. Ambrose & R. S. Barua: The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*, 43, 1731-7 (2004)
265. K. Panda, R. Chattopadhyay, D. J. Chattopadhyay & I. B. Chatterjee: Vitamin C prevents cigarette smoke-induced oxidative damage *in vivo*. *Free Radic Biol Med*, 29, 115-24 (2000)
266. E. Mendez-Alvarez, R. Soto-Otero, I. Sanchez-Sellero & M. Lopez-Rivadulla Lamas: *In vitro* inhibition of catalase activity by cigarette smoke: relevance for oxidative stress. *J Appl Toxicol*, 18, 443-8 (1998)
267. G. G. Casasola, J. L. Alvarez-Sala, J. A. Marques, J. M. Sanchez-Alarcos, D. P. Tashkin & D. Espinos: Cigarette smoking behavior and respiratory alterations during sleep in a healthy population. *Sleep Breath*, 6, 19-24 (2002)
268. P. S. Sachdev, K. J. Anstey, R. A. Parslow, W. Wen, J. Maller, R. Kumar, H. Christensen & A. F. Jorm: Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. *Dement Geriatr Cogn Disord*, 21, 300-8 (2006)
269. B. T. Hawkins, R. C. Brown & T. P. Davis: Smoking and ischemic stroke: a role for nicotine? *Trends Pharmacol Sci*, 23, 78-82 (2002)
270. V. Gerzanich, F. Zhang, G. A. West & J. M. Simard: Chronic nicotine alters NO signaling of Ca(2+) channels in cerebral arterioles. *Circ Res*, 88, 359-65 (2001)
271. E. F. Domino, L. Ni, Y. Xu, R. A. Koeppe, S. Guthrie & J. K. Zubieta: Regional cerebral blood flow and plasma nicotine after smoking tobacco cigarettes. *Prog Neuropsychopharmacol Biol Psychiatry*, 28, 319-27 (2004)
272. J. Zubieta, U. Lombardi, S. Minoshima, S. Guthrie, L. Ni, L. E. Ohl, R. A. Koeppe & E. F. Domino: Regional cerebral blood flow effects of nicotine in overnight abstinent smokers. *Biol Psychiatry*, 49, 906-13 (2001)
273. J. Ding, F. J. Nieto, N. J. Beauchamp, W. T. Longstreth, Jr., T. A. Manolio, J. B. Hetmanski & L. P. Fried: A prospective analysis of risk factors for white matter disease in the brain stem: the Cardiovascular Health Study. *Neuroepidemiology*, 22, 275-82 (2003)
274. J. A. Chalela, R. L. Wolf, J. A. Maldjian & S. E. Kasner: MRI identification of early white matter injury in anoxic-ischemic encephalopathy. *Neurology*, 56, 481-5 (2001)
275. G. Bartzokis: Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging*, 25, 5-18; author reply 49-62 (2004)
276. G. Bartzokis: Quadratic trajectories of brain myelin content: unifying construct for neuropsychiatric disorders. *Neurobiology of Aging*, 25, 49-62 (2004)
277. J. L. Cummings: Frontal-subcortical circuits and human behavior. *J Psychosom Res*, 44, 627-8 (1998)
278. J. A. Saint-Cyr: Frontal-striatal circuit functions: context, sequence, and consequence. *J Int Neuropsychol Soc*, 9, 103-27 (2003)
279. A. L. Brody, M. A. Mandelkern, G. Lee, E. Smith, M. Sadeghi, S. Saxena, M. E. Jarvik & E. D. London: Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: a preliminary study. *Psychiatry Res*, 130, 269-81 (2004)
280. G. J. Spilich, L. June & J. Renner: Cigarette smoking and cognitive performance. *Br J Addict*, 87, 1313-26 (1992)
281. U. N. Das: Can memory be improved? A discussion on the role of ras, GABA, acetylcholine, NO, insulin, TNF-alpha, and long-chain polyunsaturated fatty acids in memory formation and consolidation. *Brain Dev*, 25, 251-61 (2003)

282. N. Pitsikas, A. E. Rigamonti, S. G. Cella & E. E. Muller: The GABAB receptor and recognition memory: possible modulation of its behavioral effects by the nitrergic system. *Neuroscience*, 118, 1121-7 (2003)
283. A. H. Rezvani & E. D. Levin: Cognitive effects of nicotine. *Biol Psychiatry*, 49, 258-67 (2001)
284. K. A. Sacco, K. L. Bannon & T. P. George: Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. *J Psychopharmacol*, 18, 457-74 (2004)
285. N. A. Ceballos, R. Tivis, A. Lawton-Craddock & S. J. Nixon: Visual-spatial attention in alcoholics and illicit stimulant abusers: effects of nicotine replacement. *Prog Neuropsychopharmacol Biol Psychiatry*, 29, 97-107 (2005)
286. N. A. Ceballos, R. Tivis, A. Lawton-Craddock & S. J. Nixond: Nicotine and cognitive efficiency in alcoholics and illicit stimulant abusers: implications of smoking cessation for substance users in treatment. *Subst Use Misuse*, 41, 265-81 (2006)
287. F. J. McClernon & D. G. Gilbert: Human functional neuroimaging in nicotine and tobacco research: basics, background, and beyond. *Nicotine Tob Res*, 6, 941-59 (2004)
288. A. Mendrek, J. Monterosso, S. L. Simon, M. Jarvik, A. Brody, R. Olmstead, C. P. Domier, M. S. Cohen, M. Ernst & E. D. London: Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. *Addict Behav*, 31, 833-44 (2006)
289. J. Xu, A. Mendrek, M. S. Cohen, J. Monterosso, P. Rodriguez, S. L. Simon, A. Brody, M. Jarvik, C. P. Domier, R. Olmstead, M. Ernst & E. D. London: Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. *Biol Psychiatry*, 58, 143-50 (2005)
290. E. F. Domino, S. Minoshima, S. K. Guthrie, L. Ohl, L. Ni, R. A. Koeppe, D. J. Cross & J. Zubieta: Effects of nicotine on regional cerebral glucose metabolism in awake resting tobacco smokers. *Neuroscience*, 101, 277-82 (2000)
291. J. M. Stapleton, S. F. Gilson, D. F. Wong, V. L. Villemagne, R. F. Dannals, R. F. Grayson, J. E. Henningfield & E. D. London: Intravenous nicotine reduces cerebral glucose metabolism: a preliminary study. *Neuropsychopharmacology*, 28, 765-72 (2003)
292. K. Mann, A. Batra, A. Gunthner & G. Schroth: Do women develop alcoholic brain damage more readily than men? In: Alcohol Clin Exp Res. (1992)
293. E. V. Sullivan, M. Rosenbloom, K. L. Serventi & A. Pfefferbaum: Effects of age and sex on volumes of the thalamus, pons, and cortex. *Neurobiol Aging*, 25, 185-92 (2004)
294. J.M. Starr, I.J. Deary, H.C. Fox, L.J. Whalley Smoking and cognitive change from age 11 to 66 years: A confirmatory investigation. *Addict Behav*, 32, 63-8 (2007)
295. T.C. Durazzo, J. C. Rothlind, S. Gazdziski, P. Banys & D. J. Meyerhoff: Chronic smoking is associated with differential neurocognitive recovery in abstinent alcoholics: a preliminary investigation. *Alc Clin Exp Res* (In press)
296. A.Y. Xiao, L. Wei, S. Xia, S. Rothman, & S.P. Yu: Ionic mechanism of ouabain-induced concurrent apoptosis and necrosis in individual cultured cortical neurons. *J Neurosci*, 22, 1350-62 (2002)
297. K. Anbarasi, G. Vani, K. Balakrishna, & C.S. Devi: Effect of bacoside A on membrane-bound ATPases in the brain of rats exposed to cigarette smoke. *J Biochem Mol Toxicol*, 19, 59-65 (2005)
298. K. Anbarasi, G. Vani, K. Balakrishna & C.S. Devi: Effect of bacoside A on brain antioxidant status in cigarette smoke exposed rats *Life Sci*, 78, 1378-84 (2006)
299. S.B. Rourke & T. Loberg: The neurobehavioral correlates of alcoholism. In Neuropsychological assessment of neuropsychiatric disoders, Eds: I Grant and K.M. Adams. Oxford University Press (1996)

**Abbreviations:** ALC: alcohol dependent, AUD: alcohol use disorders, CBF: cerebral blood flow, Cho: choline-containing compounds, Cr: creatine-containing compounds, CSF: cerebrospinal fluid, CO: carbon monoxide, CT: computerized tomography, DTI: Diffusion Tensor Imaging, DNA: deoxyribonucleic acid, GABA: gamma aminobutyric acid, Glu: glutamate, GM: gray matter, HD: hazardous drinker, LD: light drinking control, NAA: N-acetylaspartate, NMDA: N-acetyl-D-aspartate, mI: myoinositol, MR: magnetic resonance, MRI: magnetic resonance imaging, nsALC: non-smoking recovering alcoholic, nsHD: non-smoking hazardous drinker ROS: reactive oxygen species, SPECT: single photon emission computerized tomography, WM: white matter, $^{1}$H MRS: proton magnetic resonance spectroscopy, $^{1}$H MRSI: proton magnetic resonance spectroscopic imaging, sALC: smoking recovering alcoholic, sHD: smoking hazardous drinker sLD: smoking light drinking control

**Key Words:** alcoholism, alcohol use disorders, cigarette smoking, cognition, magnetic resonance imaging, magnetic resonance spectroscopy, neurocognition, neuroimaging, perfusion, recovery

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