Cortical Gray Matter Loss in Treatment-Naive Alcohol Dependent Individuals

G. Fein, V. Di Sclafani, V. A. Cardenas, H. Goldmann, M. Tolou-Shams, and D. J. Meyerhoff

Background: Most studies of the impact of alcohol dependence on the brain have examined individuals in treatment. Such samples represent a small proportion of alcoholics in the general population. Such samples may embody a bias (Berkson's fallacy) if the association between variables (for example, alcoholism and cortical gray matter loss) differs between the population of alcoholics in treatment and alcoholics in the general population. Our objective was to determine if treatment-naive alcoholics show structural brain changes versus controls and to compare our findings with reports evaluating alcoholic samples drawn from treatment populations.

Methods: Structural MRI was used to assess whole brain and regional volumes of cortical gray matter and white matter in 24 young to middle-aged treatment-naive alcohol-dependent males versus 17 controls.

Results: Cortical gray matter volumes in alcohol-dependent individuals were negatively associated with age and lifetime duration of alcohol use (which were highly confounded). These subjects showed reduced whole brain (p < 0.05), prefrontal (p < 0.01), and parietal (p < 0.05) cortical gray matter compared with controls. White matter and temporal cortex, tissues that usually show volume reductions in samples drawn from treatment, did not differ between treatment-naive alcoholics and controls (all p > 0.40).

Conclusions: Our findings are consistent with the hypothesis that structural brain changes in treatment-naive alcoholics are less severe than those reported in clinical samples of alcoholics, perhaps due to less concomitant psychopathology and a reduced severity of alcoholism in treatment-naive alcoholics. However, caution must be taken when comparing our findings with results from clinical samples, as we did not directly compare treatment-naive alcoholics with treated alcoholics and our treatment-naive sample tended to be younger than the (clinical) samples reported in the literature. Nevertheless, we suggest that most of the reports of the central nervous system consequences of alcoholism may not accurately describe the majority of alcoholic-dependent individuals.

Key Words: MRI, Alcoholic, Atrophy, Cortical, Frontal Lobe.
ence of locomotor disease in the hospitalized individuals. However, Roberts found that respiratory and locomotor diseases were essentially independent in the entire random sample. The spurious association between respiratory disease and locomotor disease arose in the hospitalized group because the admission rate of people with both diseases (29%) was about three times the rate of people with only respiratory or locomotor disease or neither disease (7–10%). As Fleiss (1973) succinctly stated: "...Unless something is known about differential hospitalization rates..., a good amount of skepticism should be applied to any generalization from associations found for hospitalized patients...to associations for people at large."

Parnas and Teasdale (1987) presented an example of Berkson’s fallacy in the study of schizophrenia with direct applicability to alcoholism research. An American-Danish prospective study of children of schizophrenic mothers compared psychiatrically hospitalized and untreated cases of schizophrenia spectrum disorders on a number of characteristics. Hospitalized and untreated cases were similar on a number of measures; however, hospitalized individuals exhibited higher levels of substance abuse, affective symptoms, and psychopathic tendencies. The authors suggest that "the clinical population may not be representative of the diagnostic category in question owing to [a greater] coexistence of confounding symptomatology (Berkson’s fallacy)".

Drawing convenience samples from treatment populations could create an analogous situation in the study of alcohol dependence. Coexisting pathology (e.g., depression or bipolar affective disorder, antisocial personality disorder, attention deficit hyperactivity disorder, posttraumatic stress disorder, and other substance abuse disorders) may be greater in the treatment population than in alcoholics in the general population. This coexisting pathology may not be severe enough to result in clinical diagnoses that would exclude subjects from alcoholism research samples. Alternatively, the bias due to Berkson’s fallacy may result if the severity of alcoholism is greater in clinical versus general population samples. Again, in either case, associations found in clinical samples may not generalize to alcoholics in the general population.

How big is this potential bias? Its magnitude depends on the proportion of alcoholics who are in the treatment population. The most current data available indicate that the number of alcoholics in treatment is a small proportion of alcoholics in the general population. The 1992 National Longitudinal Alcohol Epidemiologic Survey (Grant, 1994a) estimates that over 27 million Americans exhibit alcohol abuse or alcohol dependence or both. At about the same time, Harwood et al. (1994) estimated that there were approximately 1.8 million Americans receiving treatment for alcohol problems in non-Federal hospital and community-based treatment settings. Grant (1994b) estimates that only 1 in 10 individuals who need treatment for alcohol abuse problems has sought treatment. These estimates derive from different methodologies and sampling plans; however, even assuming that three times the 1.8 million individuals from the Harwood study received some form of treatment for alcoholism, the treatment population is still less than a quarter of the population with alcohol problems. Therefore, estimates drawn from clinical samples may not represent up to three quarters of the individuals with alcohol problems.

Reports of structural imaging abnormalities associated with chronic alcohol abuse and dependence abound in the recent literature, but most (if not all) of the samples have been drawn from alcohol treatment centers (de la Monte, 1988; Harper et al., 1988; Jernigan et al., 1991,1992; Pfefferbaum et al., 1992,1995,1998; Shear et al., 1994; Sullivan et al., 1995). This study focuses on structural brain imaging in young to middle-aged treatment-naive alcohol-dependent males versus controls. We compare our results to the findings presented in the literature for alcohol-dependent samples drawn from treatment populations.

METHODS

Subjects

Subjects were recruited from the community (via advertisements for light drinkers and heavy drinkers) for an alcohol administration Magnetic Resonance Spectroscopy (MRS) study (Estilaei et al., 2001; Fein and Meyerhoff, 2000; Goldmann et al., 2000) investigating 1H MRS visibility of alcohol and the effect of alcohol tolerance on MRS alcohol visibility. Forty-one individuals, 24 heavy drinkers (HD) and 17 light drinkers (LD), were studied according to protocols approved by the local Institutional Review Board. Table 1 shows the demographic, family history, and alcohol use information for these subjects. All HD subjects satisfied DSM-IV-R criteria for lifetime dependence on alcohol. Subjects were screened to exclude individuals with a current or past history of substance abuse (other than alcohol) or major psychiatric or neurologic disorder (including history of head injury with loss of consciousness). Subjects were also screened to exclude individuals with a current or past history of medical conditions that may affect brain structure, (including diabetes, HIV, and lung, kidney, or heart disease). Lifetime drinking history was ascertained using the timeline follow-back method (Sobell and Sobell, 1992). Family history of alcoholism was assessed using a family tree questionnaire (Sobell et al., 1985). Subjects with a father or mother identified as a problem drinker were considered family history positive; subjects with only siblings or second-degree relatives identified as problem drinkers were not considered family history positive. A handheld Breathalyzer was used to confirm sobriety at the time of the magnetic resonance study (MR1).

MR Measurements

All image acquisition and analysis procedures have been described in detail previously (Fein et al., 2000).

Image Acquisition. All measurements were carried out on a whole body 1.5 T Magnetom Vision system (Siemens Medical Systems, Erlangen, Germany) equipped with a standard quadrature head coil. A vacuum-molded head holder was used to minimize motion of the subject’s head. The structural imaging protocol (before alcohol administration) consisted of: (a) a sagittal T1-weighted localizer sequence; (b) an oblique axial double spin-echo sequence (TR/TE1/TE2 = 3000/20/80 msec), angulated at −10 degrees from the planum sphenoidale. This study yielded both a T2-weighted and a proton-density (PD) weighted image and covered the entire brain in contiguous 3-mm thick slices. These slices were obtained in an interleaved manner, with an in-plane resolution of 0.94 x 0.94 mm; and (c) an oblique coronal T1-weighted gradient echo sequence (3D MP,

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PD-, and T2-weighted images were used for segmentation into tissue nerve, with a 1.5-mm slice thickness and inhomogeneity filtering of the spin-echo images. The segmentation process began with automated stripping of the skull from the images. The operator chose very conservative samples of cerebrospinal fluid (CSF), RAGE, TR/TE = 9.7/4.6 msec, angulated perpendicular to the optic nerve, with a 1.5-mm slice thickness and an in-plane resolution of 1 x 1 mm.

Image Processing. The tissue volumes in the segmented image were obtained using computer-assisted methods. The image-processing technician was blind to subject demographics and group membership. The T1-, T2-, and T2-weighted images were used for segmentation into tissue categories. The segmentation process began with automated stripping of the brain to these three tissue categories. The resulting ROIs were specific to anatomic location. We have recently demonstrated the reliability and validity of this approach to image segmentation (Cardenas et al., 2001).

Regional Processing in the Talairach Coordinate System. In the Talairach coordinate system, the brain is subdivided into a 12 (superior-inferior) x 9 (anterior-posterior) x 8 (lateral) grid, with a total of 864 voxels. The Brodmann areas encompassed by each of these 864 voxels were identified from the 1988 Talairach atlas (Talairach and Tournoux, 1988). We defined 15 cortical regions of interest (ROI) by their corresponding Brodmann areas: orbital frontal and frontal pole (10, 11); posterior prefrontal (6, 8, 44); dorsolateral prefrontal (9, 46); lateral prefrontal (45, 47); primary motor (4); primary sensory (1, 2, 3); lateral parietal (39, 40); mesial parietal (5, 7, 23, 31); anterior occipital (37); visual association (17, 18, 19); anterior temporal (21, 38); superior temporal (34, 41, 42); inferior temporal (20); anterior cingulate (24, 32); and the limbic lobe (24, 29). The ensuing transformation of each subject's T1-weighted image to the Talairach coordinate system involved piecewise linear transformations of 12 compartments for each subject's brain. The resulting ROIs were specific to each subject but reflect a common Talairach definition. The final regional tissue volumes resulted from superimposing the subject-specific ROI on the subject's segmented image (and counting the segmented pixels). This method has been described in detail elsewhere (Cardenas et al., 2001; Fein et al., 2000).

Statistics

Statistical analyses were performed using the Proc GLM routine in the SAS software package (SAS Institute, Cary, NC). Comparisons of structural imaging variables between HD and LD subjects were performed with intracranial vault volume (ICV) as a covariate. The group difference effect size (percent of variance of the imaging variable accounted for by group membership) was computed after removing imaging variable variance due to intersubject differences in ICV. Associations within each group of demographic and drinking variables with imaging measures were analyzed using partial correlations (with ICV always partialled out and other variables partialled out as indicated). LD was compared with the entire HD sample and to a subset of HD of comparable age (i.e., HD subjects over 42 years of age excluded).

RESULTS

Demographic and Alcohol-Use Variables

The LD sample was younger than the HD sample (t_{27.7} = 3.90, p = 0.0004) and had about 2 years more education (t_{23.6} = 3.20, p = 0.004). The LD had a lower proportion of individuals who were family history positive for alcoholism (19% vs. 59%, \chi^2 = 6.18, p = 0.013). Because the LD and HD samples were selected to be very different on alcohol-use variables, statistical comparisons on those variables are not appropriate. (Lifetime alcohol consumption for HD subjects was about 14 times that of LD subjects.)

We present the following analyses both for the entire HD sample (which was, on average, about 9 years older than the LD sample) and for an HD subgroup comparable in age to the LD sample. The comparison of LD to the entire HD sample provides the best estimates of the associations between age and the structural imaging variables. The comparison of the LD to an age-comparable HD subgroup examines the brain structure of untreated HD versus LD, without the confounding effect of age differences between the samples. Table 2 presents whole brain and regional cortical gray matter volume differences for LD versus both the entire HD sample and the age-comparable HD subgroup.

Structural Imaging Measures

LD Sample Versus HD Sample. The entire HD sample did not differ in ICV volume from LD (p > 0.15). HD showed reduced total cortical gray matter (45.6% vs. 46.8%, p < 0.02) and increased WMSH volume (Wilcoxon z approximation = 1.65, 1-tail p < 0.05) compared with LD. The posterior prefrontal and dorsolateral prefrontal cortex were reduced in HD versus LD (p's < 0.01) as was the
lateral and mesial parietal cortex (p's < 0.05). Sulcal CSF was increased in all regions of reduced gray matter. This is in contrast to both total and regional white matter measures which remained virtually identical between LD and HD (all p's > 0.52). Finally, we divided the gray matter regions into right and left hemisphere volumes, and reanalyzed the data using hemisphere as a within-subject factor. There was no evidence for a side × group or a side × region × group effect (both F < 1.20, p > 0.32).

**LD Sample Versus Age-Comparable HD Subgroup.** We selected an HD subgroup (n = 16) that was comparable in age to the LD sample (by eliminating all HD subjects over age 42). There were no differences between the age-comparable HD subgroup and LD for any of the whole brain volume measures (cortical gray matter, white matter, sulcal CSF, ventricular CSF, or WMSHs; all p's > 0.32). The only structural imaging differences between LD and the age-comparable HD subgroup were reduced cortical gray matter in the posterior prefrontal cortex and dorsolateral prefrontal cortex (p's < 0.05).

### Table 2. Whole Brain and Regional Gray Matter

<table>
<thead>
<tr>
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<th>Light drinker sample vs. Heavy drinker sample</th>
<th>Light drinker sample vs. Age-comparable heavy drinker subgroup</th>
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<tbody>
<tr>
<td></td>
<td>% difference from light drinkers</td>
<td>% of variance explained by group membership*</td>
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<tr>
<td>Total cortical gray matter</td>
<td>-4.6</td>
<td>14.7*</td>
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<td>Prefrontal lobe</td>
<td>-0.1</td>
<td>0.2</td>
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<td>Orbital frontal and frontal pole</td>
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<tr>
<td>Lateral prefrontal</td>
<td>-3.0</td>
<td>3.9</td>
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<td>Posterior prefrontal</td>
<td>-8.3</td>
<td>19.6*</td>
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<td>Dorsolateral prefrontal</td>
<td>-8.8</td>
<td>17.2*</td>
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<tr>
<td>Parietal lobe</td>
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<tr>
<td>Lateral parietal</td>
<td>-7.8</td>
<td>11.4*</td>
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<td>Mesial parietal</td>
<td>-7.1</td>
<td>15.6*</td>
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<td>Motor cortex</td>
<td>-4.8</td>
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<td>Sensory cortex</td>
<td>-7.6</td>
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<tr>
<td>Occipital lobe</td>
<td>-4.5</td>
<td>7.0</td>
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<td>Anterior occipital</td>
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<td>Visual cortex and Association cortex</td>
<td>-4.6</td>
<td>4.6</td>
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<tr>
<td>Temporal lobe</td>
<td>-3.2</td>
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<td>Anterior temporal</td>
<td>-4.4</td>
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<td>Superior temporal</td>
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<td>Inferior temporal</td>
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<td>Anterior cingulate</td>
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<td>Limbic lobe</td>
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<td>% difference from light drinkers</td>
<td>% of variance explained by group membership*</td>
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* After removal of variance associated with ICV volume.

*p < 0.05; **p < 0.01.

Association of Imaging Variables With Age and Alcohol Use

Within LD, there was a trend toward an association of age with total cortical gray matter (r = -0.48, p = 0.07) and total sulcal CSF (r = 0.49, p = 0.07). There were no associations of age or lifetime duration of alcohol use with any regional structural imaging variables (e.g., posterior prefrontal and dorsolateral prefrontal gray matter; r's < 0.14, p's > 0.60).

In the HD sample, there was a strong negative correlation of both age and lifetime duration of alcohol use with total cortical gray matter volume (both r's < -0.79, p's < 0.0001). Correlations between age and regional cortical gray matter volume and duration of alcohol use and regional cortical gray matter volume were nearly identical, ranging from -0.47 to -0.75 for 12 of the 15 cortical regions (excepting the anterior and inferior temporal cortex and visual cortex). The correlations with age and lifetime duration of alcohol use for sulcal CSF measures (total and regional) were similar to those observed for cortical gray matter measures, although of opposite sign.

In the age-comparable HD subgroup there were also negative correlations of age and lifetime duration of alcohol use with total cortical gray matter (r = -0.73, p = 0.003; and r = -0.81, p = 0.0004). Correlations between age and regional cortical gray matter ranged from -0.54 to -0.73 for 7 of 15 regions (posterior prefrontal, dorsolateral prefrontal, lateral prefrontal, mesial parietal, lateral parietal, motor, and sensory cortex), and correlations between lifetime duration of alcohol use and regional cortical gray matter ranged from -0.56 to -0.88 for the same 7 of 15 cortical regions, with the addition of visual cortex.

Age was confounded with lifetime duration of alcohol use in LD (r = 0.59, p = 0.02) and almost completely confounded with lifetime duration of alcohol use in both the entire HD sample (r = 0.91, p < 0.0001) and in the age-comparable HD subgroup (r = 0.86, p < 0.0001). When we attempted to disentangle the association of the imaging variables with age versus with the association of duration of alcohol use by partialling out the variance associated with one of the variables (age or duration of drinking) and then examining the remaining association of the other variable, we found no associations between age or
drinking duration with any imaging measure. Figure 1 presents the posterior prefrontal gray matter data (i.e., the variable with the largest group difference effect) for all subjects in LD and HD, illustrating both the volume reduction in HD versus LD and the association in HD of this brain volume with subject age and lifetime duration of alcohol use. We note that the data for HD is presented twice, once in relation to age and again in relation to duration of alcohol use.

There were no associations of average or peak alcohol dose with any of the structural imaging variables, except for WMSH volume (r = 0.43, p < 0.05). Finally, the entire HD sample showed no association of any imaging variable with family history of alcoholism or with years of education (all r's < 0.20, p's > 0.30).

**DISCUSSION**

We found cortical gray matter volume reductions (primarily in prefrontal and parietal regions) in male heavy drinkers who met criteria for alcohol dependence but had never been in treatment. The cortical volume loss was not correlated with family history of alcoholism nor with education, suggesting that the volume loss reflects the effect of alcohol ingestion rather than premorbid factors that predispose subjects to heavy drinking. Unlike most other studies of structural brain changes (which used samples drawn from treatment), this treatment-naïve sample showed no white matter (de la Monte, 1988; Harper et al., 1988; Jernigan et al., 1992; Pfefferbaum et al., 1995; Shear et al., 1994) or temporal lobe (Jernigan et al., 1991; Pfefferbaum et al., 1992, 1997; Sullivan et al., 1995) volume loss. Our findings are consistent with the hypothesis that structural brain changes in treatment-naïve alcoholics are less severe than those reported in clinical samples of alcoholics. However, caution must be taken when comparing our findings with results from clinical samples, as we did not directly compare treatment-naïve alcoholics with treated alcoholics. In addition, our treatment-naïve sample tended to be younger than the (clinical) samples reported in the literature. Given that increasing age magnifies the effects of alcohol on brain structure and function (Carlen et al., 1978; Jernigan et al., 1986; Lishman et al., 1987; Ron, 1983; Wilkinson, 1985), the younger age of our sample compared with clinical samples in the literature may contribute to the less morbid structural imaging findings in our study.

Preferential prefrontal gray matter atrophy associated with alcohol abuse was first suggested by Courville (1955). Prefrontal atrophy has since become one of the most frequent findings in investigations of the central nervous system (CNS) effects of alcohol dependence (Adams et al., 1993; Gilman et al., 1990; Harper and Kril, 1990; Pfefferbaum et al., 1995, 1997). Preferential frontal lobe involvement in alcoholism has also been documented with positron emission tomography (PET) (Risberg and Berglund, 1987; Volkow et al., 1992; Wang et al., 1993) and in studies of cortical neuronal counts (Harper and Kril, 1989, 1990; Harper et al., 1987; Kril et al., 1994; Kril and Harper, 1989).

While our strongest findings were in the prefrontal cortex, the parietal cortex was also adversely affected by heavy drinking. Jernigan also found the parietal cortex atrophied in a MRI study of abstinent alcoholics (Jernigan et al., 1991). Parietal gray matter volume reductions are consistent with the frequent findings of alcohol-related impairments in visuo-spatial abilities and sensory integration (Sullivan et al., 2000).

We did not observe lateralized reductions in cortical volume. This does not support the right hemisphere model of the effects of alcoholism on brain function (Hutner and Oscar-Berman, 1996). Purported right hemisphere tasks are often novel tasks requiring new learning, which is dependent on the prefrontal cortex. They also involve spatial (rather than verbal) processing of stimuli, which is dependent on the parietal cortex. We hypothesize that right hemisphere impairment is actually impairment in functions subserved by prefrontal and parietal cortices.

There was no evidence of white matter loss in the HD sample. This is in contrast to studies of alcohol-dependent samples drawn from treatment settings where white matter loss is a common finding. (However, as noted above, this study is not a direct comparison of treatment-naïve and clinical samples of alcoholics.) Our finding of intact white matter volume on structural MRI in these treatment-naïve subjects occurred in the context of a 13% reduction in the 31P MRS broad component measured in the white matter of a subset of the HD subjects compared with LD (Estilaei et al., 2001). This suggests higher rigidity of white matter phospholipids in the absence of white matter volume loss. Our hypothesis is that alterations in the composition of membrane lipids lead to changes in myelin structure and, eventually, to tissue volume loss. If this is true, then 31P MRS broad component measures should be even more reduced in clinical samples, where they occur in the presence of white matter volume reductions. We also found 1H MRS evidence for preatrophic white matter n-acetylaspartate (NAA) reductions in a subset of the HD

**Fig. 1.** Posterior prefrontal gray matter (as a percent of the intracranial vault) for LD and HD. This is the regional variable with the largest difference between LD and HD. This figure illustrates both the volume reduction in HD versus LD and the association in HD of this regional brain volume with both subject age and lifetime duration of alcohol use. We note that the data for HD is presented twice, once in relation to age and again in relation to duration of alcohol use.
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that the white matter NAA reductions may reflect changes in regional gray matter volume loss. In the HD sample (and the age-comparable HD subgroup), we found strong correlations of reductions in total and regional cortical gray matter volume with age and with lifetime duration of alcohol use; however, age and duration of alcohol use were almost totally confounded. LD showed a strong trend toward association of age with total cortical gray matter but not with any regional gray matter measures. This suggests that long-term alcohol dependence is the most likely cause of the prefrontal gray matter volume reductions in the HD sample. However, we cannot definitively say whether the volume reductions in HD are associated with long-term heavy alcohol use together with increasing age or simply with duration of alcohol use. Given that the older drinkers have a longer duration of alcohol use, the simplest interpretation of the data would be that duration of alcohol use is the operative factor in cortical volume loss in alcohol-dependent individuals. This interpretation, however, is not consistent with the literature, which tells us that there is a greater degree and persistence of irreversible brain atrophy in older compared with younger alcoholics, independent of the duration of their drinking (Fein et al., 1990).

There may be other manifestations of the bias that occurs when findings of studies of treated alcoholics are presumed to apply to all alcoholics. It is possible that there is greater psychiatric comorbidity in clinical samples than in treatment-naive samples of alcoholics. We know that comorbidity of substance use and psychiatric disorders is substantial. The Epidemiology Catchment Area (ECA) Study (Narrow et al., 1993) found a history of psychiatric disorder in 35% of the 13.5% of the general population who had a history of alcohol abuse. The ECA estimates on comorbidity of psychiatric and alcohol abuse disorders has been replicated by the more recent National Comorbidity Survey (Kessler et al., 1994). Among individuals in alcohol and drug abuse treatment, estimates are that up to 80% have psychiatric symptoms (Kosten and Kleber, 1988). These epidemiologic data address coexisting psychopathology that is severe enough to meet criteria for a psychiatric disorder. This is an underestimate of coexisting psychopathology in that it does not address pathology that is of insufficient severity to result in a clinical diagnosis (e.g., depression or bipolar affective symptoms, antisocial personality traits, attention deficit hyperactivity disorder traits, posttraumatic stress disorder symptoms, and other substance abuse history). Although we did not directly assess psychiatric comorbidity in the study sample, we hypothesize that treatment-naive samples have less psychiatric comorbidity than clinical samples of alcoholics.

We examined only men in this study. The bias inherent in studying clinical populations may be different for men and women, and the greater CNS consequences reported for female versus male clinical samples (Bergman, 1987; Jacobson, 1986) may reflect this difference. The more morbid CNS findings for women may be spurious if clinical samples of alcoholic women differ from treatment-naive alcoholic women more than clinical versus treatment-naive samples of alcoholic men vary. This is entirely possible, as women (for a variety of reasons) are less likely than men to receive treatment for alcohol problems (Center on Addiction and Substance Abuse, 1996). Therefore, clinical samples versus treatment-naive samples of female alcoholics may differ in severity of alcoholism or prevalence and severity of concomitant psychopathology more than clinical versus treatment-naive samples of male alcoholics differ.

Alcoholics in treatment need to be compared directly to non-treatment-seeking alcohol-dependent individuals to determine whether clinical samples differ from treatment-naive samples on measures of CNS structure and function. Coexisting psychopathology, prevalence and severity of predisposing factors (which may be associated with premorbid abnormalities in CNS structure and function), and severity of alcoholism should be assessed. Finally, we need to examine the more vulnerable female alcoholic pictured in the literature; are these findings a function of a bias toward sicker individuals in female versus male clinical populations?

REFERENCES


