NEURAL MECHANISMS AND BEHAVIORAL FACTORS UNDERLYING HETEROGENEITY OF ALCOHOLISM: EVIDENCE FROM IN VIVO NEUROIMAGING

Chairpersons: Adolf Pfefferbaum, M.D.¹ and Karl Mann, M.D.²

¹Neuroscience Program, SRI International and Stanford University School of Medicine, U.S.A.; ²Central Institute of Mental Health, Department of Addictive Behavior & Addiction Medicine, Mannheim, Germany

Background: Chronic alcoholism can exert widespread damage to selective brain systems, contributing to cognitive and behavioral impairments characteristic of the disease. Neuroimaging studies have been instrumental in identifying neural substrates of chronic alcoholism's effect, each of which may be modified by genetic factors. Structural brain imaging using quantitative methods have consistently identified tissue shrinkage prominent in prefrontal cortex and underlying white matter, corpus callosum, and selective limbic and cerebellar structures in treatment-seeking alcoholic men and women. In vivo studies of brain chemistry have indicated neuronal compromise, which may be reversible with abstinence. Functional brain imaging studies have revealed insights into the dynamics of alcohol craving.

Rationale: Although significant brain structural and functional abnormalities are regularly reported in groups of alcoholics, individual variation in expression of the type, locus, and extent of the abnormalities is high. This symposium will address behavioral, environmental, and genetic factors that contribute to this variance and heterogeneous manifestation of alcoholism on brain integrity as revealed by a variety of neuroimaging probes, including structural Magnetic Resonance Imaging (MRI), MR spectroscopic imaging, functional MRI, and positron emission tomography.

1. Structural Brain MRIs in a Treatment-Naïve Active Drinking Alcohol Dependent Sample.

George Fein, Ph.D., President, Neurobehavioral Research, Inc., Corte Madera, CA, U.S.A.

Most studies of the morbid impact of alcohol dependence on brain structure have examined treated individuals, generalizing to the population of ‘alcoholics,’ the majority of whom are untreated. We recently reported that adults with alcohol dependence comprise a number of different populations, showing that treated alcoholics have more intense early trajectories of alcohol consumption compared with treatment-naïve alcohol dependent individuals in the community (Fein and Landman, 2005). We have also shown that treated samples have substantially higher levels of psychiatric disorders and symptomatology (e.g., psychiatric diagnoses and symptom counts on the C-DIS) and psychological abnormality (e.g., higher scores on MMPI scales, and more deviant scores on other psychological measures) (Fein et al., 2006). In this symposium, we presented brain structural imaging data on 59 treatment-naïve active alcohol dependent individuals (24 women and 35 men) and 59 normal light/non-drinking controls (24 women and 35 men). Both samples had an average age of 31 years. The treatment-naïve alcohol dependent sample began heavy drinking (80 drinks/month for women and 100 drinks/month for men) at 16.7 years of age and had a total lifetime alcohol intake of over 17000 drinks for men and 10000 drinks for women compared with a total lifetime alcohol intake of under 1000 drinks for both male and female control samples. We examined cortical gray matter volumes in a number of different brain regions, using cranium size (premorbid brain size) as a covariate. We found an age by group interaction for gray matter volumes in the prefrontal, parietal, and temporal lobes, but not for the occipital
lobe, with steeper age-related reductions in lobar gray matter volume in the treatment-naïve alcoholics. The age effect in the alcohol group could be confounded with the lifetime duration of heavy drinking, and could easily have been a direct effect of alcohol exposure. This pattern of effects (present in prefrontal and parietal lobes, but not in the occipital lobe, see Figure 1) directly replicates our earlier study in a different sample of (male only) treatment naïve alcoholics (Fein et al., 2002).

Support: AA1311 and AA13659 from the US National Institute on Alcohol Abuse and Alcoholism.

References:

2. Gene x Neuroimaging: Identifying Neurobiological Mechanisms of Addictive Behaviour

Gunter Schumann
Section of Addiction Biology, Institute of Psychiatry, King's College London, England

Dr. Schumann described IMAGEN, a large-scale, international study intended to identify neural and genetic mechanisms of addictive behavior. The goal of the IMAGEN study is to identify the neurobiological and genetic basis of traits related to reward, punishment and emotional cues and to assess their relevance for mental disorder. To this end, the investigators will conduct the first multi-center functional and structural genetic neuroimaging study of a cohort of 2000 14-year old adolescents. Phenotypic behaviors targeted are impulsivity, emotional learning, novelty seeking, reward sensitivity, and attentional capture. Creative behavioral paradigms have been devised to operationalize these complex behaviors and have begun to be tested with functional MRI. In addition to these functional brain studies, this project is examining genotypes and haplotypes associated with addictive behavior. The overall objectives of this programmatic study are 1. identification and selection of candidate genes for behaviour related to reinforcer sensitivity; 2. neuroimaging analysis of tasks measuring specific behavioural traits in humans; 3. genetic analysis of major tasks measuring behavioural traits in humans; 4. identification of the neural basis of disorders related to reinforcer sensitivity and executive control; and 5. gender-specific analysis.

3. Chronic Drinking and Smoking: Functionally Significant Effects on Magnetic Resonance-Derived Brain Metabolite Concentrations and Neurocognition

Dieter J. Meyerhoff1,2, Timothy C. Durazzo2
1Department of Radiology, University of California San Francisco and 2Department of Veterans Affairs Medical Center San Francisco, U.S.A.

Chronic cigarette smoking is very common in alcohol use disorders (AUD). Chronic smoking has been associated with abnormalities in brain morphology, perfusion, and neurocognition (see Durazzo et al., 2006a). However, the potential effects of chronic
smoking on brain structure, perfusion, metabolites, and function in AUD have not been appreciated. Here we summarize our research on the regional cerebral effects of chronic smoking using different magnetic resonance (MR) imaging modalities and neurocognitive testing in treatment-naive chronic heavy drinkers (HD) and in treatment-seeking recovering alcoholics (RA).

Treatment-naive HD who smoke demonstrated smaller cortical gray matter (GM) volumes compared to those HD who do not smoke and compared to non-smoking light drinking controls (Durazzo et al., 2006b). HD groups did not differ on volumes of lobar white matter (WM), subcortical structures or regional cerebral spinal fluid (CSF). GM loss irrespective of etiology is functionally significant, as brain shrinkage is a risk factor for neurocognitive decline with advancing age. Accordingly, we found that the smoking HD in these studies also had greater deficits on measures of balance and executive functioning (Durazzo et al., 2005).

In RA at 1 week of abstinence, chronic smoking appeared to compound alcohol-induced neuronal injury (as measured by the neuronal marker N-acetyl-aspartate, NAA) and cell-membrane abnormalities (as measured by choline containing metabolites, Cho) in the frontal lobe (Durazzo et al., 2004). Higher smoking levels correlated with lower metabolite concentrations in select subcortical structures. Our quantitative MRI in RA provided evidence that chronic cigarette smoking may account for some of the variance of the commonly described cortical GM loss in alcohol dependent individuals. Chronic cigarette smoking in alcohol dependence also appeared to augment regional WM volumes and to affect associations between WM volumes and cognitive test performance (Gazdzinski et al., 2005). Furthermore, smoking RA showed reductions of frontal and parietal GM perfusion that were greater than those in non-smoking RA and dose-related, i.e., related to a greater number of cigarettes smoked per day (Gazdzinski et al., 2006).

Previous research using regional voluming of longitudinal MRI data indicated that alcoholism-associated brain atrophy partially resolves with sustained abstinence. We demonstrated brain volume reductions and recovery over twelve months of sobriety using boundary shift integral methods (Gazdzinski et al., 2005) and deformation based morphometry (Cardenas et al., 2006). Within the first five weeks of sobriety, regional brain NAA and Cho levels in RA increased, but metabolite levels did not normalize in all brain regions after 35 days of sobriety. Specifically, actively smoking RA appeared to show less recovery than non-smoking RA of NAA and Cho in many different brain regions, primarily in frontal and parietal lobes (Durazzo et al., 2006c). Therefore, at 1 month of abstinence from alcohol, smoking RA continued to demonstrate greater neuronal dysfunction in the frontal white matter and cell membrane injury in the basal ganglia than non-smoking RA. At one month of abstinence, non-smoking RA were superior to smoking RA on measures of auditory-verbal learning and memory, processing speed, cognitive efficiency and static postural stability (Durazzo et al. 2006a). These group differences were not a function of group disparities in age, education, estimated premorbid verbal intelligence, lifetime alcohol consumption, or other measured comorbid psychiatric or medical factors. Longer smoking duration was inversely related to performance on measures of executive skills, visuospatial learning, general cognitive efficiency, and static postural stability.

Taken together, the presented data suggest that smoking explains part of the neurobiologic and neurocognitive dysfunction in AUD that traditionally has been attributed solely to the effects of chronic and excessive alcohol consumption. Greater consideration of the effects of continued cigarette smoking on the neurobiologic and neurocognitive injuries and their recoveries in alcohol-dependent individuals is warranted. Furthermore, chronic smoking may also affect brain abnormalities in
pathologies commonly associated with heavy smoking, such as schizophrenia-spectrum and mood disorders.

**Support:** NIH R01 AA10788, P01 AA11493

**References:**


4. **Cue-Induced Brain Activity in Alcoholics: A combined PET and f-MRI studies**

Karl Mann, Michael Smolka, Andreas Heinz

Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany

**Background:** Imaging studies consistently found cue-elicited brain activity in the striatum, amygdala, anterior cingulate cortex and the prefrontal cortex. We investigated the association of cue-induced brain activity with (1) treatment outcome, (2) opioidergic (OP) and dopaminergic (DA) neurotransmission in the brain reward system and (3) a VNTR polymorphism (L/S) of the DA D4 receptor.

**Methods:** Visual alcohol-related and control stimuli were presented in a block design during functional magnetic resonance imaging (fMRI). OP and DA neurotransmission was measured using [11C]carfentanil, [18F]desmethoxyfallypride and [18F] fluoro-L-DOPA positron emission tomography (PET).
**Results:** Cue-induced activity in the putamen, anterior cingulate cortex and adjacent medial prefrontal cortex was positively correlated with risk for relapse during a 3-month period. Availability of mu opiate receptors correlated with subjective craving measures. Combining fMRI and PET data, we found that reduced availability of DA D2 receptors in the ventral striatum was associated with increased cue-induced activation of the medial prefrontal cortex and anterior cingulate cortex as assessed with fMRI, and that a DA deficit in the striatum was correlated with self reported craving. Concerning the impact of genetic variation we found increased cue-elicited brain activity in the anterior cingulate cortex and adjacent medial prefrontal cortex in DA D4 L carriers compared to DA D4 S subjects.

**Conclusions:** Cue-induced brain activity in alcoholics could predict treatment outcome. This might be useful for the identification of patients with high risk for relapse and to provide individually adapted interventions. The association of neuronal cue reactivity and craving with OP and DA neurotransmission and genetic variation of the DA receptors supports the possibility that the function of the brain reward system has substantial impact on development and maintenance of addictive behavior in humans.

**Support:** This work was supported by the BMBF (01EB0110&01EB0410) and the DFG (He 2597/4-1&4-2; Sm 80/1-1)

5. **Discussion: Neuroimaging Applications in Alcoholism**

Adolf Pfefferbaum, M.D., Professor, Stanford University School of Medicine
Director, Neuroscience Program, SRI International, Menlo Park, CA, U.S.A.

A common observation in nearly three decades of structural neuroimaging studies of chronic alcoholics is considerable variability in the extent of alcoholism-related brain abnormalities detected, with some individuals having massive tissue shrinkage and others with little observed effect. Occasionally, a dose-response relation is demonstrated with brain tissue volume shrinkage or CSF space expansion related to lifetime alcohol exposure, but such associations are elusive and do not account for a substantial portion of morphological variance. Possible explanations include individual differences in susceptibility, alcohol use pattern (quantity, frequency, duration), and nutrition, especially when drinking. For example, the incidence of undetected Wernicke’s encephalopathy (WE) associated lesions among alcoholics at autopsy (e.g., mammillary body swelling or shrinkage) suggests greater influence of nutritional deficiency (especially thiamine) than generally appreciated clinically. Individuals with clinical WE have specific acute brain pathology detectable with neuroimaging, as do those who progress to the amnesic Korsakoff’s Syndrome (KS), with nonamnesic alcoholics demonstrating neuropathology similar to those of KS, albeit to a lesser degree.

The participants of this symposium provided further quantitative data, elucidating significant factors contributing to observed variance in neuroimaging studies of alcoholism. As noted in the lecture by Dr. Fein, non-treatment seeking alcoholics have less brain pathology than those seeking treatment, despite meeting criteria for alcohol dependence, and may represent individuals with lesser predisposing susceptibility or better nutrition. Dr. Schumann found that processing of aversive emotional stimuli in limbic structures is additively affected by a functional polymorphism in the COMT gene and two functional polymorphisms in the regulatory region of the 5-HTT gene. Taken together, these genetic factors explain 37% of the variance in the fMRI BOLD signal change. With functional imaging, Dr. Mann’s research team found that neuronal alcohol-relevant cue reactivity associated with treatment response elicited activity in the anterior cingulum and medial prefrontal cortex, which are associated with striatal dopamine (DRD2) availability and the DRD4 genotype. These imaging results confirm a key role of
the dopamine system and other genetic variants of this neurotransmitter system in cue reactivity. Drs. Meyerhoff and Durazzo identified chronic smoking, which is perhaps the most common addiction comorbidity in alcoholism, to be a significant factor in mitigating recovery in brain metabolite and cognitive health. The myriad potential indogenous and exogenous factors contributing to the heterogeneity of presentation, course, and sequelae of alcoholism highlight the need for studies to model amenable sources of variance with subhuman primates and rodents.

Support: This work was supported by the NIAAA AA05965, AA12388, AA12999, AA13521 (Integrative Neuroscience Initiative on Alcoholism—INIA), and an NIAAA Travel Award.