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Applications of Morphometric and Diffusion Tensor Magnetic Resonance Imaging to the Study of Brain Abnormalities in the Alcoholism Spectrum

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Background: The International Conference on Applications of Neuroimaging to Alcoholism was held at Yale University in New Haven, CT, in January 2004. The following is a brief summary of the contributions of five speakers who presented their work during the magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) session.

Methods: This session addressed how MRI and DTI are used to assess macro- and microstructural brain alterations in alcoholism. Structural MRI methods can address regional gray and white matter volumetric/morphometric abnormalities, and DTI methods can address microstructural disruptions of white matter tracts. These methods can be applied across the spectrum of alcoholism to elucidate distinct brain abnormalities underlying clinical subtypes, to disentangle brain volume deficits that precede, from those that follow, the onset of alcoholic drinking in chronic alcoholics, and to examine effects of prenatal alcohol exposures on brain development in children. The presentations highlighted recent scientific findings and methodological advances in these areas.

Results: Disease-specific probabilistic atlases, designed to reflect the unique anatomy and physiology of particular clinical subpopulations, can be developed for alcoholism. Such an atlas can be used to identify efficiently patterns of altered structure or function in alcoholism and can guide algorithms for knowledge-based image analysis. DTI is sensitive to constraints on the random diffusion of water molecules in axons, allowing assessment of white matter tract integrity in neuropsychiatric diseases, including alcoholism. Recent MRI and DTI data were presented showing region-specific brain abnormalities at both macro- and microstructural levels that varied differentially according to sex, time of alcohol exposure in life, and alcoholism subtype.

Conclusion: The International Conference on Applications of Neuroimaging to Alcoholism brought together leading experts in MRI and DTI techniques to discuss their applications to the study of alcoholism. The extant and new imaging technologies provide us with multiple modalities to study the brain in vivo. These noninvasive tools enable us to monitor the time course of alcohol effects on the brain and to characterize macro- and microstructural brain abnormalities across the full spectrum of alcoholism, including its precursors and its sequelae.

Key Words: Magnetic Resonance Imaging, Diffusion Tensor Imaging, Alcoholism, Fetal Alcohol Syndrome, Hippocampus, Gray Matter, White Matter.

CHRONIC ALCOHOLISM IS associated with adverse changes in brain structure and function (Charney, 1993; Kril et al., 1997). Although prolonged abstinence

leads to significant recovery of alcohol-induced brain impairments, some deleterious effects of heavy alcohol intake persist throughout life (Rosenbloom et al., 2004; Trabert et al., 1995). Neuroimaging techniques have begun to shed new light on this addictive disorder by allowing in vivo, noninvasive examination of the effects of heavy alcohol intake at anatomic, micro- and macrostructural, chemical, and functional levels. The International Conference on Applications of Neuroimaging to Alcoholism (ICANA) was held on the Medical Campus of Yale University in New Haven, CT, on January 17–19, 2004. The meeting was hosted by the National Institute on Alcohol Abuse and Alcoholism Center for the Translational Neuroscience of Alcoholism directed by John Krystal, MD, and featured sessions that combined neuroimaging methodology and applications to alcoholism, including morphometric magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional MRI, magnetic resonance spectroscopy, positron

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emission tomography, and single photon emission computed tomography research. One session, chaired by Daniel Mathalon, PhD, MD, of the Department of Psychiatry at Yale University, addressed morphometric MRI and DTI methods and their application to the study of macro- and microstructural brain alterations in alcoholism. Arthur Toga, PhD, from the Department of Neurology at the UCLA School of Medicine, described the basic approach and the underlying mathematical constructs that enable the calculation of probabilistic three-dimensional brain atlases as well as the results of their application to several different normal and diseased populations. Derek Jones, PhD, from the Laboratory of Integrative Medicine and Biophysics at the National Institute of Child Health and Human Development branch of the National Institutes of Health, presented the methodology of DTI and its applications to alcoholism. Hannu Aronen, MD, PhD, from the Helsinki Brain Research Center at the University of Helsinki in Finland, presented volumetric findings on the hippocampus in type 1 and 2 alcoholics. Daniel Hommer, MD, from the Laboratory of Clinical Studies at the National Institute on Alcohol Abuse and Alcoholism branch of the National Institutes of Health, followed with a presentation on brain growth and shrinkage in alcoholism. Terry Jernigan, PhD, from the Laboratory of Cognitive Imaging at UCSD and the University of Copenhagen in Denmark, finished the session by presenting data showing the neuroanatomical effects of fetal alcohol exposure on brain development in children. The following is a brief summary of the proceedings from this session.

MAPPING MORPHOLOGICAL CONCOMITANTS TO BRAIN DISEASE, PRESENTED BY ARTHUR TOGA, PHD

Morphometric variability of the human brain poses significant challenges for the creation of population-based atlases. The ability to statistically and visually compare and contrast brain imaging data from multiple individuals is essential for understanding normal variability within a particular population as well as for differentiation of normal and diseased populations. In his presentation, Dr. Arthur Toga introduced the application of probabilistic atlases to describe specific subpopulations, measure their variability, and characterize the structural differences between them. Using structural MRI data, Dr. Toga and his colleagues have built atlases with defined coordinate systems, creating a framework to map data from functional, histological, and other studies of the same population. These structural atlases provide an indexed and robust framework for the mapping of functions and other attributes. In his presentation, Dr. Toga described the basic approach and provided a brief description of the underlying mathematical constructs that enable the calculation of probabilistic atlases along with examples of their results from several different normal and diseased populations.

Perhaps surprising, few atlases of neuropathology use a standardized three-dimensional coordinate system to inte-

grate data across patients, techniques, and acquisitions. Atlases with a well defined coordinate space (Drury and Van Essen, 1997; Evans et al., 1992; Friston, 1995), together with algorithms to align data with them (Toga et al., 1998), have enabled the pooling of brain mapping data from multiple subjects and sources, including large patient populations. Automated algorithms then can capitalize on atlas descriptions of anatomic variance to guide image segmentation (Le Goualher et al., 1999; Pitiot et al., 2002), tissue classification (Zijdenbos and Dawant, 1994), functional image analysis (Dinov et al., 2000), and pathology detection (Thompson and Toga, 1997; Thompson et al., 2000).

Without methods to overcome the problems of anatomic variability, the statistical power to resolve disease and treatment effects relating to alcoholism is seriously undermined. First, normal anatomic variation results in an overlapping of diseased and normal subjects on most anatomic measures. Second, these difficulties are exacerbated in disease-related changes such as atrophy (Mega et al., 1998; Meltzer et al., 1996; Thompson et al., 1998; Woods, 1996) or other progressive and dynamic anatomic changes. In the case of the cortex, profiles of gray matter loss are difficult to calibrate against a reference population due to the lack of statistics on expected changes in these populations. To capitalize fully on neuroimaging data in disease, an appropriately complex mathematical framework is needed to address these challenges. Once resolved, brain maps then can be compared across patients and across time (Mazziotta et al., 1995; Miller et al., 1997; Thompson and Toga, 1997; Thompson et al., 2000).

Dr. Toga's presentation reviewed the construction and application of normal population-based atlases and included descriptions of the concept of disease-specific atlases, designed to reflect the unique anatomy and physiology of a particular clinical subpopulation (Mega et al., 1997, 1999, 1998; Narr et al., 2001, 2004, 2000; Thompson et al., 2001, 1998; Thompson and Toga, 1997) such as alcoholism. On the basis of well-characterized patient groups, these atlases contain composite maps and visualizations of structural variability, asymmetry, and group-specific differences. This quantitative framework can be used to recognize anomalies and label structures in new patients. Because they retain information on group anatomic variability, disease-specific atlases are a type of probabilistic atlas specialized to represent a particular clinical group. The resulting atlases can identify patterns of altered structure or function and can guide algorithms for knowledge-based image analysis (Dinov et al., 2000; Pitiot et al., 2002).

Data were presented from several ongoing projects the goals of which are to create disease-specific atlases of the brain in Alzheimer's disease, schizophrenia, and several neurodevelopmental disorders, demonstrating the applicability to conditions such as alcoholism. In addition, such atlases allow pathological changes to be tracked over time

to resolve further disease-specific features. Rather than simply fusing information from multiple subjects and sources, strategies that resolve group-specific features that are not apparent in individual scans were described.

DIFFUSION TENSOR MRI—WHAT CAN IT TELL US ABOUT WHITE MATTER IN ALCOHOLISM? PRESENTED BY DEREK JONES, PHD

Whereas postmortem studies of alcoholism report degeneration of brain white matter microstructure including demyelination and axonal deletion (Krill et al., 1997; Krill and Harper, 1989), *in vivo* MRI studies have shown white matter volume reductions at a macrostructural level (Estroff et al., 1997; Hommer et al., 2001; Pfefferbaum et al., 1992, 1997; Sullivan et al., 1996). The development of magnetic resonance DTI provides a unique noninvasive tool for the *in vivo* quantification of the directionality and coherence of white matter fiber tracts and might also be able to provide useful information on the connectivity between different cortical regions. Dr. Derek Jones presented a didactic on the technical background of DTI, as well as a description of data from the two published studies (Pfefferbaum and Sullivan, 2002; Pfefferbaum et al., 2000) using DTI to assess white matter microstructure in chronic alcoholism.

DTI is based on the underlying phenomenon of Brownian motion of water molecules. The mobility or diffusion of water molecules is affected by several factors such as molecular weight, viscosity, and temperature, but also by the properties of the medium in which diffusion occurs (Beaulieu, 2002). In unconstrained medium, such as cerebrospinal fluid, where movement of water molecules is random and equal in all directions, diffusion is called “isotropic.” However, if movement is hindered or restricted by physical boundaries with a predominant orientation on the length scale of the observation, then diffusion of water molecules is called “anisotropic.” Within white matter, the mobility of water molecules is hindered, and the axonal membrane is generally considered to be the major barrier to diffusion, although this is modulated by myelin (Thomsen et al., 1987). Water diffusion is greater along the length of the axons than perpendicular to the axons, where diffusion would be hindered by microstructural boundaries, *i.e.*, myelin, axonal membrane, and neurofibrils (Le Bihan, 1991; Moseley et al., 1991). The degree of hindered diffusion, or anisotropy, within a voxel can be expressed using several scalar indices, but the most popular is the fractional anisotropy (FA) (Pierpaoli and Basser, 1996). FA is independent of the orientation of the diffusion in the voxel but reflects rather the deviation from isotropic diffusion.

In the first published study, Pfefferbaum et al. (2000) showed disruption of white matter microstructure in detoxified alcoholic men ($n = 15$) compared with nonalcoholic age-matched control men ($n = 19$). The alcoholic group had lower FA than the control group in the corpus callosum

and the centrum semiovale. Intervoxel fiber coherence (C), a measure of orientational coherence of white matter on a larger scale, was also calculated and revealed that C was also lower in the alcoholic group but only in the splenium of the corpus callosum. In contrast, in the second published study (Pfefferbaum and Sullivan, 2002), detoxified alcoholic women ($n = 12$) had lower FA and C in the genu of the corpus callosum and the centrum semiovale relative to nonalcoholic age-matched control women ($n = 18$). It should be highlighted that anisotropy measurements provided evidence of white matter abnormalities in alcoholic women that could not be detected at the macrostructural volumetric level with conventional structural MRI.

By comparing DTI measurements of alcoholic women with those from the first study on alcoholic men, it seemed that alcoholic women and men had similar FA deficits in the genu of the corpus callosum and the centrum semiovale compared with control subjects. Correlations of performance on attention and memory tests with DTI measures have also been examined in alcoholic men (Pfefferbaum et al., 2000). Positive correlations of working memory performance with splenium FA and of attention performance with genu FA were reported, suggesting that disruption of white matter fiber coherence may contribute to deficits in attention and working memory in alcoholism.

MRI VOLUMETRIC STUDIES IN ALCOHOLISM AND PSYCHOPATHOLOGY: A FOCUS TO THE MEDIAL TEMPORAL LOBE STRUCTURES, PRESENTED BY HANNU ARONEN, PHD

Hippocampal-dependent cognitive impairments, such as anterograde learning deficits, as well as hippocampal volume reduction have been shown in chronic alcoholics (Agartz et al., 1999; Sullivan et al., 1995). However, variation in the degree of hippocampal volume deficits in distinct subtypes of alcoholism has received relatively little attention in the literature. One subtype dichotomy that has generated much interest in the alcoholism field is the type 1 versus type 2 distinction (Cloninger, 1987). Type 1 alcoholism is characterized by a late onset, relatively preserved social and occupational functioning, intact impulse control, anxiety-prone personality, and typical drinking patterns consisting of alternating periods of binges and abstinence. In contrast, type 2 alcoholism is characterized by an early onset, impulsivity, and euphoria-seeking personality and is often associated with criminal, antisocial, and/or violent behavior. Dr. Hannu J. Aronen reported results from two structural MRI studies of hippocampal volume in type 2 alcoholism (Laakso et al., 2001, 2000).

In the first study (Laakso et al., 2000), Dr. Aronen and his team measured hippocampal volume in 17 late-onset type 1 alcoholics and 19 early-onset type 2 alcoholics as defined by Cloninger (1987), as well as 34 healthy control subjects. Subjects with type 2 alcoholism also presented antisocial personality disorder and were violent offenders

recruited from forensic psychiatric evaluations. Hippocampal volumes were manually traced from contiguous coronal 2.0-mm-thick images oriented perpendicular to the intercommisural line and included the dentate gyrus, the hippocampus proper, and the subicular complex. The intracranial area obtained from a coronal section at the level of the anterior commissure was used to normalize the data. Both alcoholic subtypes had smaller right hippocampal volume compared with controls. Whereas hippocampal volume was not correlated with age in the control group, there was a positive correlation between the right hippocampal volume and age in type 2 alcoholics. Type 1 alcoholics had a tendency toward decreased volumes with aging and with duration of alcoholism. One hypothesis in connection with this surprising finding may be that these type 2 alcoholics also had severe psychopathic behavior and therefore may have differed in their genetic and/or developmental backgrounds.

This hypothesis was examined by Dr. Aronen and his colleagues in a more detailed analysis (Laakso et al., 2001) of the hippocampus in the same type 2 alcoholics originally described by Laakso et al. (2000). The total as well as the regional volumes along the anteroposterior axis of the hippocampus were correlated with the subjects' degree of psychopathy as evaluated by the Psychopathy Checklist-Revised (Hare, 1991). The Psychopathy Checklist-Revised is a 20-item measure of clinical psychopathy, based on biological trait theories and behavioral psychology, that assesses interpersonal, affective, and behavioral features of the disorder. Sagittal profiles of the hippocampi were created to evaluate the distribution of volume loss along its longitudinal axis. Each profile was formed from each measured slice, displayed on the *y* axis, and the length (number of slices) on the *x* axis. Because of slightly different numbers of slices between individuals, the volumes were transformed into standard space for purposes of statistical analysis. Strong negative correlations were found in type 2 alcoholics between the psychopathy scores and the posterior half of the hippocampus. In accordance with the functional organization of the hippocampus (Gabrieli et al., 1997) and the role of dorsal hippocampus in the acquisition of fear conditioning (Maren et al., 1998; Phillips and LeDoux, 1992), Dr. Aronen concluded that the results of these studies give further support to the idea that a deficit in the acquisition of conditioned fear might be a central feature in the etiology of psychopathy. He also suggested that type 2 characteristics might represent a primary antisocial personality disorder rather than primary alcoholism.

BRAIN GROWTH AND SHRINKAGE IN ALCOHOLISM, PRESENTED BY DANIEL HOMMER, MD

Postmortem and *in vivo* quantitative volumetric MRI studies have found significantly smaller volumes of gray and white matter in alcoholics compared with nonalcoholics (Courville, 1995; Harper and Kril, 1990; Harper et al., 1990; Hommer et al., 2001; Jernigan et al., 1991a; Pfeffer-

baum et al., 1992, 1997; Sullivan et al., 1998). The extent to which these brain volume deficits in alcoholics are due to alterations in brain growth before or brain shrinkage after the onset of alcoholic drinking was addressed by Dr. Daniel Hommer in a presentation of MRI data from a sample of 252 alcoholics (76 women) and 118 healthy nonalcoholics (59 women).

Brain size during adulthood is a function of two processes: brain growth and brain shrinkage. Maximum brain growth is achieved in early adolescence and is reflected by the intracranial volume (ICV), estimated by outlining the inner table of the skull. Dr. Hommer reviewed evidence indicating that alcoholics have smaller ICVs than healthy control subjects, suggesting that less brain growth could be a risk factor for alcoholism. The smaller ICV among alcoholics was not due to maternal or paternal alcohol abuse or dependence, comorbid psychiatric disorders, tobacco use, or education level.

Brain shrinkage due to normal aging begins in the third decade of life and continues throughout the lifespan (Coffey et al., 1998, 1992; Courchesne et al., 2000; Ge et al., 2002; Jernigan et al., 1990; Matsumae et al., 1996; Pfefferbaum et al., 1994; Raz et al., 1997). Brain shrinkage due to alcoholic drinking begins early in the illness course and is dependent on factors such as age (Pfefferbaum et al., 1992) and sex (Agartz et al., 1999; Hommer et al., 2001, 1996; Pfefferbaum et al., 2001, 1997). The ratio of brain volume to ICV provides a good measure of brain shrinkage from its maximum size. Many previous studies have shown alcoholics to have reduced brain volume compared with healthy control subjects (e.g., Fein et al., 2002; Jernigan et al., 1991a; Pfefferbaum et al., 1992, 1997), with some studies (Hommer et al., 2001) but not others (Pfefferbaum et al., 2001) showing alcoholic women to have a greater reduction in brain volume than alcoholic men.

How brain shrinkage in alcoholism interacts with other illicit drug dependence comorbidity has received relatively little attention in previous research, despite the fact that such comorbidity is common. Dr. Hommer presented data examining ICV and brain shrinkage estimates among alcoholic and nonalcoholic men who differed in comorbid substance dependence. Subjects were between 30 and 50 years of age and had alcohol dependence alone ($n = 51$) or alcohol dependence plus cocaine ($n = 50$) or cannabis dependence ($n = 33$) or were healthy nonalcoholics ($n = 32$). Comorbid drug dependence did not increase the extent of brain shrinkage among alcoholic men. However, cumulative duration of alcohol exposure, as opposed to the cumulative amount of alcohol consumed, was shown to be an important factor in determining brain shrinkage among alcoholics. Indeed, independent of age or illicit drug use, years of heavy drinking predicted brain shrinkage among all three of the alcoholic patient subgroups, whereas estimated lifetime alcohol consumption did not.

Postmortem studies indicate that alcoholism is associated with reductions in neuronal density, neuronal size, and

dendritic processes (Harper and Kril, 1989, 1990; Kril et al., 1997; Kril and Harper, 1989, but see Badsberg-Jensen and Pakkenberg, 1993), consistent with gray matter compromise, but tissue volume reduction has been most evident in white matter (de la Monte, 1988; Harper et al., 1985; Harper et al., 1990; Kril et al., 1997). In vivo MRI studies show that alcoholism is associated with reduced volumes of gray matter (Fein et al., 2002; Hommer et al., 2001; Jernigan et al., 1991a; Pfefferbaum et al., 1992, 1997; Sullivan et al., 1998) and white matter (Hommer et al., 2001; Pfefferbaum et al., 1992; Sullivan et al., 1998). By comparing the ratio of gray to white matter volume, Dr. Hommer's group has shown that both alcoholics and nonalcoholics lose gray matter as they age but that alcoholics lose proportionally more gray matter than white matter. This finding is consistent with earlier reports showing a significant reduction of gray matter but not of white matter among non-treatment-seeking alcoholics in their fourth decade of life (Fein et al., 2002) and in a subgroup of younger (age range 26–44 years) detoxified alcoholics (Pfefferbaum et al., 1997). Dr. Hommer suggested that the difference between his MRI gray:white ratio data and the postmortem studies may be due to differential effects of postmortem fixation on cerebral tissue types, because the MRI tissue segmentation algorithm that he used produced gray:white matter ratios that were virtually identical to those reported in a study that examined fresh, unfixed postmortem human brains (Paul, 1971).

Dr. Hommer then turned to the question of the specificity of volumetric brain deficits to particular brain regions. Previous data have shown shrinkage of the hippocampus in alcoholism (Laakso et al., 2000; Sullivan et al., 1995), but some data suggest that this reduction is proportional to overall brain shrinkage (Agartz et al., 1999). In addition, some studies have suggested that the frontal lobes are more vulnerable to alcoholism than other regions (Pfefferbaum et al., 1997; Sullivan et al., 1998). When covarying for overall cortical volume, Dr. Hommer's group found that the mesial frontal cortex and left dorsolateral prefrontal cortex are selectively affected in alcoholism. The largest amount of cortex loss was found in the outer half of the mesial frontal cortex.

Finally, Dr. Hommer presented data examining the relationship between brain volume and intelligence test scores (IQ). Among alcoholics but not healthy control subjects, greater brain shrinkage was associated with poorer performance IQ scores independent of age. In addition, performance IQ decreased and brain shrinkage increased with age among alcoholics, and both were significantly different from control subjects.

NEUROANATOMICAL EFFECTS OF ALCOHOL
EXPOSURE IN DEVELOPMENT, PRESENTED BY
TERRY JERNIGAN, PHD

One of the most severe effects of prenatal exposure to alcohol is fetal alcohol syndrome (FAS). FAS is a physically

and mentally disabling condition characterized by abnormal facial features, developmental deficiencies, and central nervous system abnormalities (Jones and Smith, 1973; Mattson and Riley, 1998; Roebuck et al., 1998). Severe fetal alcohol exposure and chronic heavy alcohol use during adulthood have been associated with abnormalities in brain structures as well as with neurocognitive deficits. How the regional pattern of abnormalities produced by severe fetal alcohol exposure differs from the one found in the adult brain in chronic alcoholism and to what extent these anatomic abnormalities might mediate neurocognitive impairments were discussed by Dr. Terry Jernigan.

Brain morphological abnormalities have been shown using quantitative volumetric MRI in children and adolescents who were exposed prenatally to alcohol. Cerebral hypoplasia in FAS involves the white and gray matter; the parietal lobe and striatal structures are disproportionately affected (Archibald et al., 2001). In this study, cerebellar hypoplasia was greater than cerebral hypoplasia, white matter hypoplasia was more significant than gray matter hypoplasia, and the hippocampal volume was relatively preserved. Furthermore, a surface-based image analysis procedure was performed in the same group of children and adolescents and revealed regional brain shape abnormalities in the bilateral inferior parietal and perisylvian areas and in the left orbitofrontal cortices (Sowell et al., 2002). The distance from center (DFC), which provides a measure of the radial expansion from the center of the brain, was significantly reduced in these regions, indicating a decreased brain surface extent or reduced brain growth in frontal and inferior/parietal and perisylvian cortices in children and adolescents who were exposed prenatally to alcohol.

In chronic alcoholics, tissue loss has been observed in the cerebellum (Sullivan et al., 2000) and within the gray matter of striatal, diencephalic, and limbic structures (Jernigan et al., 1991a). More modest but widespread cortical gray and white matter losses have been found in the cerebrum. Frontal lobe loss has been shown to be prominent, particularly in older patients (Pfefferbaum et al., 1992, 1997). Alcoholics with Korsakoff syndrome have been shown to exhibit a pattern of tissue loss that includes loss of white matter in the cerebrum and the cerebellum, relatively greater involvement of the temporal lobe, and prominent diencephalic and amygdala losses (Jernigan et al., 1991b).

Vulnerability of cerebellum, disproportionate effects on white matter, and pronounced effects in diencephalic structures and amygdala seem to be consistent effects associated with alcohol exposure. Although there are similarities of alcohol exposure-induced brain abnormalities across the three conditions, i.e., severe fetal alcohol exposure, chronic alcoholism, and alcoholism with Korsakoff syndrome, the extent of cortical involvement, the effects on subcortical nuclei, and the regional effects across the cerebral lobes differ significantly across the three groups. These differ-

ences might be related, in part, to prenatal interactions between alcohol effects and ongoing maturation processes.

On the basis of these data, Dr. Jernigan offered the following conclusions. (1) Given the aberrations observed in FAS, the focus on hippocampal effects in animal studies and the presumption of a hippocampal basis for spatial learning deficits in FAS perhaps should be reconsidered. (2) The unexpected dramatic effects of fetal alcohol exposure on caudate nucleus and on parietal cortex structures warrant further scrutiny. Because increased vulnerability of parietal lobe is not observed in adult populations, the mechanisms underlying this effect may depend on specific developmental cofactors. (3) Although white matter is highly vulnerable to the effects of heavy alcohol exposure, it seems that exposure very early in development and very late in the course of alcoholism may lead to more enduring effects than exposure earlier in adult alcoholism. (4) More research is needed to elucidate the mechanisms by which diencephalic and temporal lobe structures are disproportionately affected in alcoholic Korsakoff patients.

CONCLUSION

These studies overtly demonstrated the utility of morphometric MRI and DTI in assessing the macro- and microstructural brain abnormalities associated with the full clinical spectrum of alcoholism. Structural neuroimaging has produced a variety of observations, including brain shrinkage in chronic alcoholism, the possibility of deficient brain growth in those who are vulnerable to developing alcoholism, regionally specific white and gray matter morphometric abnormalities associated with particular clinical subtypes such as type 2 alcoholism and FAS, and disruption of white matter microstructure. These observations collectively provide significant insights into the neuropathological heterogeneity of alcoholism and highlight its pathophysiological interactions with a host of other variables, including processes of maturation and aging, sex, personality traits, and neurocognitive function. Consideration of these interactions is of paramount importance if we are to understand the complex effects of alcoholism on the brain.

Important new developments in structural neuroimaging are moving the field to an increasingly precise delineation of the locations and nature of brain abnormalities in the alcoholism spectrum. The field is making a transition from volumetric quantification of predefined brain regions of interest to voxel-based morphometric approaches that rely on increasingly sophisticated deformation methods, leading to the development of detailed disease-specific atlases that can incorporate and map a wide range of information about brain integrity derived from multiple neuroimaging and neuropathological techniques, including MR-DTI approaches to characterizing the fine structure of white matter fiber tracts. The power of these new approaches lies not only in the efficiency with which imaging data from large numbers of subjects can be precisely co-registered, increas-

ing the capacity of investigators to conduct large-scale studies, but also in their potential to identify the nature and the location of brain abnormalities in alcoholism with increasingly fine precision. Such precision strengthens the tie of in vivo clinical neuroimaging studies to basic neuroscience research, promotes the development of mechanistic pathophysiological hypotheses, and provides feedback on efforts to develop informative animal models of alcoholism. In addition, increasingly precise neuroanatomic and microstructural information may provide novel neurobiological targets for treatment as well as specific measures for monitoring the ability of such treatments to prevent, arrest, or reverse the deleterious effects of alcoholism on the brain.

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