Neuroimaging in Alcoholism: Ethanol and Brain Damage

Karl Mann, Ingrid Agartz, Clive Harper, Susan Shoaf, Robert R. Rawlings, Reza Momenan, Daniel W. Hommer,
Adolf Pfefferbaum, Edith V. Sullivan, Raymond F. Anton, David J. Drobes, Mark S. George, Roland Bares,
Hans-Juergen Machulla, Goetz Mundle, Matthias Reimold, and Andreas Heinz

This article represents the proceedings of a symposium at the 2000 ISBRA Meeting in Yokohama, Japan. The co-chairs were Karl Mann and Ingrid Agartz. The presentations were (1) Neuropathological changes in alcohol-related brain damage, by Clive Harper; (2) Regional brain volumes including the hippocampus and monoamine metabolites in alcohol dependence, by Ingrid Agartz, Susan Shoaf, Robert R, Rawlings, Reza Momenan, and Daniel W Hommer; (3) Diffusion tensor abnormalities in imaging of white matter alcoholism, by Adolf Pfefferbaum and Edith V. Sullivan; (4) Use of functional MRI to evaluate brain activity during alcohol cue exposure in alcoholics: Relationship to craving, by Raymond F. Anton, David J. Drobes, and Mark S. George; and (5) μ-Opiate receptor availability in alcoholism: First results from a positron emission tomography study, by Karl Mann, Roland Bares, Hans-Juergen Machulla, Goetz Mundle, Matthias Reimold, and Andreas Heinz.

Key Words: Brain Damage, White Matter Abnormalities, Function Magnetic Resonance Imaging, μ-Opiate Receptor.

THERE ARE A number of ways in which alcohol (ethanol) is thought to impact the central nervous system: direct neurotoxicity, the toxicity of metabolic by-products (e.g., acetaldehyde), and the effects of secondary nutritional deficiency states and chronic liver disease. Heavy alcohol intake is associated with both structural and functional changes in the central nervous system (Charness, 1993). Brain atrophy is present in a majority of alcoholics and can be detected with structural brain imaging. Brain atrophy is partially reversible during abstinence (Kril et al., 1997; Mann et al., 1995). Neurodegeneration can be assessed with magnetic resonance spectroscopy by measuring the concentrations of substances like N-acetyl-aspartate, normalized to phosphocreatine/creatine concentrations

(Ross and Michaelis, 1994). Functional brain imaging measures change in relevant neurotransmitter systems and in stimulus-induced brain activation (Heinz et al., 1998; Hommer, 1999; Tiihonen et al., 1995). A central increase in μ-opiate receptors in vivo was associated with drug craving among patients with cocaine dependence (Zubieta et al. 1996). This symposium, which dealt with our current knowledge about alcoholic brain damage and dysfunction, brought together leading experts in the fields of neuropathology and structural and functional imaging. A short version of their contributions is given in this overview.

The symposium showed clearly how fast the field is moving. Through the development of new imaging technologies, we shift from structural imaging to studying brain function in vivo. These new approaches allow us to better study the pathophysiology of alcoholic brain damage and open pathways for a more profound understanding of physiological and pathological functioning of the brain even beyond the effects of alcohol.

NEUROPATHOLOGICAL CHANGES IN ALCOHOL-RELATED BRAIN DAMAGE

Clive Harper

Methods. Our focus of research has been the pathological, neurochemical, and neuropharmacological changes that can be identified in brains after the long-term use and abuse of alcohol. All cases are categorized based on historical, clinical, and pathological information. The categories include controls, moderate drinkers, "uncomplicated" alco-

Table 1. Summary of Quantitative Neuropathological Data in Different Groups of Alcoholic Patients (%)

Region	Alcoholic[a]	Chronic WE[b]	Korsakoff psychosis[c]
Brain shrinkage (↑ pericerebral space)	36	77	77
↓ Frontal cortical neurons	77	80	84
↓ Cortical neuronal dendrites	81	NA	NA
↓ White matter volume	98	79	83
↓ Mamillary body neuronal number	98	53	32
↓ Thalamic neurons (mediodorsal)	100	52	36
↓ Thalamic neurons (anterior principal)	100	86	47
↓ Basal forebrain neurons	100	76	79
↓ Median raphe neurons	95	30	NA
↓ Dorsal raphe neurons	98	36	NA
↓ Cerebellar vermis Purkinje cells	95	57	NA

The figures for each group are expressed as a percentage of control data, and the arrows indicate the direction of change (increase or decrease). 100% means no variation from control data.

[a] Uncomplicated alcoholic (no liver disease or Wernicke-Korsakoff syndrome); [b] nonamnestic Wernicke-Korsakoff syndrome; [c] amnestic Wernicke-Korsakoff syndrome.

holics, alcoholics with cirrhosis, and alcoholics with Wernicke-Korsakoff syndrome.

The more recent studies of subcortical regions and cerebellum employed quantitative analyses (Baker et al., 1999). The volume of each zone was determined by fluid displacement, and 50 μm serial frozen sections were cut and stained with cresyl violet. The proportion of each cerebellar section occupied by white matter, molecular, Purkinje, and granule cell layers was determined by point counting. The number of granule and Purkinje neurons was estimated by the optical dissector technique.

Results. Table 1 summarizes some of the quantitative neuropathological data in different groups of alcoholic patients expressed as a percentage of control data. The arrows indicate the direction of change (increase or decrease). One hundred percent means that there was no variation of the group data from control data.

Discussion. Earlier studies (Kril and Harper, 1989) confirmed that there is brain shrinkage in many cases of alcoholism and that the white matter is the primary target. Reduction in vermal white matter volume correlated with the severity of ataxia. The reduced white matter volume is not related to changes in hydration or changes in the chemical structure of the myelin. Select populations of neurons appear to be susceptible to alcohol-related brain damage. There is a 20% reduction in numbers of neurons in the superior frontal cortex (Kril and Harper, 1989). Cortical neuronal dendritic arborization is reduced in the alcoholic cases in all cortical regions studied.

Selective neuronal loss in the anterior nucleus of thalamus accounts for the amnestic syndrome in Wernicke-Korsakoff syndrome (Harding et al., 2000), but neuronal loss also was documented in medial dorsal thalamus, basal forebrain, mamillary bodies, and median and dorsal raphe nuclei in alcoholics with Wernicke-Korsakoff syndrome (Harper, 1998).

A recent study to determine the amount of neurodegeneration in the different functional zones of the cerebellum in different subgroups of chronic alcoholics (Baker et al., 1999) found no gross volume loss of any cerebellar zone.

However, all alcoholics had reduced white matter volume (all zones) and decreased Purkinje cell density (spinocerebellum) that correlated negatively with the amount of alcohol consumed per day. In alcoholics with Wernicke's encephalopathy, there was a 40% loss of Purkinje cells in the flocculus (vestibulocerebellum).

Based on clinical and radiological studies and on experimental models, some alcohol-related damage appears to be reversible. The pathological explanation for this phenomenon remains uncertain, but studies suggest that some of the damage to the white matter and the shrinkage of the neuronal dendritic arbor can be reversed.

REGIONAL BRAIN VOLUMES INCLUDING THE HIPPOCAMPUS AND MONOAMINE METABOLITES IN ALCOHOL DEPENDENCE

Ingrid Agartz, Susan Shoaf, Robert R, Rawlings, Reza Momenan, and Daniel W Hommer

Brain volume shrinks over the life span of the adult, and women have smaller intracranial volumes than men. In the current studies, we did not find significant differences in intracranial volumes between alcoholic and healthy subjects. To control for individual differences in head size, we created ratios between the volume of interest and the remainder of the intracranial volume, that is, the intracranial volume minus the volume of interest. Thus, we created relative volumes or volume ratios.

Methods. The patients were examined after 3 weeks of supervised abstinence. They were selected not to have any neurological or hepatic (cirrhosis or hepatitis) complications of alcoholism, delirium tremens, epilepsy, significant head injury, or signs or symptoms of dementia, or any significant organic or psychiatric disease.

Among alcoholics, women had a later age of onset of heavy drinking. On average, women started drinking at 26 years of age whereas the men started at 23. Women had significantly fewer years of heavy drinking (typically 8 years vs. 14 years in men). With respect to lifetime drinking measures, women drank less than men but this difference

was not statistically significant. We measured alcohol intake 6 months before admission. This measure was corrected for sex differences in alcohol distribution volume and did not differ between sex (Agartz et al., 1999; Hommer et al., 1996, unpublished data, 2000; I. Agartz et al., unpublished data, 2000).

Results. The brain (cerebral) volumes of the alcoholic subjects ($n = 143$) were significantly smaller than the controls ($n = 103$) [$F(1,244) = 52.3, p < 0.00001$]. A comparison of the relative brain volumes between 140 alcoholic women and men showed that the women had greater reduction in brain volume than alcoholic men. This sex difference was highly significant [$F(1,183) = 17.1, p < 0.0001$]. We found that the amount of alcohol reported to have been consumed, presence or absence of comorbid psychiatric disorders (mostly depression or posttraumatic stress disorder), and presence or absence of other substance abuse did not affect brain volume during aging of alcoholics. The only significantly influential factors were age and sex.

Differences in gray and white matter and sulcal (surface) cerebrospinal fluid volumes between alcoholics and controls were highly significant ($p < 0.0001$). There was a significant sex effect ($p < 0.0001$) for the white matter, with smaller white matter in women, which is in accordance with previous investigations that have found smaller white matter volumes and larger gray matter volumes in women compared with men. The ventricular cerebrospinal fluid volume difference was not significant.

The hippocampus is rich in glucocorticoid receptors and is considered particularly vulnerable. During withdrawal, stress-induced corticosteroid elevation may act in concert with alterations in excitatory neurotransmission. We predicted that the hippocampus would be more affected than other structures (the rest of the brain volume) by alcohol's neurotoxic effects. The hippocampus was manually outlined from reformatted magnetic resonance images, on average 17–22 1-mm sections on the left and on the right side. We compared the volumes of the hippocampi of hospitalized alcoholics ($n = 52$) and healthy controls ($n = 36$).

Both alcoholic men and women had significantly smaller right hippocampi than healthy subjects of the same sex, but only among the women was the left hippocampus and the nonhippocampal brain volume significantly smaller. The proportion of hippocampal volume relative to the rest of the brain volume was the same in alcoholics and healthy subjects, in both men and women. We found no evidence that the hippocampus is selectively affected by alcoholism.

We measured the concentrations of the monoamine metabolites 5-hydroxy-indoleacetic acid, homovanillic acid, and 3-methoxy-4-hydroxyphenylethylenglycol, which constitute the main metabolites of serotonin, dopamine, and norepinephrine in lumbar cerebrospinal fluid in 74 alcoholics and healthy subjects, women and men. There were no significant correlations or trends ($p < 0.1$) between the cerebrospinal fluid metabolites and any of the magnetic resonance imaging (MRI) volumes in any of the groups.

DIFFUSION TENSOR ABNORMALITIES IN IMAGING OF WHITE MATTER ALCOHOLISM

Adolf Pfefferbaum and Edith V. Sullivan

Magnetic resonance diffusion tensor imaging (DTI) offers a method for depiction and quantification of the diffusion properties of white matter expressed as intravoxel and intervoxel coherence of tracts and fibers. Application of this MRI technique in human alcohol studies provides the unique opportunity of in vivo examination of white matter microstructural degradation reported in neuropathological study and possible previously only on postmortem examination (de la Monte, 1988; Harper et al., 1985; Jensen and Pakkenberg, 1993). White matter is subject to volume reduction, demyelination, and axonal deletion, likely due in part to regional neuronal loss that can occur especially in the superior frontal cortex (Harper et al. 1987; Kril et al. 1997).

DTI permits quantification of the directionality and coherence of white matter fiber tracts and is based on the measurement of self-diffusion of water molecules. When unrestricted, the movement has no directional preference and is isotropic. When motion is restricted by physical boundaries with a predominant direction, such as a white matter tract, the diffusion is greater parallel to the tract and thus is anisotropic. The degree of anisotropy within a voxel (intravoxel) is expressed as fractional anisotropy. Intervoxel coherence, a measure of coherence on a larger scale, also can be calculated.

Here, we employed DTI to quantify intravoxel and intervoxel coherence of brain white matter tracts of the genu and splenium of the corpus callosum and of the centrum semiovale in detoxified alcoholic men in comparison with the previously studied nonalcoholic control subjects. Furthermore, we tested the functional consequences of these white matter measures by correlating them with tests of attention and working memory. A full version of this article appears in Pfefferbaum et al. (2000b).

Methods. The patients with chronic alcoholism included 15 men (40–72 years old), with a median time between last drink and MRI scanning of 332 days (range, 25 to 5110 days). The healthy control subjects included 31 men (23–76 years old).

DTI was performed by using a single-shot, spin-echo, echo-planar imaging technique (5 mm thick slices, 0 mm slice gaps, TR = 6000 msec, TE = 106 msec, 128 × 128 zerofilled to 256 × 256 acquisition matrix, field of view = 24 cm, 18 slices at the location of the anatomic MRI). The amplitude of the diffusion-sensitizing gradients was 1.4 Gauss/cm with 32 msec duration and 34 msec separation. This resulted in a total b-value of 860 sec/mm². Diffusion was measured along six noncollinear directions. Diffusion images were spatially warped to correct for the spatial distortion inherent in echo-planar imaging (Pfefferbaum et al., 2000a). White matter intervoxel coherence images were constructed by using the average of the angle (α) between the eigenvector of the largest eigenvalue of a given voxel and its

neighbors, which represents the extent to which the vectors point in the same direction and are, therefore, coherent.

Subjects received tests of attention and working memory, from which composite scores were formed. The attention subscore of the Dementia Rating Scale (Mattis, 1988) served as the attention composite score. The working memory composite comprised Backward Digit and Block Spans (Wechsler, 1981) and Trail Making Part B (Lezak, 1995).

Results. Analysis of variance revealed that age-corrected fractional anisotropy was lower in all regions in the alcoholics than the controls ($p < 0.006$) with no significant interaction. These differences were greatest in the genu ($p < 0.05$) and centrum semiovale ($p < 0.01$). The group differences in fractional anisotropy and coherence were independent of the volume measured in a region. This was to be expected because the regions were defined geometrically to ensure fully volumed samples of the target structures. In contrast to fractional anisotropy, intervoxel coherence yielded no significant effects, although intervoxel coherence in the splenium of the alcoholic group was nearly 1 standard deviation lower than that in the controls.

Lower fractional anisotrophy and coherence in the genu correlated with time from last drink to MRI (fractional anisotropy $\rho = 0.69$, $p < 0.001$; intervoxel coherence $\rho = 0.47$, $p < 0.08$). Within the alcoholic group, the attention composite positively correlated with genu intervoxel coherence ($r = 0.50$, $p = 0.03$), whereas the working memory composite positively correlated with splenium fractional anisotropy ($r = 0.59$, $p = 0.01$). Multiple regression analyses indicated selectivity of these correlations.

Discussion. This diffusion imaging study provides in vivo evidence for disruption of brain white matter microstructure in alcoholism. The white matter structures examined that showed the greatest fractional anisotropy deficits were the centrum semiovale and the genu of the corpus callosum. These microstructural abnormalities occurred even though the macrostructural volumes of the regions measured were similar in the two subject groups. The results also suggest that declines in both intravoxel and intervoxel white matter fiber coherence may contribute to deficits in attention and working memory, which commonly occur in patients with chronic alcoholism.

The mechanism for low white matter fractional anisotropy in chronic alcoholics remains unclear but probably involves changes in myelination, axonal integrity, and accumulation of extracellular fluid observable best at the microstructural level.

USE OF FUNCTIONAL MRI TO EVALUATE BRAIN ACTIVITY DURING ALCOHOL CUE EXPOSURE IN ALCOHOLICS: RELATIONSHIP TO CRAVING

Raymond F. Anton, David J. Drobes, and Mark S. George

A growing number of studies suggest that various aspects of craving may predispose alcoholics to relapse (Flannery et al., 1999; Roberts et al., 1999) and that environmental stimuli (cues) related to alcohol can trigger "urges to drink." Animal studies indicate that certain brain regions may underlie rewarding aspects of alcohol consumption (Koob and Roberts, 1999) but also may be involved with environmental stimuli associated with past drinking (Katner and Weiss, 1999). In the clinical laboratory, alcohol-dependent individuals respond to the sites and tastes of alcohol by experiencing increased "craving." In one human study, alcoholics exposed to a sip of alcohol during brain imaging (SPECT) showed enhanced activity in the right caudate (basal ganglia) that correlated highly with their increase in craving (Modell et al., 1990).

Methods. By using functional MRI (fMRI), we studied 10 non-treatment-seeking alcoholics and 10 socially drinking controls during alcohol cue exposure in the fMRI scanner. All subjects were free of alcohol for at least 24 hr before the study. While in the scanner, during acquisition of a static MRI brain image, subjects were shown pictures of affectively neutral scenes. Then a tube was placed in their mouths and a sip of their favorite alcoholic beverage was allowed (producing a negligible blood alcohol level) immediately before the start of the fMRI scanning.

Results. The findings of this initial study are interesting and encouraging. Alcoholics had higher levels of craving before, during, and after the fMRI procedure compared with controls. Although there was some concern that in the sterile environment of a MRI suite, alcoholics would have no urge to drink, this did not appear to be the case.

On the negative side, there was not much mean increase in craving (as retrospectively rated) during the alcohol picture exposure; that is, alcoholics started high and stayed high throughout the procedure.

Both the left dorsolateral prefrontal cortex (DLPC) and thalamus showed greater activity during alcohol cue exposure in the alcoholics. Only the alcoholics had more activity in these areas after we subtracted the neutral beverage activity. The social drinkers did not show alcohol-cue-induced specific increase in activity in any brain area. Preliminary data analysis did not suggest any relationship between brain activity and basal levels of craving, retrospective ratings of craving during alcohol picture exposure, or final craving.

Discussion. The implications of this work are several. We have shown that it is possible to image regional brain changes related to alcohol stimuli (taste and visual). In this early work we did not attempt to distinguish whether the taste or visual picture was the more powerful cue. We initially thought that the combination of stimuli would be more powerful than either one alone. In fact, because we found a difference in brain activity in alcoholics between alcohol-specific versus neutral pictures, this does suggest that the visual images were important. Whether the same effect would have been observed without giving a taste cue is unknown.

The brain areas (DLPC and thalamus) that showed the alcohol-cue-specific increase in activity in this study also

have shown activation during cocaine stimulation (Grant et al., 1996). These regions are implicated in affective control, sensory integration, and perhaps reward memory. Work in animals suggests that the ablation of the DLPC reduces cocaine sensitization (Pierce et al., 1998). If replicated, these data suggest that this brain area may be particularly important for craving activation or may play a role in alcohol relapse as it relates to memories of alcohol effects or impulse inhibition to drink alcohol. In this regard, it is not certain whether the activation of these structures is a primary effect related to a positive alcohol stimulatory activity or an attempt to inhibit, or balance, this activity in a setting where drinking is not expected or possible.

M-OPIATE RECEPTOR AVAILABILITY IN ALCOHOLISM: FIRST RESULTS FROM A POSITRON EMISSION TOMOGRAPHY STUDY

Karl Mann, Roland Bares, Hans-Juergen Machulla, Goetz Mundle, Matthias Reimold, and Andreas Heinz

In alcoholism, changes in μ-opiate receptor availability may be associated with an increased relapse risk and the response to naltrexone medication. We measured in vivo μ-opiate receptor availability with carfentanil positron emission tomography (PET).

Methods. Twenty alcohol-dependent patients were assessed with [C-11]carfentanil PET after 3 weeks of supervised abstinence. Patients were assessed before naltrexone treatment and again after 2 months, after either open naltrexone application or a similar, drug- and medication-free observation period. Patients received 700–800 MBq of [C-11]carfentanil. The distribution volume ratio of specific to nonspecific binding at pseudoequilibrium (Frost et al., 1990) was measured in regions of interest drawn on coregistered MRI scans. The availability of μ-opiate receptors in the ventrostriatal circuit and limbic system was compared with the severity of alcohol craving, treatment outcome, and μ-opiate receptor genotype.

Results. A preliminary analysis of central μ-opiate receptors measured with carfentanil PET showed no significant changes during the follow-up period of 2 months in patients without naltrexone. Among patients with an early disease onset and a long duration of illness, we observed an elevation of μ-opiate receptors in the striatum and thalamus and some cortical regions. Patients on 50 mg of naltrexone showed a complete blockade of μ-opiate receptors.

Discussion. We found that μ-opiate receptors were not decreased but rather were elevated among alcoholics with early onset disease, and the increased carfentanil binding showed a trait-like stability during the observation period. We currently are assessing whether μ-opiate receptor genotype (Bond et al., 1998) is associated with elevated carfentanil binding in alcoholism. Our next study measures μ-opiate receptor availability in relationship to the response to naltrexone medication.

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