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Structural and microstructral imaging of the brain in alcohol use disorders

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INTRODUCTION

Apart from direct effects on the brain, excessive alcohol consumption is associated with increased risk for trauma (i.e., traumatic brain injury) (e.g., Alterman and Tarter, 1985; Chen et al., 2012), seizures (Eyer et al., 2011; Martindale et al., 2011), and stroke (de los Rios et al., 2012; Suzuki and Izumi, 2012), each of which can have effects on brain structure independently of alcohol or each other. Further, by affecting peripheral organs (including the alimentary tract (e.g., Bienia et al., 2002; Duell et al., 2012), liver (e.g., Cederbaum, 2012), heart (e.g., Roerecke et al., 2011), pancreas (e.g., Andersen et al., 2008), kidneys (e.g., Schaeffner and Ritz, 2012), and lungs (e.g., Yeligar et al., 2012)), alcohol can alter the brain. Mechanisms of indirect alcohol effects on brain via peripheral changes are likely mediated via soluble factors (e.g., de la Monte et al., 2012). Particularly well described are the effects of alcohol-related thiamine deficiency on the brain (Zahr et al., 2011). Malnutrition, vomiting, and diarrhea are common in chronic alcoholism and can contribute to thiamine deficiency (Morgan, 1982; Fields et al., 1994; Gloria et al., 1997; Ross et al., 2012). In addition, the ability of the gastrointestinal tract to absorb necessary quantities of thiamine is diminished in alcoholics (Hoyumpa, 1980; Thomson, 2000) and the liver, which stores a large part of the body's supplies of thiamine, if diseased, can have a reduced capacity to store thiamine (Levy et al., 2002; Butterworth, 2009). Consequently, the function of essential thiamine requiring enzymes in the brain (e.g., transketolase, pyruvate dehydrogenase, and a-ketoacid dehydrogenase) is compromised, leading to oxidative stress, cellular energy impairment, and eventually neuronal loss (Thomson et al., 2012).

In order to evaluate its central nervous system (CNS) effects, researchers distinguish "uncomplicated alcoholism" from the various clinically diagnosable consequences of chronic alcohol consumption, including Wernicke's encephalopathy (WE: i.e., the disease associated with thiamine deficiency), Korsakoff's syndrome (KS), hepatic encephalopathy (HE), central pontine myelinolysis (CPM), alcoholic cerebellar degeneration (ACD), alcoholic dementia, and Marchiafava–Bignami disease (MBD). The radiologic evaluation of clinically defined syndromes associated with chronic alcoholism, each with relatively unique

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radiologic signatures (Table 17.1 and Fig. 17.1), provides guideposts for the interrogation of the brain in uncomplicated alcoholism. The aim of this chapter, then, is to review current macrostructural findings from magnetic resonance imaging (MRI) studies and microstructural findings from diffusion tensor imaging (DTI) studies of alcohol-related CNS disorders as a framework for findings in uncomplicated alcoholism, while additionally covering results in abstinence and relapse.

STRUCTURAL MAGNETIC RESONANCE IMAGING

Since the early 1980s, conventional structural MRI has made possible the visualization of the living human brain. MRI is possible because the nuclei of certain atoms exhibit nuclear magnetic resonance (NMR). When exposed to a strong magnetic field, nuclei with NMR potential spin at a particular rate (the resonant frequency, determined by the strength of the magnetic field), and align themselves with the field. If nuclei are then presented with radio waves at their resonant frequency, they absorb this energy, and their alignment in the magnetic field is disturbed. When the radio waves are turned off, the relaxation (i.e., free induction decay) of the nuclei as they return to thermodynamic neutrality induces a small current in the receiver coil, an “antenna” used to detect this MR signal. Magnetic field gradients can be used to vary the static magnetic field so that variable precession frequencies become associated with different spatial locations. Hydrogen is the most frequently imaged nucleus in MRI because it is present in great abundance in biologic tissues; detailed images of the brain are possible because the different brain tissue types (i.e., gray matter, white matter, cerebrospinal fluid (CSF)) contain different proportions of water (Rumboldt et al., 2012).

The magnetic resonance image is primarily determined by three variables: proton density, T1, and T2. Proton density reflects the number of hydrogen nuclei stimulated; T1 is an exponential time constant describing the time required for nuclei to realign with the external magnetic field (higher T1 values reflect a longer time required by nuclei to return to equilibrium after perturbation); and T2 is a tissue-specific time constant describing signal loss due to the exchange of energy between hydrogen protons and adjacent nuclei. T1 and T2 tend to reflect the proportion of free to bound water in tissue. The concentration of mobile hydrogen atoms (i.e., water) and therefore proton density, as well as T1 and T2, differs in various biologic tissue types, thereby providing the contrast necessary to visualize details of brain structure. The biologic significance of these variables, however, is not yet fully understood.

MRI, in contrast to computed tomography (CT), offers flexibility in the plane in which the brain is visualized. Because magnetic gradients can be applied in the three (orthogonal) directions to provide information about the spatial location of signals, the brain can be viewed from bottom to top (axial), as in conventional CT images, from front to back (coronal), from left to right (sagittal), or at any oblique angle to these planes. This flexibility also enables greater accuracy in aligning images with internal landmarks, an essential consideration for ensuring consistency of data from replicate images from the same individual (Rohlfing, 2006).

STRUCTURAL MRI FINDINGS IN SYNDROMES ASSOCIATED WITH ALCOHOLISM

The nutritional deficiency for thiamine in chronic alcoholism results in WE; if untreated, WE patients can develop KS, a severe neurologic disorder characterized by anterograde amnesia (Harper, 2006). In acute WE, MRI can detect symmetric, bilateral hyperintense foci, clearly visible on T2-weighted and fluid attenuation inversion recovery (FLAIR) images, in periaqueductal gray matter, mammillary bodies, and tissue surrounding the third ventricle (Lenz et al., 2002; Sullivan and Pfefferbaum, 2009) (Fig. 17.2). Additionally observed hyperintense areas in WE include the dorsal medulla, tectal plates (Ha et al., 2012), olivary bodies, and dorsal pons (Liou et al., 2012). MRI group analysis of KS patients compared with control subjects reveals substantial volume loss of the mammillary bodies in some, but not all, affected alcoholics (but see Victor et al., 1989; Shear et al., 1996; Sheedy et al., 1999; Sullivan et al., 1999b). In contrast to early MR studies suggesting that KS affects the mammillary bodies while sparing the hippocampi (Squire et al., 1990), more recent work demonstrates hippocampal volume deficits in KS (Sullivan and Marsh, 2003). Other regions affected by KS are the thalamus, orbitofrontal cortex (Jernigan et al., 1991a), cerebellum, and pons (Sullivan and Pfefferbaum, 2009).

HE, occurring in acute or chronic liver disease, including acute liver failure and cirrhosis, is believed to arise, at least partially, from elevations in circulating levels of ammonia. HE presents with confusion, disorientation, and poor coordination (Vaquero et al., 2003; Prakash and Mullen, 2010). T1-weighted imaging in HE reveals bilateral, symmetric, high-intensity signals in basal ganglia structures, particularly the globus pallidus and substantia nigra (Naegele et al., 2000; Cordoba et al., 2002) (Fig. 17.3), probably due to manganese deposition and T1 shortening (Butterworth, 2013), while T2-weighted FLAIR shows hyperintense signals along the corticospinal tract and diffuse increases in white-matter signal intensities in the cerebral hemispheres (Rovira et al., 2002, 2008). Of note, although discriminating features of WE and HE have been outlined, these diseases can be difficult to differentially diagnose and distinguish, as they can present with similar clinical features and comparable changes on MRI, especially among alcoholics (Thorarinsson et al., 2011).

CPM, associated with electrolyte disturbances, specifically with aggressive correction of hyponatraemia (Chua et al., 2002), can manifest with clinical features such as pseudobulbar palsy, ataxia, and acute changes in consciousness (Kumar et al., 2006). Classically, CPM was characterized by the presence of a symmetric triangular or “bat-wing” lesion in the pons, as visualized with hypointense T1 and hyperintense T2-weighted images (Kleinschmidt-Demasters et al., 2006) (Fig. 17.4) and reflecting demyelination (Goldman and Horoupian, 1981). Because extrapontine regions (e.g., basal ganglia, thalami, and cerebral gray–white-matter junctions) have also been reported as affected in CPM, the term “osmotic myelinolysis” has been coined (Chua et al., 2002), despite suggestions that pathology in extrapontine regions may not strictly represent demyelination (Kleinschmidt-Demasters et al., 2006; Kumar et al., 2006).

ACD presents most frequently with ataxia, although clinical signs can include nystagmus and dysarthria (Fitzpatrick et al., 2012). Neuroimaging in ACD demonstrates damage

disproportionately apparent in anterior superior portions of the cerebellar vermis (Sullivan et al., 2000c), with postmortem pathology indicating loss of cerebellar Purkinje cells (Feuerlein, 1977).

Alcoholic dementia, or alcohol-related dementia (ARD), a currently preferred term, remains a controversial diagnosis because of confounding syndromes such as WE and HE. Nevertheless, certain clinically distinguishing features of ARD include its presence in socially isolated men at a younger age of onset than other types of dementia (Draper et al., 2011; Ridley et al., 2013), deficits in visuospatial, executive, and mnemonic functions (Schmidt et al., 2005), slower progress compared with other types of dementia (Gupta and Warner, 2008), and partial reversibility (Oslin and Cary, 2003). ARD is considered a frontal dementia (Stewart, 2006); in support of such categorization, forensic evaluation of a sample of alcoholic brains noted a consistent pattern of synapse loss in the superior laminae of the frontal cortex (i.e., Brodmann's area 10), not related to liver disease (Brun and Andersson, 2001).

The pathogenesis of MBD, a disease marked by mildly impaired mental status (e.g., confusion) and sometimes dysarthria (Lee et al., 2011) or ataxia (Arbelaez et al., 2003), is poorly understood but may be related to nutritional deficiencies in addition to chronic alcohol consumption (Kawamura et al., 1985). Although traditionally characterized by demyelination and necrosis of the corpus callosum, a number of reports identify cortical lesions in so-called MBD (Johkura et al., 2005; Khaw and Heinrich, 2006; Ihn et al., 2007; Yoshizaki et al., 2010; Namekawa et al., 2013). Such data, however, represent single case studies and may reflect inaccurate MBD diagnoses.

Given the aforementioned findings in clinically differential and diagnosable alcohol-related syndromes, the question whether similar brain insults also appear in alcoholics who do not manifest the full spectrum of symptoms present in these clinically recognized conditions is posed; that is, what is observed in brains of uncomplicated alcoholics? Quantitative MRI has shown that relatively mild yet significant structural deficits characteristic of alcoholic syndromes can occur in uncomplicated alcoholics.

STRUCTURAL MRI FINDINGS IN UNCOMPLICATED ALCOHOLISM

Although less severe than observed in KS, mild volume deficits in the mammillary bodies (Shear et al., 1996; Sullivan et al., 1999a), hippocampi, and thalami are reported in uncomplicated alcoholics (Sullivan, 2003; De Bellis et al., 2005; Chanraud et al., 2007; Pitel et al., 2012; van Holst et al., 2012). These structures show a graded effect of volume deficits (KS > uncomplicated alcoholism > normal controls; Fig. 17.5). That atrophic changes are not unique to amnesic KS alcoholics implies that mammillary body damage is not a prerequisite for the development of amnesia in alcoholism (Shear et al., 1996). MR findings also show hippocampal volume deficits in alcoholics compared with controls (Sullivan et al., 1995b; Agartz et al., 1999; Laakso et al., 2000; Kurth et al., 2004; Beresford et al., 2006; Wilhelm et al., 2008). Hippocampal volume deficits in alcoholism are influenced by age (Sullivan et al., 1995a), even though age-related decline is difficult to detect in cross-sectional study (Sullivan et al., 2005a; Raz et al., 2010; Pfefferbaum et al., 2013). While

deficits in hippocampal volume are not related to seizure incidence (Sullivan et al., 1996; Bleich et al., 2003), temporal lobe white matter may be sensitive to alcohol withdrawal seizures (Sullivan et al., 1996). Hippocampal volume shrinkage in alcoholism is attributed to loss of white matter and decreased axonal diameter (Harding et al., 1997). Glial cell loss (Korbo, 1999) or reduced incorporation of newly formed neurons to the dentate gyrus (Nixon and Crews, 2004; He et al., 2005), however, could also affect hippocampal volume in alcoholism.

Other regions selectively affected in WE and KS include the orbitofrontal cortices (KS), periaqueductal gray matter, and tissue surrounding the third ventricle (WE). With respect to uncomplicated alcoholics, reports suggest that propensity to relapse following sobriety is related to pronounced atrophy in bilateral orbitofrontal cortices (Cardenas et al., 2011; Durazzo et al., 2011; Beck et al., 2012) and the third ventricle can be further enlarged with resumption of chronic alcohol consumption (Sullivan et al., 2000b; Pfefferbaum et al., 2001). There are currently no studies regarding periaqueductal gray-matter volume in uncomplicated alcoholics. Acute alcohol exposure to mice, however, results in robust enhancement of glutamatergic synaptic transmission and increased firing rate of glutamatergic neurons in ventral periaqueductal gray matter (Li et al., 2013). In rats, anxiety-like behavior following alcohol withdrawal also involves glutamatergic transmission in periaqueductal gray matter (Ezequiel Leite and Nobre, 2012). The key regions affected in HE include the globus pallidus and substantia nigra. Volume effects on these two structures have not been reported in uncomplicated alcoholics, but in children with fetal alcohol syndrome, globus pallidus volume is reduced in size compared with unaffected children (Nardelli et al., 2011). By contrast, other basal ganglia nodes of reward circuitry have been described as affected in uncomplicated alcoholism (Makris et al., 2008; Durazzo et al., 2011): MRI studies have revealed smaller volumes of caudate (Boutte et al., 2012), putamen (Jernigan et al., 1991b), amygdala (Fein et al., 2006), and nucleus accumbens, especially in more recently sober alcoholics compared with controls (Sullivan et al., 2005b). Given the role of the amygdala in emotional regulation and behavioral control (for review, see McBride, 2002), however, there is speculation that premorbid amygdala volume deficits put individuals at heightened risk for developing alcohol use disorders (Kamarajan et al., 2006; Benegal et al., 2007; Clarke et al., 2008).

The pons is targeted by CPM and the cerebellum by ACD. Total infratentorial volume (including pons, cerebellar hemispheres, vermis, fissures, cisterns, and fourth ventricle) is significantly smaller in uncomplicated alcoholics than controls. The volume of the pons (Pfefferbaum et al., 2002b; Sullivan, 2003; Chanraud et al., 2009c) and cerebellum (i.e., hemispheres: Sullivan et al., 2000a, c; De Bellis et al., 2005; Chanraud et al., 2007, 2009a; Boutte et al., 2012) (Fig. 17.6). is smaller in uncomplicated alcoholics than controls. Alcoholism-related volume deficits are also prevalent in gray and white matter (Shear et al., 1996; Sullivan et al., 2003) of the cerebellar vermis (Antunez et al., 1998; Piguet et al., 2006; Sullivan et al., 2006, 2010a), predominantly in anterior superior but not posterior inferior regions (Sullivan et al., 2000c).

The frontal cortex is selectively damaged in ARD. With respect to cortical regions in uncomplicated alcoholism, various methods, including semiautomated procedures for brain

tissue segmentation (Pfefferbaum, 1992), voxel-based morphometry (Jang et al., 2007; Mechtcheriakov et al., 2007), and deformation-based morphometry (Cardenas et al., 2007), report significant widespread shrinkage of both cortical gray and white matter with corresponding increases in CSF-filled spaces (Jernigan et al., 1991b; Pfefferbaum et al., 1992). In particular, older, but not younger, adult alcoholics show disproportionate deficits in both gray- and white-matter cortical volume, especially in the frontal lobes when volumes are statistically adjusted for brain tissue decline associated with normal aging (Pfefferbaum et al., 1997; Cardenas et al., 2005, 2007). This is the case even in comparisons made in groups selected on alcohol consumption, where older alcoholics have drunk equivalent amounts over their lifetime as younger alcoholics.

Thinning of the corpus callosum occurs in uncomplicated alcoholics and is more prominent in the anterior than posterior regions (Pfefferbaum et al., 1996; Estruch et al., 1997) (Fig. 17.7). As with WE and KS, evidence for MBD-like pathology in uncomplicated alcoholism raises the possibility of a continuum of graded brain dysmorphology.

STRUCTURAL MRI FINDINGS IN RECOVERY FROM ALCOHOLISM

Longitudinal MRI investigations show reduction of ventricular dilatation following weeks (Schroth et al., 1988; Zipursky et al., 1989) or months (Shear et al., 1994) of drinking cessation. Reduction of lateral ventricles precedes reduction of third ventricular volume (Pfefferbaum et al., 1995) and may be related to improvement in hematocrit, hemoglobin, and red blood cell counts (Pfefferbaum et al., 2004). Structures showing volume gains with abstinence include the entire cerebral cortex (Liu et al., 2000), temporal, insular, and anterior cingulate cortices (Cardenas et al., 2007), the amygdala (Wrase et al., 2008) (a finding which would argue against a premorbid volume deficit), thalamus (Cardenas et al., 2007), hippocampus (Liu et al., 2000; Wrase et al., 2008), brainstem, and cerebellar cortex (Liu et al., 2000; Cardenas et al., 2007).

Sober alcoholics reveal several associations between brain volume gain as determined by MRI and improvement in neuropsychologic test performance: reduction in the volume of the lateral ventricles is related to improved memory performance (Rosenbloom et al., 2007), third ventricle to improved non-verbal short-term memory performance (Sullivan et al., 2000b), and fourth ventricle to improvement in measures of ataxia (Rosenbloom et al., 2007).

The brain’s capacity to return to “normal” following long-term sobriety is unknown. Short-term (6 weeks) abstinence seems sufficient to observe some brain volume recovery, but does not result in equivalent brain volumes between recovering chronic alcoholics and controls (Mann et al., 2005). Whether recovery is complete is difficult to determine. Aging is a factor since older compared with younger alcoholics exhibit reduced capacity for recovery (Fein et al., 1990; Reed et al., 1992; Rourke and Grant, 1999; Munro et al., 2000); longer periods of abstinence may be required for follow-up investigations; some brain damage, such as neuronal loss (Harper, 2007), may be irreversible, even with extended abstinence; and alcohol-dependent subjects may have premorbid brain volume deficits (Schottenbauer et al., 2007).

Despite evidence for recovery of brain volume with abstinence, the mechanisms accounting for recovery remain unclear. The hypothesis of brain rehydration was not supported by evidence for increased T2, which reflects fluctuation in brain free water levels (Schroth et al., 1988). An alternative explanation, neurogenesis (e.g., Mandyam and Koob, 2012), is not likely to be substantial enough to replace the volume loss observed in chronic alcoholism, nor is it clear that new neurons can migrate from neurogenic zones to distant areas of volume loss (Rakic, 2002). On the other hand, adequate volume recovery may be explained by white-matter regeneration since oligodendrocytes have the capacity to repair myelin and remyelinate neurons (Kipp et al., 2012) and oligodendrocyte progenitor cells have the potential to migrate long distances (Tirotta et al., 2010). Indeed, alcoholics who relapse show decrease of white matter (Pfefferbaum et al., 1995), while continued abstinence is associated with increased white matter (Shear et al., 1994), notably in the corpus callosum and subcortical white matter (Cardenas et al., 2007). DTI, by allowing microstructural examination of white matter, has begun to help answer questions such as whether alcohol predominantly affects white more than gray matter and whether brain volume recovery in abstinence can be accounted for by recovery of white-matter volume.

DIFFUSION TENSOR IMAGING

A number of books and papers provide extensive descriptions of the principles of DTI (Chien et al., 1990; Pierpaoli et al., 1996; Poupon et al., 1999; Le Bihan et al., 2001; Basser and Jones, 2002; Le Bihan, 2003; Gerig et al., 2005; Jones, 2005; Sullivan and Pfefferbaum, 2010). Here, only a brief description of DTI and its metrics is provided. DTI takes advantage of the fact that MR images of the brain are predominantly maps of water protons with contrast created by their immediate environment and their motility. In regions with few or no constraints imposed by physical boundaries, such as CSF in the ventricles, water movement is random and uniform in every direction and is therefore isotropic. In contrast to CSF, the path of a water molecule along a white-matter fiber is constrained by physical boundaries such as the axon sheath causing movement to be greater along the long axis of the fiber than across it. This movement is called anisotropic; diffusion along the long axis of a fiber (axial or longitudinal diffusion) is greater than diffusion across the fiber (radial or transverse diffusion) (Song et al., 2002).

The application of several magnetic gradients during image acquisition allows the detection of microscopic water movement. Freely diffusing particles will move more during image acquisition than those with physical restrictions. To characterize the orientation of the diffusion motion in three-dimensional space, observations are made by applying the diffusion gradients in at least six non-collinear orientations. For each voxel, the amount of diffusion is quantified by calculating the ratio of the signals with and without the diffusion gradients for each of the six or more gradient directions, resulting in at least six different diffusion-weighted images, each comprising signal decrease due to the movement of water protons in the orientation of that particular gradient application.

DTI quantification requires computation of a tensor, which is a mathematic description of a three-dimensional ellipsoid depicting the magnitude and orientation of diffusion in individual voxels. The tensor is associated with three corresponding orientational vectors

(eigenvectors, λ_1, λ_2, λ_3), describing the diffusion ellipsoid by its major axes. The eigenvalue average, or trace, reflects the magnitude of diffusion, referred to as mean diffusivity (MD) or the apparent diffusion coefficient (ADC). The extent to which one eigenvalue, λ_1, dominates the other two, λ_2 and λ_3, determines the degree of anisotropy, that is, the degree of orientational preference within a voxel, typically measured as fractional anisotropy (FA), ranging between 0 and 1 on a normalized scale (Pierpaoli et al., 1996). The largest eigenvalue, λ_1, is the axial (or longitudinal) diffusivity, λ_L, and reflects axonal integrity, whereas λ_2 and λ_3 quantify radial (or transverse) diffusivity, $\lambda_T = (\lambda_2 + \lambda_3)/2$, and reflect myelin integrity (Song et al., 2002; Sun et al., 2006). Thus, disruption of white-matter microstructure detectable with DTI can reflect compromise of myelin, cytoskeletal structure, or axonal density (Basser, 1995; Basser and Pierpaoli, 1996; Spielman et al., 1996).

FA is the most commonly reported DTI metric, varying in magnitude with the characteristics of the tissue microstructure. For example, FA of the ventricular system, which contains mostly CSF, is near 0, whereas FA of the corpus callosum, where fibers are arranged in a regular and parallel fashion, can approach 0.8–0.9. Lower than expected FA (and the typically associated higher MD/ADC) in a region of fully volumed white matter can be an index of compromised white-matter integrity. FA, however, is quite sensitive to tissue inhomogeneity from crossing fibers within a voxel (Pierpaoli et al., 2001) and partial voluming (Pfefferbaum et al., 2003). Thus, if the fully volumed white-matter voxels are in a region where multiple fiber tracts cross in different directions, such as adjacent to the corpus callosum, FA will be lower, not necessarily because of reduced fiber integrity but because no single orientation predominates within a voxel (Virta et al., 1999; Pierpaoli et al., 2001).

Several approaches have been used to quantify DTI metrics, including identification of regions on FA maps or voxel-by-voxel comparison with statistical parametric mapping (http://www.fil.ion.ucl.ac.uk/spm/) of brains normalized to a common space or template. One of the more desirable approaches is the use of quantitative fiber tracking to depict selective commissures (e.g., corpus callosum), projection fibers, and association fibers.

Whole-brain analysis

One of the approaches to DTI quantification is voxel-based analysis of whole-brain DTI data, which is useful for identifying regions that differ with respect to diffusion metrics between groups when researchers do not have an *a priori* hypothesis regarding specific brain region. In voxel-by-voxel analysis, each subject's diffusion images are registered into standard space, and then voxel-wise statistics are carried out to detect regional differences between populations or to find areas that correlate with a covariate of interest. The voxel-based approach is less sensitive than other methods of DTI quantification because spatial normalization processes can be imperfect (see Snook et al., 2007 for a further description of whole-brain DTI quantification methodologies), and a certain amount of residual morphometric differences might remain. A new approach named tract-based spatial statistics (TBSS), however, aims to remove such differences completely by using a "mean FA skeleton" (Smith et al., 2006), representing the center of fibers that is common to all subjects. Then, in the individual images, FA values can be assessed in the "heart" of the fiber

of interest (Douaud et al., 2007). An advantage of TBSS over region of interest (ROI)-based methods is that it provides an automated, observer-independent method of analyzing DTI data. However, TBSS is prone to partial volume effects, is sensitive to crossing fibers in areas of multiple fiber orientation, and is inappropriately named as it is not a depiction of tracts, but a sample-based method, and the “FA skeleton” does not necessarily represent meaningful anatomic tracts.

Region of interest analysis

When a study is focused on a particular brain region, ROI analysis that involves operator-dependent manual outlining or automated parcellation routines is often employed. ROI analysis is time consuming and requires practice to achieve adequate measurement reliability. Inaccurate ROI segmentation can also result in partial voluming of tissue or CSF unintended for inclusion. Another problem is the choice of images on which to draw the ROIs. One study overcame this problem by using a tissue segmentation procedure for distinguishing different brain tissue types in the tensor images and then applying ROIs based on anatomic images to the segmented DTI data (Pfefferbaum et al., 2000a). Overall, while manual ROI placement has its own challenges, it can provide complementary information and convergent validity to whole-brain analysis and furthermore allows relevant correlational analyses with cognitive measures.

Quantitative fiber tracking and tractography

The degree to which the diffusion orientation of a voxel is similar to its neighbors, that is, shows orientational coherence between voxels (Jones et al., 1999; Pfefferbaum et al., 2000b), serves the conceptual basis for quantitative fiber tracking (e.g., Fillard and Gerig, 2003; Gerig et al., 2005; Mori et al., 2005; Le Bihan, 2007) and provides exquisite visual modeling of fiber systems. Analogous to following the linear trajectory of the longitudinal axis of bricks in a path, intervoxel coherence requires that neighboring eigenvectors do not vary by more than a set criterion and that intravoxel FA reaches a minimum value. An advantage of quantitative fiber tracking over other methods of DTI quantification is its ability to measure the diffusion properties of isolated fiber tracts along their full extent. A number of methods are now available for fiber identification and tracking quantification (e.g., Gerig et al., 2005; Mori et al., 2005; Le Bihan, 2007).

DTI FINDINGS IN SYNDROMES ASSOCIATED WITH ALCOHOLISM

Relatively few DTI studies have been conducted in the syndromes associated with alcoholism. Diffusion-weighted imaging in a 31-year-old alcoholic man with WE revealed high diffusivity specific to tissue in the mammillary bodies that resolved following 2 weeks of thiamine treatment. The authors concluded that the high diffusion was indicative of extracellular edema rather than cellular damage, which would not have resolved at follow-up (Bergui et al., 2001). Another case study indicated that, although diffusion-weighted imaging was useful in visually identifying thalamic signal abnormalities in an alcoholic with WE, diffusivity values were normal (Ducreux et al., 2002). In a final case study of WE resulting from alcohol abuse, diffusivity was low, paralleling the pattern observed in the chronic phase of ischemic stroke (Doherty et al., 2002).

HE due to alcoholism compared to other forms of HE (e.g., as a result of viral infection or primary biliary cirrhosis) appears to have different effects on DTI parameters (Miese et al., 2006). ROI (Kale et al., 2006) and voxel-based (Kumar et al., 2008) analysis in alcohol-related cirrhosis with or without HE showed that MD was elevated, while FA was not affected, in corpus callosum, internal capsule, and frontal white matter; the ROI-based study found only MD effects, while the voxel-based study found effects on both FA and MD of occipital white matter. These findings suggest an increase in the interstitial brain water in alcoholic HE patients compared with controls.

A DTI study of a single case of presumed CPM showed elevated MD in the middle cerebellar peduncles and no effects on the corticospinal tract (Min et al., 2012). FA values of seven segments of the corpus callosum in a single MBD patient compared with a normal control were diminished progressively in an anteroposterior fashion (Sair et al., 2006). Another DTI study of a single case of MBD similarly found that the corpus callosum fibers most affected were closest to the frontal horn of the lateral ventricles, presumably affecting fibers destined for the prefrontal regions of the formal lobe, while fibers to the cingulate region and from anterior corona radiata seem to be relatively spared (Pacheco et al., 2012).

DTI FINDINGS IN UNCOMPLICATED ALCOHOLISM

DTI has revealed microstructural damage related to alcoholism in cerebral areas that appear intact in structural MRI analyses (e.g., Pfefferbaum and Sullivan, 2002; Sullivan et al., 2003). Corpus callosum findings in uncomplicated alcoholics are common and, as observed for MBD, show greater anterior than posterior effects (e.g., Schulte et al., 2005; Arnone et al., 2006; Liu et al., 2010; Pitel et al., 2010; Konrad et al., 2012). A study using both voxel-based and ROI approaches in alcoholics found that FA was diminished in right but not left superior longitudinal fasciculus, orbitofrontal white matter, and cingulum bundles (Harris et al., 2008). Quantitative fiber tracking has demonstrated in alcoholics compared with controls greater FA deficits in anterior than in posterior fibers of supratentorial and infratentorial white-matter bundles as well as diminished FA in tracts of the corpus callosum, centrum semiovale (Pfefferbaum et al., 2000b, 2002a; Pfefferbaum and Sullivan, 2005), internal and external capsules, fornix, superior cingulate, longitudinal fasciculi (Pfefferbaum et al., 2009a), corticopontine bundles (Chanraud et al., 2009c), and frontolimbic fibers (Harris et al., 2008).

Alcoholics demonstrate an age–alcoholism interaction in which older alcoholics have higher diffusivity in callosal genu than would be expected based on age (Pfefferbaum et al., 2006) and women appear to have more severe white-matter fiber damage than men, despite having similar lifetime alcohol consumption (Pfefferbaum et al., 2007). Inverse correlations between FA and diffusivity in genu and centrum semiovale suggest that damage of white matter in alcoholism is attributable, at least in part, to the accumulation of intracellular and extracellular fluid in excess of that occurring in aging, and that the differential influence of these fluid compartments can vary across brain regions (Pfefferbaum and Sullivan, 2005). Exercise might attenuate the effects of heavy alcohol consumption on white-matter damage, as suggested by a report evaluating both heavy drinking and aerobic exercise (Karoly et al., 2013).

Regarding DTI–function relationships in alcoholism, FA in right anterior cingulate and left motor areas correlates with executive and psychomotor performance (Konrad et al., 2012) and splenium correlates with working memory (Pfefferbaum et al., 2000b). A double dissociation was found, showing that higher diffusivity in sensorimotor and parietal bundles was associated with poorer balance but not psychomotor speed, whereas higher diffusivity in prefrontal and temporal bundles was associated with slower psychomotor speed but not balance (Pfefferbaum et al., 2010). DTI changes in multiple supratentorial and infratentorial fiber systems in alcoholics correlate with impairment in speeded performance and postural stability (Pfefferbaum et al., 2009b), frontal fibers connecting left and right hemispheres predict performance on a coordinated psychomotor task (Rosenbloom et al., 2008), and number of reconstructed fibers running between the pons and the midbrain is related to cognitive flexibility performance (Chanraud et al., 2009c). Gray-matter diffusivity in hippocampus, which is lower in alcoholics than in controls, is related to episodic memory impairment (Chanraud et al., 2009b).

DTI FINDINGS IN RECOVERY FROM ALCOHOLISM

Similar to structural MRI findings demonstrating pronounced atrophy of orbitofrontal cortices in abstinent alcoholics who were likely to resume drinking (i.e., Cardenas et al., 2011; Durazzo et al., 2011; Beck et al., 2012), DTI identified alcoholic individuals more likely to resume drinking 6 months following initial evaluation based on lower FA and higher diffusivity in frontal white matter at baseline (Sorg et al., 2012). Increases in FA and decreases in diffusivity have been interpreted as evidence for white-matter recovery with abstinence. Substantiation for recovery has been shown in corpus callosum genu and body at 1 year compared with 2 weeks of abstinence (Alhassoon et al., 2012), and in frontal white matter at 1 month compared with 1 week of abstinence, at least in non-smoking, sober alcoholics (Gazdzinski et al., 2010).

CONCLUSION

Despite evidence for damage, alcoholics who maintain sobriety over extended periods show improvements in both brain volume and white matter integrity, potentially reflecting fiber reorganization and myelin restoration, indicative of a neural mechanism explaining recovery and perhaps enhancing chances for sustained sobriety.

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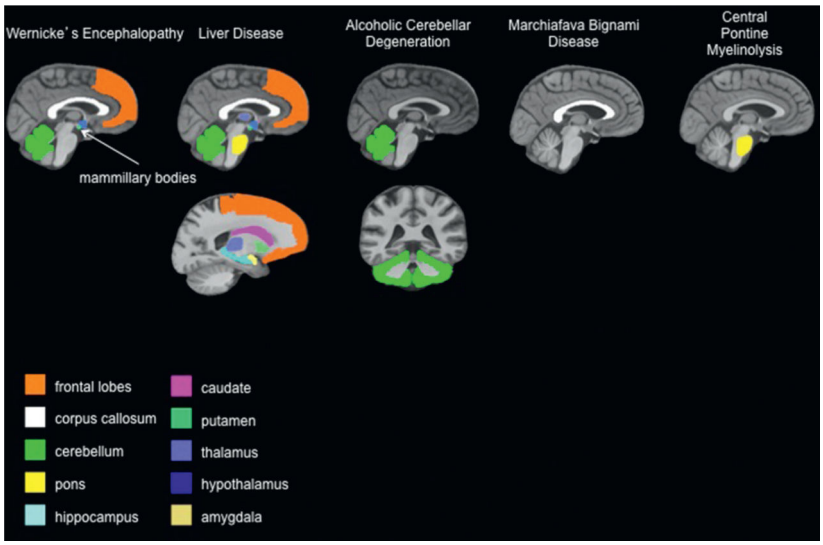

Fig. 17.1.
Brain regions targeted by alcohol-related disease. (Adapted from: Zahr et al., 2011.)

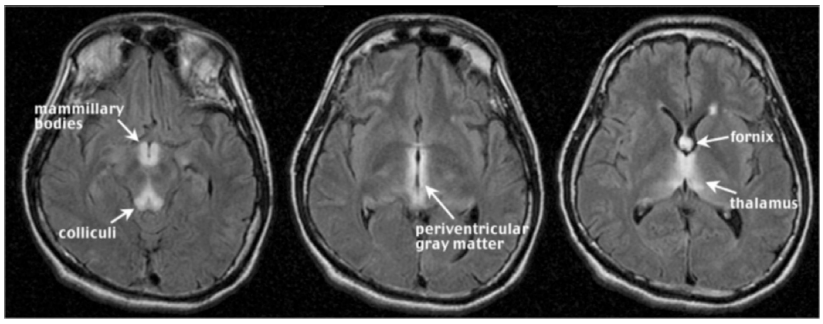

Fig. 17.2.
Wernicke's encephalopathy. (Reproduced from Sullivan and Pfefferbaum, 2009.)

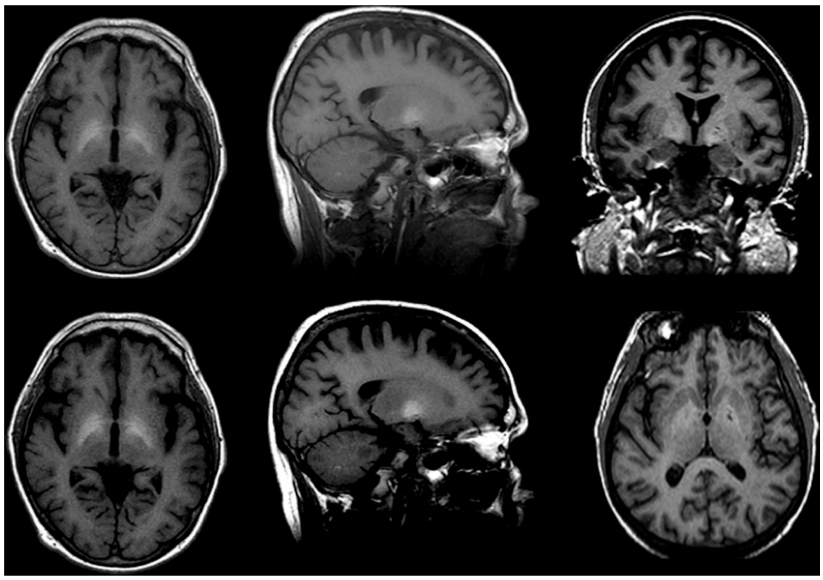

Fig. 17.3.
Hepatic encephalopathy. (Reproduced from Rosenbloom et al., 2010.)

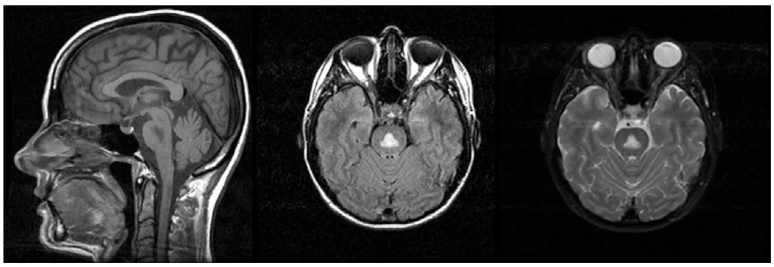

Fig. 17.4.
Central pontine myelinolysis.

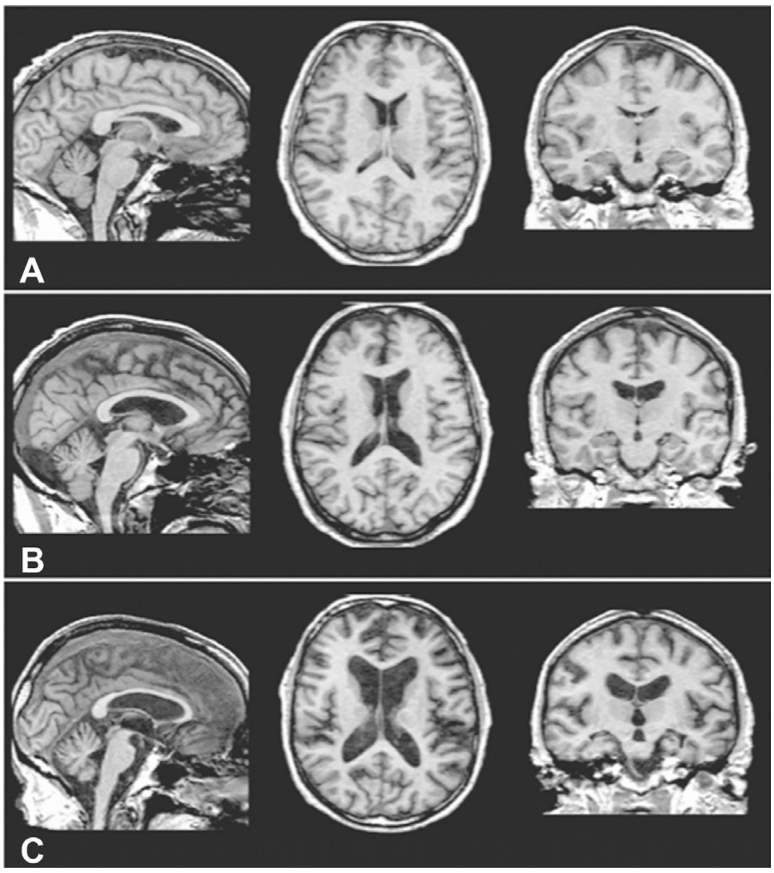

Fig. 17.5.
Brain volume deficits in Korsakoff's syndrome compared with uncomplicated alcoholism. (Reproduced from Zahr et al., 2011.)

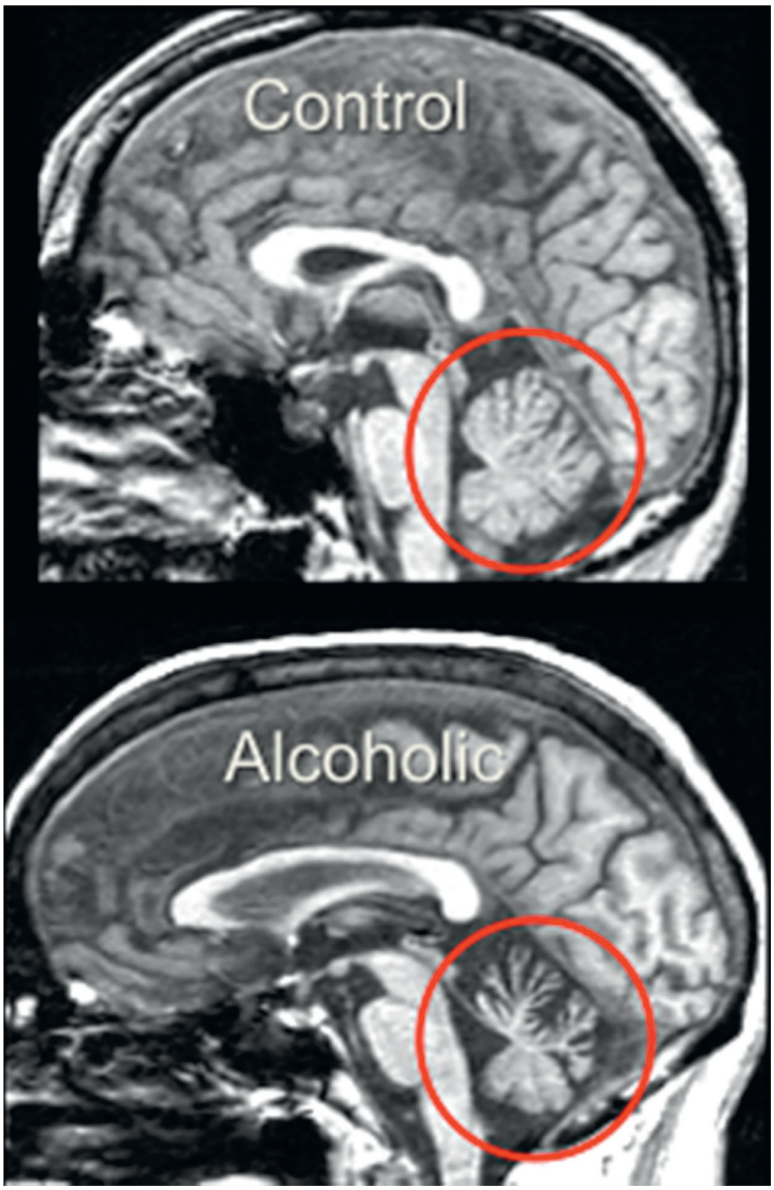

Fig. 17.6.
Cerebellar volume deficits in uncomplicated alcoholism. (Reproduced from Sullivan et al., 2010b.)

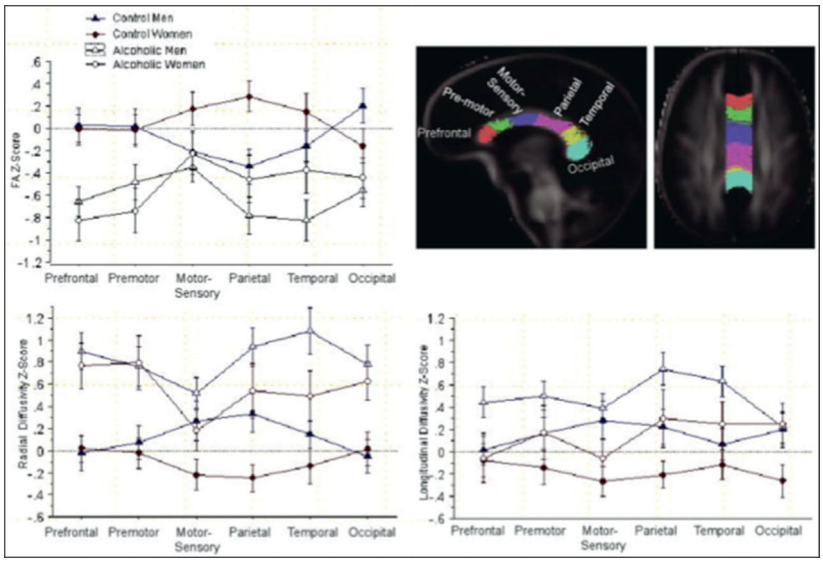

Fig. 17.7.

Corpus callosum microstructural compromise in uncomplicated alcoholism. (Reproduced from Pfefferbaum et al., 2010.)

Table 17.1

Primary and secondary brain regions that are targets of alcohol-related syndromes

Alcoholism-related syndrome	Abbreviation	Primary targeted region(s)	Secondary targeted regions
Wernicke's encephalopathy	WE	Mammillary bodies, periaqueductal gray matter, tissue surrounding third ventricle	Dorsal medulla, tectal plates, olivary bodies, pons
Korsakoff's syndrome	KS	Mammillary bodies, hippocampus, thalamus, orbitofrontal cortices	Cerebellum, pons
Hepatic encephalopathy	HE	Globus pallidus, substantia nigra	Corticospinal tract, cortex
Central pontine myelinolysis	CPM	Pons	Basal ganglia, thalamus, cerebral gray–white-matter junctions
Alcoholic cerebellar degeneration	ACD	Cerebellum	
Alcohol-related dementia	ARD	Frontal cortex	
Marchiafava–Bignami disease	MBD	Corpus callosum	Cortex

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