Alcohol's Effects on Brain and Behavior

Edith V. Sullivan, Ph.D.; R. Adron Harris, Ph.D.; and Adolf Pfefferbaum, M.D.

Over the past 40 years, rigorous examination of brain function, structure, and attending factors through multidisciplinary research has helped identify the substrates of alcohol-related damage in the brain. One main area of this research has focused on the neuropsychological sequelae of alcoholism, which has resulted in the description of a pattern of sparing and impairment that provided an essential understanding of the functional deficits as well as of spared capabilities that could be useful in recovery. These studies have elucidated the component processes of memory, problem solving, and cognitive control, as well as visuospatial, and motor processes and their interactions with cognitive control processes. Another large area of research has focused on observable brain pathology, using increasingly sophisticated imaging technologies—progressing from pneumoencephalography to computed tomography, magnetic resonance imaging (MRI), diffusion tensor imaging, and functional MRI—that have enabled ever more detailed insight into brain structure and function. These advancements also have allowed analysis of the course of brain structural changes through periods of drinking, abstinence, and relapse. *KEY WORDS: Alcohol dependence; alcohol use disorders; alcoholism; alcohol and other drug effects and consequences; brain; brain function; brain structure; brain imaging; neuroimaging; neuroscience; cognition; cognitive process; magnetic resonance imaging*

Lingering and accruing untoward consequences of alcohol use disorders (also referred to as chronic alcoholism and alcohol dependence and abuse) on cognitive and motor functions, recognized for centuries, commonly have been attributed to generalized toxic effects of alcohol on the brain. (For more information, see the sidebar "History of Neurobiological Studies in Alcohol Research.") This depiction has the patina of a complete understanding of alcohol-induced problems but actually has required rigorous examination of brain function, structure, and attending factors through multidisciplinary experimentation to determine the substrates of alcohol-related damage to the brain. Advancement of this knowledge has been underwritten by 40 years of intramural and extramural funding by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Achievement of a mechanistic understanding of this complex behavioral and medical condition has required numerous innovations on many levels of neuroscience investigation. These have included the development of quantitative neuroimaging approaches for safe, in vivo interrogation of brain structure, tissue quality, and neurochemistry, as well as of assessment tools for characterizing the patterns of sparing and impairment of the constellation of functions and their component processes affected by alcoholism. This brief history recounts the state of knowledge in the early days of alcoholism research and highlights progress achieved in the application and development of neuroscience methods directed toward an empirical and mechanistic understanding of the effects of the "alcohol dependence syndrome" on human brain and behavior. The focus of this review is on human studies of brain structure and function, and the imaging approaches are limited to structural and magnetic resonance (MR)[1]-based functional methods.

Neuropsychological Sequelae of Alcoholism

Cognitive psychology in the early 1970s was ripe with newly evolving theories about the complexities of cognition, and scientists had developed

[1] For a definition of this and other technical terms, see the Glossary, pp. 161–164..

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History of Neurobiological Studies in Alcohol Research

Looking at publications from the early 1970s, one is struck by the lack of research on alcohol's actions on the brain. However, closer consideration shows that there also was a lack of neurobiology research in general; moreover, most of the techniques critical to modern neuroscience were not available in 1970. Behavioral genetics and electrophysiological recording from slices of brain tissue were in their infancy, and other tools (e.g., recombinant receptors, patch-clamp recording, single-channel analysis, microdialysis, gene expression measurement, and recombinant inbred mice) that commonly are used today simply did not exist. What research areas were emerging in the 1970s and how have they contributed to the success of alcohol research over the past 40 years?

The Role of Acetaldehyde

One prescient idea was that the primary breakdown product of alcohol, acetaldehyde, rather than the alcohol itself (i.e., ethanol), may have a key role in brain changes produced by chronic alcohol consumption. The observation that opiates in the poppy plant are produced in a chemical reaction called condensation from dopamine and acetaldehyde led to the hypothesis that excessive alcohol consumption might generate sufficient acetaldehyde in the brain to allow condensation with biogenic amines including dopamine, serotonin, and norepinephrine to produce psychoactive alkaloids such as salsolinol. These ideas first were developed in a series of articles from the laboratory of Virginia Davis, including articles published in *Science* and *Nature* (Davis and Walsh 1970; Yamanaka et al. 1970). The idea that alcohol is only a "pro-drug" and that acetaldehyde is the effective agent has a boomerang quality because it is discarded every few years, only to return later. In fact, evidence continues to accumulate that alcohol consumption can result in brain acetaldehyde levels that may be pharmacologically important (Deng and Deitrich 2008). However, the role of acetaldehyde as a precursor of alkaloid condensation products is less compelling. Lee and colleagues (2010) concluded that alcohol consumption does not result in production of salsolinol; however, initial studies by other researchers have provided some evidence that another alkaloid, tetrahydropapavroline, may be formed in the brain from ethanol and has important pharmacological properties—bringing the discussion full circle to Davis' proposal of 40 years ago.

Alcohol's Actions on Neurotransmitters

Alcohol's actions on synaptic transmission essentially were unknown in 1970 and only have been slowly (and sometimes painfully) established during the past decades. One of the first studies showed that ethanol inhibited the release of the signaling molecule (i.e., neurotransmitter) acetylcholine from the cortex (Phillis and Jhamandas 1970); these studies subsequently were extended to show ethanol-related inhibition of release of other neurotransmitters. One of the mechanisms responsible was an inhibition of voltage-dependent ion channels (Harris and Hood 1980). These studies initiated exploration of ethanol's actions on ion channels, which has become central to the neurobiology of alcohol. One prescient study by Davidoff (1973) found that ethanol enhanced neurotransmission using the neurotransmitter γ-aminobutyric acid (GABA) in the spinal cord. This was ignored until the mid-1980s (e.g., Allan and Harris 1986), but since then, GABA receptors have emerged as a major target of ethanol's actions and continue to be an area of intense research interest (Kumar et al. 2009).

Another receptor now recognized as central to alcohol's actions is the *N*-methyl-D-aspartic acid (NMDA) subtype of glutamate receptors. This receptor forms a channel through the cell membrane that upon activation allows the flow of positively charged ions (e.g., Na^+, K^+, or Ca^{2+} into and out of the cell). Remarkably, the inhibitory action of alcohol on these key receptors was not identified until 1989 (Lovinger et al. 1989). Another type of channel affected by alcohol is known as calcium-activated potassium channels. These channels now are known to be very sensitive to ethanol and important for alcohol's actions in animal models, such as the fruit fly *Drosophila* and round worm *Caenorhabditis,* as well as in the mammalian nervous system (Treistman and Martin 2009). This was first noted by Yamamoto and Harris (1983) using biochemical measurements, but further progress required development of electrophysiological techniques to measure currents from these channels as well as cloning of the cDNAs encoding a family of channels known as big-conductance K^+ (BK) channels. Ethanol's actions on these channels were not defined until the mid 1990s (e.g., Dopico et al. 1996).

The neurotransmitter dopamine now occupies a place of prominence in the neurobiology of alcoholism because acute alcohol exposure activates dopaminergic reward pathways and chronic treatment produces a hypodopaminergic state associated

with dysphoria and, perhaps, relapse (Koob and Volkow 2010). However, dopamine is a relative newcomer to neuropharmacology, and interest in alcohol's actions on dopaminergic systems developed slowly. A pioneering study (Black et al. 1980) noted decreased dopaminergic function during alcohol withdrawal in mice. Only much later (e.g., Samson et al. 1992) was alcohol self-administration linked to release of dopamine in the nucleus accumbens.

Other Research Directions

It also is informative to consider ideas that have not contributed markedly to current science. One research theme of the 1970s was ethanol interactions with membrane lipids. The rationale was that ethanol is such a small nondescript molecule that it is unlikely to have specific binding sites on proteins and is likely to nonspecifically enter the cell membranes and alter the physical properties of the lipids found in these membranes. Indeed, evidence emerged that ethanol could disorder brain membranes and that chronic alcohol treatment resulted in tolerance to this action (Chin and Goldstein 1977). This was an exciting development—a neurochemical action of alcohol that resulted in tolerance! However, rather large concentrations of alcohol were required to produce small changes in membrane structure. Moreover, it was difficult (perhaps impossible) to show a link between the lipid changes and changes in the functions of one or more proteins that could account for altered neuronal excitability. These considerations lead to a paradigm shift and the search for alcohol-responsive sites on brain proteins (Franks and Lieb 1987; Harris et al. 2008). Nevertheless, emerging evidence shows a role for lipids in the regulation of many ion channels, and there still is interest in the possibility that alcohol can alter these lipid–protein interactions and thus alter protein function (Yuan et al. 2008).

Conclusions

In summary, the technology for neurobiological studies was remarkably primitive in 1970, and few laboratories were applying even these limited approaches to understanding neuronal actions of ethanol. However, several prescient ideas emerged quite early, including a role for acetaldehyde and its condensation products in alcohol's action, as well as the identification of GABAergic synapses and ion channels as sensitive targets of alcohol in the brain. ■

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paradigms useful for testing hypotheses about the new theories. These model-driven tests provided the basis for recognizing that 33 to 50 percent of people with alcohol use disorders exhibit detectable cognitive or motor impairments (Arciniegas and Beresford 2001). Many of the early theorists initiated application of test paradigms in acute alcohol consumption (Tamerin et al. 1971; Weingartner and Faillace 1971), blackouts (Goodwin et al. 1969), alcoholism detoxification (Eckardt et al. 1978; Parsons 1983; Ryan and Butters 1983; Ryback 1971; Tarter 1975), and alcoholism complicated by the amnesia marking Korsakoff's syndrome (KS), a result of Wernicke's encephalopathy (WE) (Lishman 1990; Talland 1965; Victor et al. 1971). Application of information processing theories, cognitive models, and paradigms useful in testing selective components of complex functions ultimately provided adequate tools for examination and detection of the mild to severe impairments that alcoholics without KS (i.e., "uncomplicated" alcoholics) sustain. Taken together, this extensive body of literature resulted in the careful description of the pattern of sparing and impairment characteristic of the typical recovering chronic alcoholic, thus providing an essential understanding of the functional deficits suffered in the context of those spared and useful in recovery. On a basic science level, these patterns directed neuroimaging, neuropathology, cell physiology, and neurochemistry efforts in seeking neural substrates of the identified deficits. (For more information on the development of these technologies, see the sidebar "History of Neurobiological Studies in Alcohol Research.")

Component Processes of Memory: Then and Now

Alcoholics with KS were of special value to memory theorists (Butters and Cermak 1980; Oscar-Berman and Ellis 1987; Squire et al. 1993; Warrington and Weiskrantz 1970). Their innovative test paradigms resulted in data contributing substantially to current knowledge about component processes of memory applicable to alcoholism complicated with KS and to milder forms of memory impairment found in uncomplicated alcoholism. These theorists found that memory comprises multiple, dissociable functions supported by different brain regions and systems (Squire and Butters 1992). KS amnesia is characterized by severe and relatively circumscribed deficits in remembering new information (i.e., forming new memories), regardless of type of memoranda material (e.g., words, pictures, odors, touches). The capacity for "remembering" can be tested with paradigms for explicit memory and implicit memory. Paradigms for explicit memory include approaches such as free or cued recall tests (e.g., asking people to repeat elements of a story they heard an hour ago) or recognition tests (e.g., asking people to select from a series of items the ones that were presented on a test). Implicit memory tests assess, for example, improved performance on a motor skill or ability to select a word infrequently used to complete a word stem (e.g., when asked to complete "STR _ _ _," answer "STRAIT" instead of the more commonly used "STREET"). Alcoholic KS patients show notable impairment on tests of explicit memory, especially those requiring open-ended recall without cues, but are relatively spared on verbal (i.e., word stem completion [Verfaellie and Keane 2002]) and nonverbal (i.e., picture completion [Fama et al. 2006]) tests of implicit memory. That cueing can enhance remembering of new explicitly learned information by KS patients suggested that retrieval processes are more affected than encoding or consolidation processes.

On a practical level, this depiction of memory abilities could mean that when provided with adequate aids, patients with KS may be able to enhance their otherwise fragile memory. Combined with evidence that alcoholic KS amnesia can range from mild to profound (Pitel et al. 2008), this possibility suggested that the brain substrate for amnesia could be different from another type of amnesia resistant to memory enhancement cueing (Milner 2005). Such differences support a distinction between behavioral types and neural causes of amnesia and provide further evidence for the nonunitary concept of memory.[2] Moreover, the retrieval deficit foundation of KS led memory theorists to seek nonmnemonic bases for fragile memory performance and in doing so to place KS amnesia in the context of the additional cognitive deficits characteristic of uncomplicated alcoholism.

Problem Solving and Cognitive Control Processes: Then and Now

A striking feature of alcoholics is their continued drinking despite their knowledge of the untoward physiological or psychological consequences of their behavior. This characteristic became one of the diagnostic criteria for alcohol dependence specified in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM–IV) (American Psychiatric Association 1994). It also fits the description of people with lesions of the frontal lobes, who are characterized as "impulsive, inconsiderate, uninhibited, inflexible, or ill-mannered...." (Brewer 1974, p. 41). As a group, alcoholics share this constellation of behaviors characteristic of frontal lobe dysfunction, which also can include impaired judgment, blunted affect, poor insight, distractibility, cognitive rigidity, and reduced motivation.

Originally described clinically, most of these behaviors now have received empirical support through creative behavioral testing and currently through functional imaging studies. A subgroup of these behaviors are considered "executive functions" (Oscar-Berman et al. 2004). These include processes such as working memory (i.e., the ability to keep a number of items in a short-term memory store for evaluation or modification, such as remembering a

[2] The nonunitary concept of memory posits that different types of memory exist (e.g., short term versus long term; episodic versus implicit) that represent either different mnemonic systems or different component processes of a system. Each system and component requires different brain regions for processing, and disruption of local brain regions or systems are the foundation of different types of memory impairment or amnesia.

string of numbers to perform mental arithmetic), problem solving, attentional focus (i.e., the ability to attend to one focus and exclude extraneous information from distracting from focus), and sequencing and temporal ordering (i.e., putting items into a logical order or prioritizing tasks to accomplish throughout the day) (Salmon et al. 1986; Sullivan et al. 1997).

Vulnerability to distraction by irrelevant information (Hada et al. 2000) and engagement in risky behavior (Bjork et al. 2004; Fein et al. 2006) each may contribute to difficulty in establishing and maintaining mental set (that is, a cognitive strategy) when solving a problem (Fabian and Parsons 1983; Tarter and Parsons 1971). Therefore, rather than being hampered by perseverative responding—that is, giving the same response that was correct for a previous question to a new question requiring a different response—alcoholics are more prone to failure in finding a theme when solving a problem (Sullivan et al. 1993).

It may be of little surprise that alcoholics are particularly challenged in reordering their everyday living and work activities considering these deficits in working memory, maintenance of mental set, distractibility, and sequencing. Together, these difficulties could result in "learned helplessness" and dampened motivation to face the challenge of change. Not all alcoholics, however, exhibit impairment in all of these functions, thereby adding to the heterogeneity of the expression of the alcohol dependence syndrome. Recognition of which of these processes are spared and which are impaired in a given patient could provide an empirical basis for targeted behavioral therapy during periods of recovery.

Visuospatial Processes: Then and Now

Early neuropsychological studies of alcoholism often focused on KS and used test batteries (e.g., the Wechsler-Bellevue, Halstead-Reitan, Luria-Nebraska tests) that were quantitative and standardized but not necessarily selective to specific components of cognitive functions. Nonetheless, difficulties in performing tests of visuospatial ability were commonly identified with the Wechsler tests of intelligence (Victor et al. 1989). These tests were found to be reliably sensitive to alcoholism-related dysfunction, including the block design test, in which patients are timed while copying two-dimensional designs using three-dimensional blocks, and the object assembly test, in which patients are timed while constructing a common object from puzzle pieces (Parsons and Nixon 1993). Longitudinal assessment identified enduring impairments in visuospatial perception (e.g., seeing a figure embedded in a complex drawing) (Fama et al. 2004) and construction (e.g., copying a complex line drawing) (Sullivan et al. 1992) in both uncomplicated alcoholics (Beatty et al. 1996; Brandt et al. 1983) and alcoholics with KS (Victor et al. 1989).

Recognizing the complexity of visuospatial processing, later studies employed new paradigms to parse its components. An example demonstrating the interaction of perceiving complex visual information and the ability to focus attention without distraction comes from the global–local test. This test requires subjects to attend and respond to either a large letter or tiny letters presented in the form of the large letter. A large letter is a considered a global stimulus, which usually is processed by the right cerebral hemisphere; conversely, a tiny letter is considered a local stimulus, which usually is processed by the left cerebral hemisphere. When the large (global stimulus) and tiny (local stimulus) letters both contain target letters, responses are fast. However, when global and local information are contradictory, alcoholics find it difficult to disengage from one level of processing to the other. Moreover, the degree of difficulty in disengaging correlates with the integrity of the corpus callosum, the brain structure that connects the two cerebral hemispheres and enables transfer and integration of information (like global and local features) between the hemispheres (Müller-Oehring et al. 2009). Such disruption of information sharing between the hemispheres in alcoholics was predicted by experiments predating quantitative brain-imaging methods that provided behavioral evidence for callosal dysfunction long before it was demonstrated with behavior-neuroimaging studies (Oscar-Berman 1992). Similarly, another brain region that had been implicated in visuospatial processing deficits in alcoholics was the parietal lobes, assumed from studies of focal lesions; however, only recently was this association confirmed with MRI and visuospatial testing in alcoholics (Fein et al. 2009).

Motor Systems, Speed of Movement, and Interaction with Cognitive Control Processes: Then and Now

Dramatic improvement occurs from acute alcohol intoxication to sobriety in eye–hand coordination, stability in gait and balance, and speeded performance. This clinically obvious improvement may have diminished the recognition of residual impairment in upper- and lower-limb motor control, which alcoholics can sustain even with prolonged sobriety. Thus, relative to cognitive studies, this area may have received short-shrift in formal testing. Nonetheless, a common theme did emerge when formal studies of motor performance were included in neuropsychological assessment—namely, that alcoholics can perform eye-hand–coordinated tasks at normal levels but do so at slower speed (Johnson-Greene et al. 1997; Sullivan et al. 2002). This speed–accuracy trade off may underlie performance deficits noted on timed tests, whether of a cognitive or motor nature.

Caricatures depict "drunkards" as stumbling and uncoordinated, yet these motor signs are, for the most part, quelled with sobriety. More detailed quantitative assessment of gait and balance using walk-a-line testing or force platform technology, however, has revealed an enduring instability in alcoholic men and women even after prolonged abstinence. Thus, even with sobriety,

recovering alcoholics are at a heightened risk of falling. Although the severity of this instability has been found to relate to the condition of the brain (especially the cerebellum, which is a brain structural substrate of gait and balance), alcoholics often are able to overcome this impairment by use of simple aids from vision, touch, and broad-based stance (Sullivan et al. 2006) (see figure 1).

Brain Pathology

Postmortem Studies: Then and Now

Both postmortem and in vivo studies of the brains of alcoholics have contributed to understanding the permanent central nervous system damage inflicted by chronic alcoholism. Evolving methods have enabled study of brain tissue at different levels of analysis. Initial studies focusing on larger structures (i.e., gross morphology) revealed shrinkage of total brain size, with disproportionately greater volume deficits in frontal superior cortex in uncomplicated alcoholics (Courville 1955; Kril et al. 1997). Cases with medical comorbidities common to chronic alcoholism exhibited additional focal pathology. For example, alcoholics with WE, which is caused by severe deficiency of thiamine (vitamin B1) associated with poor eating habits of some chronic alcoholics, typically showed shrinkage of the mammillary bodies,[3] thalamus, and cerebellar vermis. Cases with Marchiafava-Bignami disease showed thinning or lesions of the corpus callosum; with central pontine myelinolysis show degradation of myelin sheathing of the white matter in the central pons, and alcoholic cerebellar degeneration is marked by shrinkage of the cerebellar hemispheres and vermis (Victor et al. 1989).

Because of the high prevalence of WE pathology seen in autopsy cases in Australia (Harper et al. 1995)—upwards of 80 percent of WE cases had been overlooked in clinical neuropathology examination and about 90 percent of them were associated with alcoholism—Harper et al. campaigned to have bread and rice products enriched with thiamine (for a personal recounting by Dr. Harper, go to http://www.rsoa.org/profileharper.htm). Later neuropathological studies reported a significant decrease of WE lesions detectable postmortem (Harper 2006). Regardless of whether the improved condition of the brains of chronic alcoholics was solely attributable to thiamine-enriched food, this public health precaution may well have saved lives and reduced the debilitating effects of WE, whether related to alcoholism or other causes of thiamine deficiency.

An outcome of this series of pathological studies was the development of the New South Wales Tissue Resource Centre (Sheedy et al. 2008) at the University of Sydney, Australia, funded in part by the NIAAA. More than 2,000 cases of alcoholism and other neuropsychiatric conditions and controls are being obtained prospectively, with extensive antemortem characterization. Postmortem brains undergo standardized preservation procedures, enabling studies, for example, of neurochemical and genetic markers of alcoholism, by researchers throughout the world.

[3] Shrinkage of the mammillary bodies is observed only after chronic alcohol consumption, whereas swelling can be observed with acute consumption (Sheedy et al. 1999).

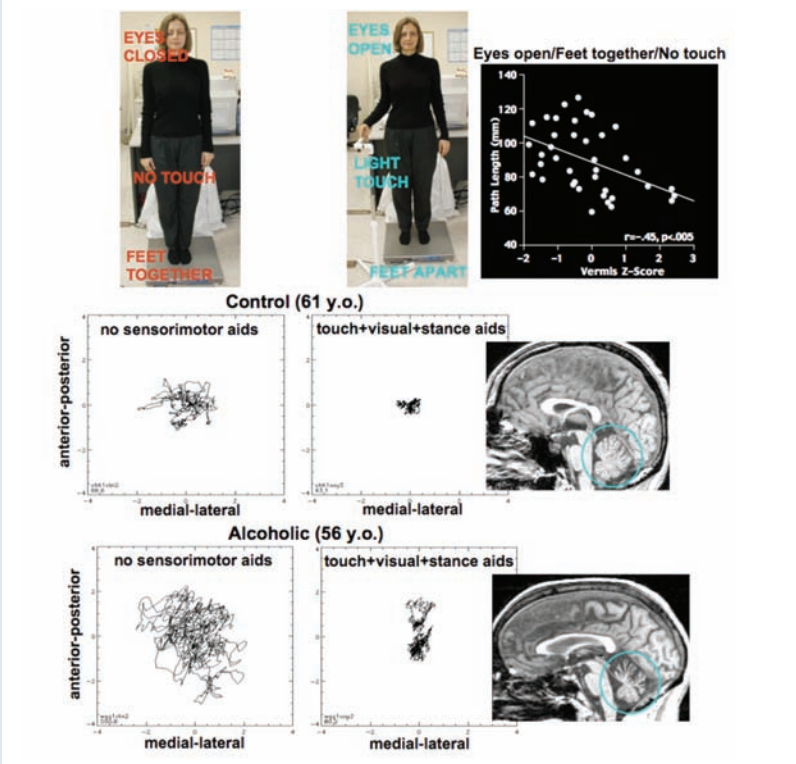

Figure 1 Relationship between alcoholism, balance with and without use of stabilizing aids, and the cerebellar vermis. Balance testing is conducted using a force platform, which detects sway as people attempt to stand still. Study participants try to maintain quiet balance for 30 seconds under different experimental conditions. When no stabilizing aids can be used, the sway paths are quite long, especially in alcoholics (see stabilograms on the left). With sensory (i.e., vision or light touch) or stance (feet apart) aids, the sway paths are short, even in alcoholics. In alcoholics, longer sway path length correlated with smaller volumes of the anterior vermis of the cerebellum, circled in turquoise on magnetic resonance images (correlation plot).

In Vivo Neuroimaging Studies: Then and Now

Pneumoencephalography. Initial in vivo studies of the brains of alcoholics were conducted using pneumoencephalography (PEG). To obtain images of the brain, the ventricular system was drained of cerebrospinal fluid (CSF), which was then replaced with air, usually resulting in severe headache. The images obtained with PEG were two dimensional only and provided tissue contrast of little use for quantification; however, they did provide initial in vivo evidence for ventricular enlargement in detoxifying alcoholics (see figure 2A) (Brewer and Perrett 1971).

Computed Tomography. With the advent of computed tomography (CT), significant progress was made in indexing the severity of brain shrinkage in terms of enlargement of the ventricles and regional cortical sulci (see figure 2B and C). The expansion of the fluid-filled spaces of the brain was interpreted as a sign of local tissue shrinkage rather than as irreversible tissue loss (i.e., atrophy) (Ron et al. 1982). The distinction between permanent and transient brain tissue damage was made in light of the landmark longitudinal imaging study of Carlen and colleagues (1978), who reported at least partial reversal of ventricular and sulcal enlargement in alcoholics who had remained sober for about 1 month to 2 years compared with an initial CT taken a few weeks after detoxification.

Although imperfect (see Hill and Mikhael 1979), this seminal longitudinal study was an impetus for developing quantitative methods for deriving regional volumes of CSF in alcoholics and for employing adequate control groups to adjust volume measurements for variation attributable to sex differences, normal aging, and measurement error (e.g., resulting from differences in head placement in the scanner). Later controlled studies generated objective evidence for an age–alcoholism interaction, in which older alcoholics had more enlarged ventricles than would be expected for their age (Jernigan et al. 1982; Pfefferbaum et al. 1986, 1988).

MRI. A quantum leap for in vivo image resolution and differentiation of tissue type and quality came with MRI (for a review of methods and findings, see Rosenbloom and Pfefferbaum 2008). Some of the quantitative methods developed for CT also were applicable to MRI (see figure 2D), but additional ones needed to be developed to differentiate gray matter from white matter (Lim and Pfefferbaum 1989). Application of semiautomated segmentation methods to measure volumes of gray matter (which contains cell bodies of neurons) and white matter (which contain the fiber bundles and extension of neurons that connect brain regions) revealed profiles of regional differences between alcoholics and control subjects that were modulated by age. In particular, among adults, older, but not younger, alcoholics showed a disproportionate deficit in both gray matter and white matter cortical volume when the volumes were statistically adjusted for brain tissue declines associated with normal aging in adulthood (Pfefferbaum et al. 1997). This age–alcoholism interaction also was present in other brain structures, including the corpus callosum (Pfefferbaum et al. 1996), hippocampus (Sullivan et al. 1995), and cerebellum (Sullivan et al. 2000*a*). Although it is likely that older alcoholics could have consumed more alcohol in their lifetimes than younger ones, differences in amount drunk over a lifetime was not the only reason for the age–alcohol interaction.

In vivo neuroimaging using conventional MRI has provided convergent validity for the gross white matter structural abnormalities (i.e., dysmorphology) observed postmortem by showing evidence for white matter volume shrinkage with chronic heavy drinking (Estruch et al. 1997; Hommer et al. 1996, 2001; Pfefferbaum et al. 1992, 1996; Symonds et al. 1999). Although postmortem studies have been essential in identifying sources of microstructural abnormalities in alcoholism, the process

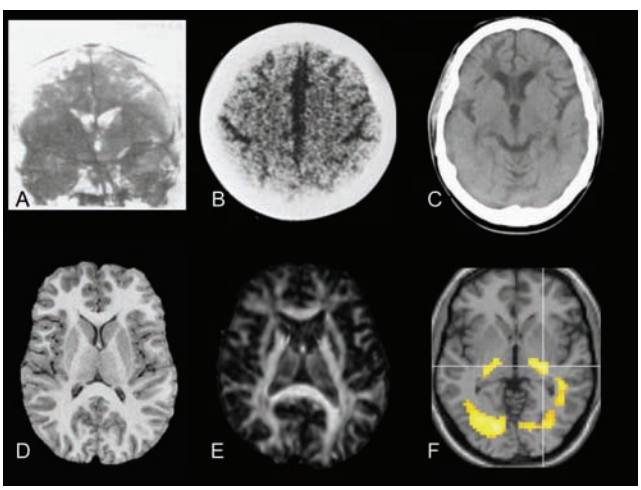

Figure 2 Examples of different neuroimaging modalities. **A)** Pneumoencephalogram—the air in the ventricles shows up white. Adapted from (Brewer 1974). **B)** Early-generation computed tomography (CT)—the cerebrospinal fluid (CSF) in the large sulci shows up black. **C)** Second-generation CT—bone shows up white, brain tissue is gray, CSF is black. **D)** T1-weighted magnetic resonance (MR)—gray matter shows up gray, white matter is white, CSF is black. **E)** Diffusion tensor fractional anisotropy image—white matter tracts show up white. **F)** Regions showing activation on functional MR imaging (fMRI) (yellow) are superimposed on a T1-weighted MRI.

of preparing brain samples for analysis (i.e., fixation) and postmortem collapse of fluid-filled spaces (e.g., ventricles, sulci, and blood vessels) alter brain morphology from the living state; thus, postmortem results do not necessarily reflect all of the alcohol-related effects on the living brain (Pfefferbaum et al. 2004) (see figure 3). Therefore, depiction of the gross anatomy of the living alcoholic brain was a critical initial step for verifying alcoholism-associated untoward effect on brain structure; however, the characterization of the microstructural integrity of the residual white matter volume in vivo required further innovations in neuroimaging.

MR Diffusion Tensor Imaging. The development of MR diffusion tensor imaging (DTI) provided a noninvasive approach for in vivo examination of the microstructure of brain tissue, particularly white matter (for a review of the method, see Rosenbloom and Pfefferbaum 2008). White matter pathology is a consistent finding in the brains of alcohol-dependent people. Postmortem study of alcoholics had identified pathology in white matter constituents and noted demyelination (Lewohl et al. 2000; Tarnowska-Dziduszko et al. 1995), microtubule disruption (Paula-Barbosa and Tavares 1985; Putzke et al. 1998), and axonal deletion. Other studies detected morphological distortion of cell extensions (Harper et al. 1987; Pentney 1991) and volume reduction arising from shrinkage or deletion of cell bodies (Alling and Bostrom 1980; Badsberg-Jensen and Pakkenberg 1993; De la Monte 1988; Harper and Kril 1991, 1993; Lancaster 1993).

DTI permits assessment of water diffusion orientational coherence, measured as anisotropy, by quantifying the magnitude and orientation of water mobility on a voxel-by-voxel basis in a structure of interest. Tissue with high anisotropy is indicative of restricted diffusion that typically is found in a regularly organized region, such as a white matter fiber (see figure 2E). Evidence for microstructural degradation of white matter integrity that evades detection with conventional structural MRI is detectable with DTI. In alcoholics, such disruption of white matter microstructure is especially prominent in frontal brain regions, such as the genu of the corpus callosum. The alcohol-related deficits in white matter anisotropy exceed those observed in normal aging (Pfefferbaum et al. 2000*b*; Sullivan et al. 2001), cannot be accounted for by shrinkage in the underlying tissue mass (Pfefferbaum and Sullivan 2003), and occur in both men (Pfefferbaum et al. 2000*a*) and women (Pfefferbaum and Sullivan 2002). These findings are functionally meaningful because the degree of abnormality detected in certain fiber tracts correlated with compromised performance on tests of attention and working memory (Pfefferbaum et al. 2000*a*), cognitive flexibility (Chanraud et al. 2009), and speeded performance and postural stability (Pfefferbaum et al. 2010). (For more information on ways to establish an association between changes in brain structures and functional alterations, see the sidebar "Double Dissociation.")

One of the most appealing applications of DTI is fiber tracking and the quantification of the exquisite visual modeling of fiber systems (see figure 4). Quantitative fiber tracking has revealed degradation of selective fiber systems in alcoholics that are greater in anterior and superior than posterior and inferior fiber bundles (Pfefferbaum et al. 2009, 2010). Although the pattern of disruption can be different in alcoholic men and women, both sexes are affected (Pfefferbaum et al. 2009).

Analyses of individual components of DTI metrics have provided novel in vivo information about myelin integrity (measured as radial diffusivity) and axonal integrity (measured as axial diffusivity). In general, DTI findings in alcoholism indicate a

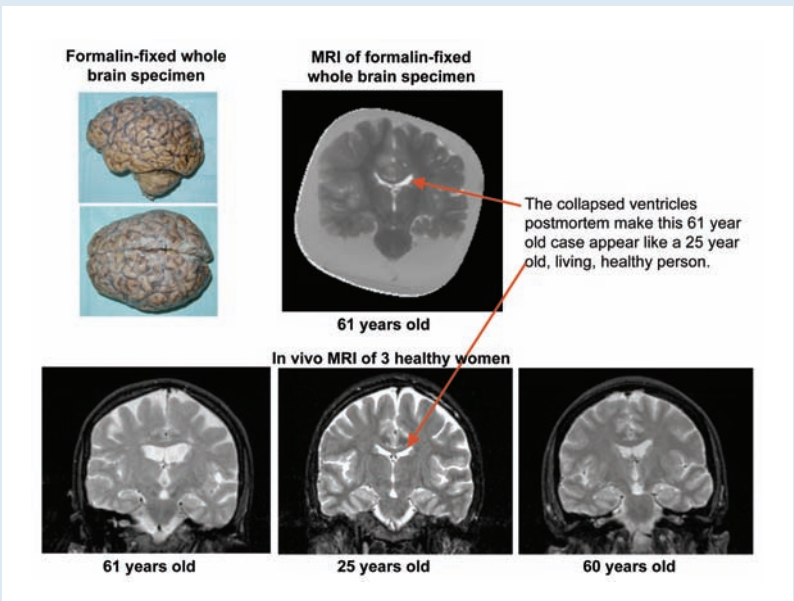

Figure 3 Comparison of magnetic resonance imaging (MRI) data obtained postmortem or in vivo. **Top, left:** Views from the side and the top of a formalin-fixed whole-brain specimen. This brain was then set in a gel-like material (i.e., agar) for MRI studies (middle top figure). All MRIs are coronal sections showing the lateral ventricles, which are seen as bright or light gray. In the living brain, the lateral ventricles expand with age, as is evident when comparing the 25-year-old with the 60- and 61-year-old brains. With postmortem fixation, the ventricles of the brain collapse, making the fixed brain from a 61-year-old case look like the in vivo brain of a 25-year-old control subject.

SOURCE: Adapted from Pfefferbaum et al. 2004.

greater role for demyelination than axonal degeneration in the compromise of white matter integrity. This distinction provides convergent validity with postmortem findings, establishing DTI metrics as in vivo markers of white matter neuropathology.

Functional MRI. Whereas MRI and DTI provide visual and quantitative information about brain structure, functional MRI (fMRI) can detect changes in blood oxygenation that occur when a subject performs cognitive or motor tasks while in the scanner (see figure 2F). In short, fMRI is a safe, noninvasive method that can detect the small but consistent changes in blood oxygenation when a specific brain region is activated (i.e., the blood oxygen level–dependent or BOLD response) (Adalsteinsson et al. 2002). It has enabled detection of how alcoholics and control subjects may differ in the brain systems that are recruited to perform a task. For example, fMRI studies performed in recovering alcoholics have revealed that in test situations in which alcoholics are adequately practiced to perform cognitive tasks on which they usually show impairment, the brain systems activated during task performance differ from those activated by control subjects. A theme emerging from these studies has been that alcoholics can show performance compensation at the price of cortical processing inefficiency. For instance, when engaging spatial working memory and attention, control subjects activate the dorsal neural stream and dorsolateral prefrontal cortex. By contrast, alcoholics activate the ventral neural stream and ventrolateral prefrontal cortex (Pfefferbaum et al. 2001). In a verbal working memory setting, alcoholics recruit more widely spread areas of frontal and cerebellar brain regions than do control subjects to achieve normal levels of performance (Desmond et al. 2003). Finally, in a task requiring resolution of proactive interference (that is, interference resulting from previously encountered information), alcoholics activate a frontally based brain system associated with high-level executive function rather than the basal forebrain system that is activated in control subjects and which is adequate for completing this low-level function (De Rosa et al. 2004).

Degradation of brain structure appears to underlie alcoholism-related alterations in the selection of cognitive strategies to execute a task, and the new neural pathways taken can be identified with fMRI. These analyses found that a change in processing strategy occurs, where alcoholics use inefficient neural systems to complete a task at hand because the preferred neural nodes or connecting fiber tracks are compromised. Such compensatory activation may be crucial for adequately completing a task but curtails available capacity to carry out multiple activities in parallel. Ultimately, structural abnormalities impose a fundamental change in the choice of cognitive operations possible for the alcoholic (see figure 5). In this way, alcohol-induced insult to the brain that limits higher-order cognitive capacity may sustain the propensity to engage in harmful drinking and enable the alcohol dependence syndrome. These compensatory brain mechanisms identified with fMRI are consistent with earlier theories about processing inefficiency based on cognitive testing only (Nixon et al. 1995; Ryback 1971).

Another theme of fMRI studies has been the identification of reward, emotional control, and oversight systems in recovering alcoholics; youth with low versus high risk for developing alcohol use disorders; or in craving paradigms. In discerning emotional information suggested by pictures focusing on facial features, high-risk youth displayed less brain activation compared with low-risk youth, suggesting a predisposition for attenuated ability to interpret facial emotion (Hill et al. 2007). Craving paradigms use alcohol beverage stimuli (e.g., a chilled glass of foaming beer) to examine differences between alcoholics and control subjects in brain activation in response to alcohol-relevant stimuli (Myrick et al. 2004; Tapert et al. 2003). These studies have resulted in the identification of alcohol reward brain systems (Makris et al. 2008) (see figure 6). Brain regions commonly invoked in rewarding conditions are the nucleus accumbens and ventral tegmental area. As a point of translation, these brain regions identified in humans also are implicated in animal models of

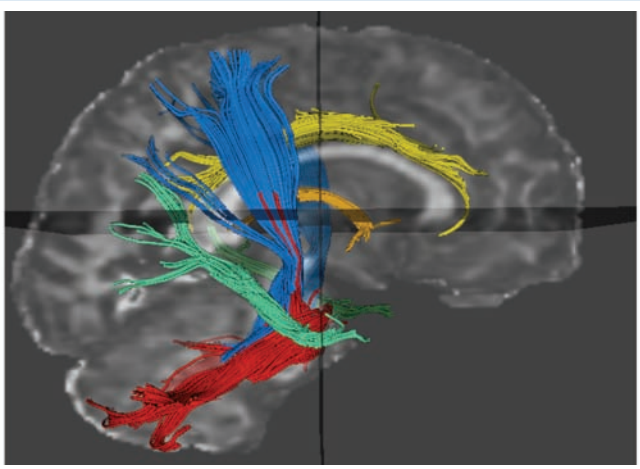

Figure 4 An example of fiber tracking. Midsagittal view of a diffusion tensor image (DTI) of fractional anisotropy in gray tones, where brighter intensities in white matter reflect a more highly and linearly organized microstructure. Superimposed are three-dimensional, bilateral depictions of fiber bundles identified with fiber tracking of DTI data: mustard = superior cingulate bundle; green = inferior cingulate bundle; blue = corticospinal tracts; orange = fornix; red = pontocerebellar tracts.

The Double Dissociation Model

One benefit of the development of technologies for quantitative analysis of brain structure and neuropsychological test performance was the introduction of a new way to establish associations and dissociations between brain structures and function using a modified version of the "double dissociation" model (Teuber 1955) (see figure 1). According to the classical double dissociation model, to be able to draw the conclusion that a certain brain structure or network is the neural source of a particular cognitive or motor function, it is essential to demonstrate first an association between the two. This can be done by demonstrating that compromised performance on a test assessing the function (e.g., on the matrix reasoning test, which assesses nonverbal intelligence) occurs with a brain lesion in the hypothesized neural source (e.g., the parietal cortex). Then, the next crucial step is to demonstrate a double dissociation using tests for two different functions (e.g., the matrix reasoning test and a test of spatial working memory) and assessing lesions in two different brain regions (e.g., the parietal cortex and the prefrontal cortex). Double dissociation exists if compromised performance on test 1 (i.e., matrix reasoning) occurs with a brain lesion in site 1 (i.e., parietal cortex) but not site 2 (i.e., prefrontal cortex), whereas compromised performance on test 2 (i.e., spatial working memory test) only occurs with a brain lesion in site 2 (i.e., prefrontal cortex). However, uncomplicated alcoholics normally do not endure discrete and complete structural brain lesions, per se. Therefore, the traditional double dissociation approach would require identification of two subject groups—one group with a brain lesion in one location and another group with a

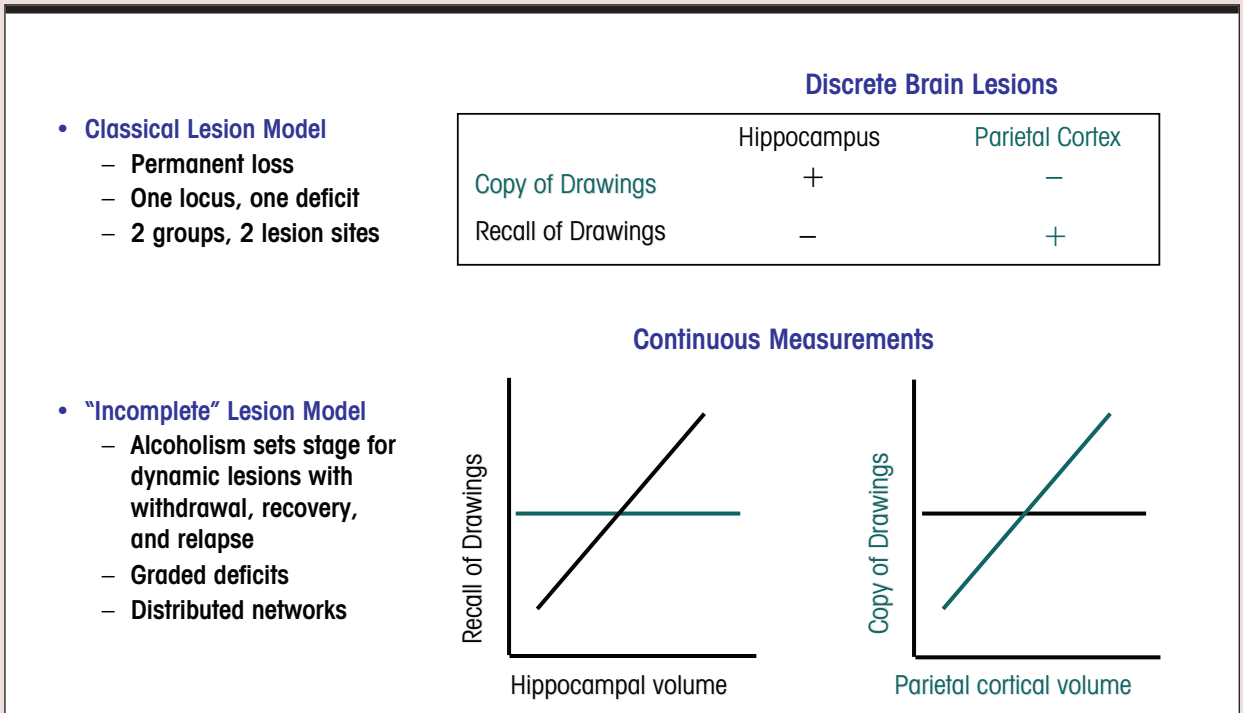

Figure 1 Overview of the double dissociation model. The "classical" approach assesses lesions in a specific brain region that are associated with circumscribed deficits. The incomplete model allows assessment of associations between dynamic lesions (e.g., lesions that may decrease and increase with sobriety and relapse) and deficits in performance that can vary in severity along a continuum.

lesion in a different location—and tests of two functions, one related to the brain lesion in one subject group and the other function related to the brain lesion in the other subject group.

Instead of two separate groups of alcoholics, however, Pefferbaum and colleagues (2006) studied a group of alcoholics who were heterogeneous with respect to both behavior and brain integrity. Some exhibited behavioral deficits on tests of spatial working memory and others on matrix reasoning testing (see figure 2). In addition, some of the alcoholics showed compromise (i.e., abnormally high diffusivity) of the genu and the splenium of the corpus callosum. Correlational analysis indicated a double dissociation: Poor working memory performance correlated with greater diffusivity in the genu but not the splenium, whereas poor matrix reasoning performance correlated with greater diffusivity in the splenium but not the genu.

The development of quantitative measures of brain structure (e.g., regional tissue volume) joined with quantitative measures of cognitive or motor performance enabled quantification of the relationship on a continuum (see figure 1). Establishment of double dissociation indicates that significant variability is present in brain structural and functional measures of alcoholics and provides evidence that the cognitive and motor deficits of alcoholics are not simply the result of generalized brain insult but rather are related to compromise of specific brain systems. ■

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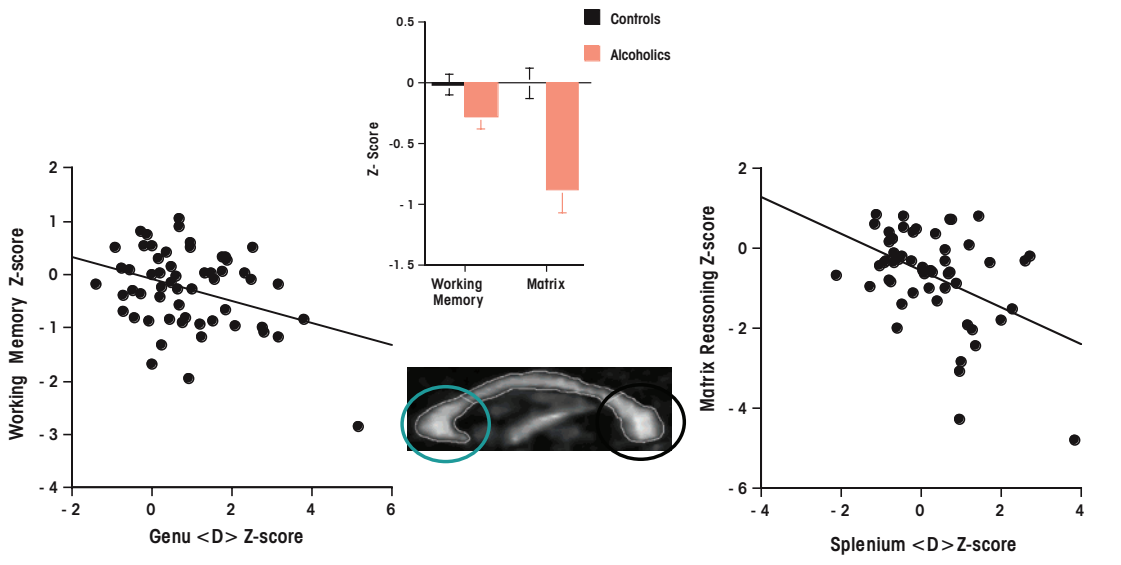

Figure 2 Example of a demonstration of double dissociation establishing the association between lesions in different regions of the corpus callosum and specific cognitive deficits. Thus, deficits in working memory were associated with compromised structure of the frontal end (i.e., genu) of the corpus callosum, whereas deficits in matrix reasoning were associated with compromised structure of the posterior end (i.e., splenium) of the corpus callosum.

alcohol dependence and craving (Koob 2009).

Course of Brain Structural Changes in Alcoholism

Alcoholism follows a dynamic course, with alternating periods of excessive drinking and sobriety. Concomitant with this course, measurable decline and improvement occurs in selective functions of cognitive and motor abilities (Brandt et al. 1983; Parsons 1983). But only with the advent of in vivo longitudinal neuroimaging have researchers been able to document changes in brain structure in parallel with drinking behavior and functional changes (e.g., Rosenbloom et al. 2007; Sullivan et al. 2000*b*). These studies began with the landmark study of Carlen and colleagues (1978), who used CT to show recovery of brain tissue with sobriety.

Longitudinal MRI studies of alcoholics have found that following about 1 month of abstinence from alcohol, cortical gray matter (Pfefferbaum et al. 1995), overall brain tissue (Gazdzinski et al. 2005), and hippocampal tissue (Gazdzinski et al. 2008) increase in volume. With longer-term follow-up, alcoholics who maintain sobriety may show shrinkage of the third ventricular volume (Pfefferbaum et al. 1995) or a general increase in brain volume (Gazdzinski et al. 2005) notable in frontal and temporal regions (Cardenas et al. 2007). Alcoholics who relapse into drinking, in contrast, show expansion of the third ventricle and shrinkage of white matter (Pfefferbaum et al. 1995) or loss of overall brain tissue relative to that seen at study entry (Cardenas et al. 2007; Gazdzinski et al. 2005). Cortical white matter volume may be particularly amenable to recovery with prolonged sobriety (Agartz et al. 2003; Meyerhoff 2005; O'Neill et al. 2001; Shear et al. 1994) or vulnerable to further decline with continued drinking (Pfefferbaum et al. 1995). Over a 5-year longitudinal study, prolonged sobriety was associated with improvement or stabiliza-

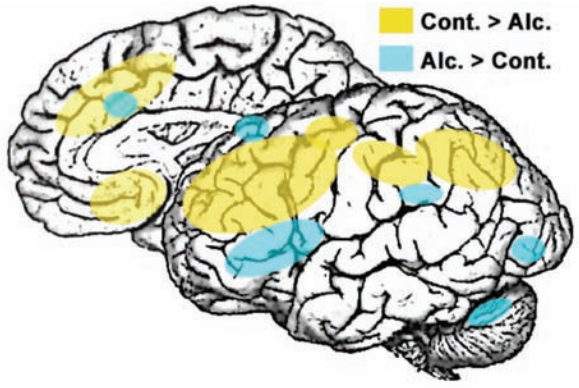

Figure 5 Different patterns of brain activation exist in alcoholics and control subjects. The figure is a composite of images from several functional magnetic resonance imaging (fMRI) studies. Brain regions showing greater activation in controls than alcoholics to accomplish a given task are highlighted in yellow and brain regions showing greater activation in alcoholics than in controls are shown in turquoise. On a functional level, the shift in functional anatomy (as determined by fMRI) combined with incomplete brain lesions (indicated by diffusion tensor imaging) can result in apparently normal performance, but at the price of usurping reserves that reduce processing capacity for conducting multiple tasks simultaneously or efficiently.

SOURCE: Oscar-Berman and Marinkovic 2007.

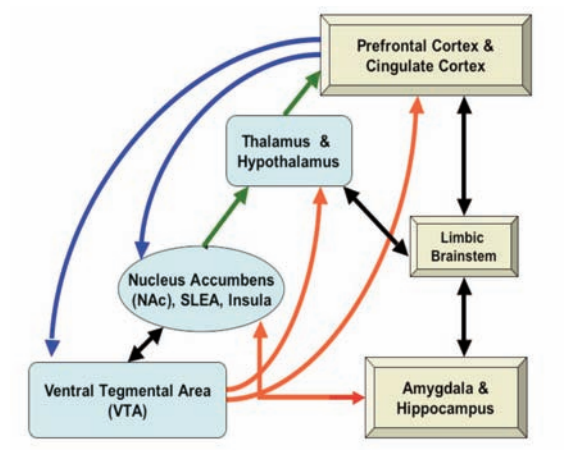

Figure 6 The reward model developed by Oscar-Berman. Using evidence from structural and functional magnetic resonance imaging (MRI), Oscar-Berman and colleagues proposed this model of brain regions involved in what they termed is the extended reward and oversight system. The arrows indicate known directional connections between brain structures of the extended reward and oversight system. SLEA, sublenticular extended amygdala.

SOURCE: Adapted from Makris et al. 2008.

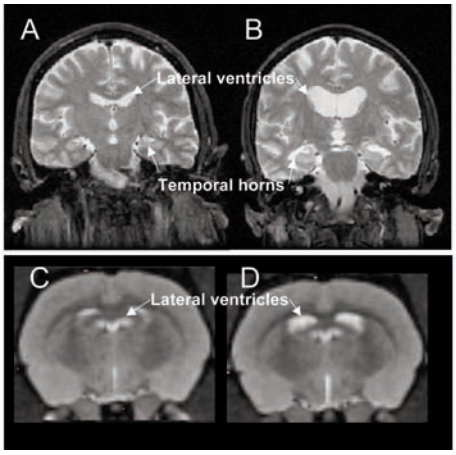

Figure 7 Ventricular size in alcoholic and nonalcoholic humans and in alcohol-exposed and nonexposed rats. **A)** A 61-year-old control man. **B)** A 51-year-old alcoholic man. Note the markedly enlarged lateral ventricles and temporal horns in the alcoholic man. **C)** Wistar rat before alcohol exposure. **D)** Wistar rat after 16 weeks of chronic exposure to alcohol vapor. Note the markedly enlarged lateral ventricles, similar to those seen in the alcoholic man.

SOURCE: A and B were adapted from Rosenbloom and Pefferbaum 2008; C and D were adapted from Pfefferbaum et al. 2008.

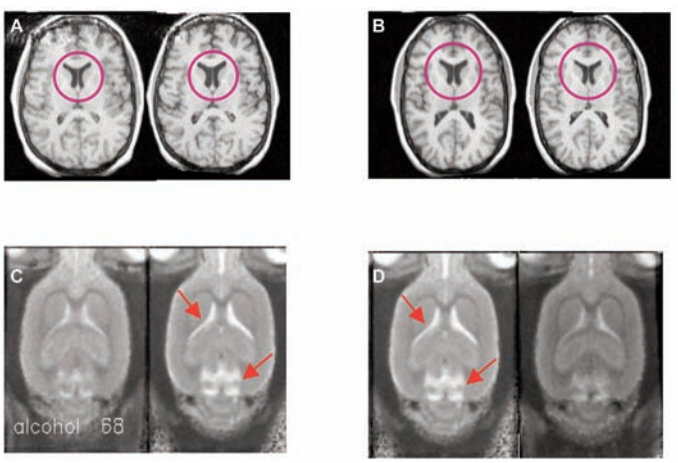

Figure 8 Changes in ventricular size in humans and rats after resumption of drinking or continued sobriety. **A)** A 41-year-old alcoholic woman when sober (left) and 1 year later after resuming drinking (right). Note the ventricular expansion (red circle). **B)** A 48-year-old woman before (left) and after (right) 1 year's continued sobriety. Note the ventricular contraction (red circle). **C)** Wistar rat before (left) and after (right) acute binge alcohol gavage for 4 days. Note the ventricular and pericollicular expansion of cerebrospinal fluid (CSF) (red arrows). **D)** The same animal after 1 week recovery (right), showing return to pre-exposure CSF-filled spaces.

tion of measures of brain tissue volume. By contrast, a return to drinking was associated with ventricular enlargement and cortical gray matter loss, especially in the frontal lobes, and the extent of cortical volume shrinkage correlated with the amount drunk over the 5 years (Pfefferbaum et al. 1998).

Several factors can diminish the likelihood of recovery of brain structure with sobriety, including older age, heavier alcohol consumption, concurrent hepatic disease, history of withdrawal seizures, malnutrition, and concurrent smoking (Yeh et al. 2007). Inability to ethically enforce control over drinking and other factors in human alcoholism limits these studies to naturalistic designs. By contrast, animal studies afford control over factors contributing to change for the better or the worse with continued or discontinued alcohol exposure. Animal models of alcoholism may also advance our understanding of the brain volume changes documented in the course of human alcoholism (see figures 7 and 8).

Advances in Neuroscience

The advances made over these first 40 years have enriched understanding of alcoholism from a neuroscience perspective and have expanded concepts of neuroplasticity in the human brain. The innovations enabling discoveries also have generalized to other areas of neuroscience, exemplified by our understanding of neural degradation with chronic alcoholism and repair with sobriety. Original concepts of brain structure modification were unidirectional—that is, degradation occurred with age or disease without the chance of neuronal regeneration. Now, evidence supports the possibility of neurogenesis as part of a repair process (Nixon and Crews 2004) or at least for creating a milieu for repair of cell bodies and their processes. Repair of white matter constituents, including myelin, also can transpire. A greater understanding of this process is emerging following the identification, for example, of altered myelin repair gene

expression in the frontal cortex of alcoholics (Liu et al. 2006). The fate of cortical volume in chronic alcoholism also may be related to genetic regulation that selectively affects gray but not white matter (Srivastava et al. 2010).

Although the neuropsychological impairments attendant to alcoholism have existed through the centuries, understanding of their neural mechanisms has required identification of selective functional components and brain integrity affected and not affected, together with the knowledge of the course, extent, and loci of disruption and repair. What researchers found 40 years ago is a likely reflection of the disorder seen today, but a mechanistic understanding of the full constellation of effects and the scope and limit of improvement with sobriety has evolved from being considered widespread and nonspecific to being specific in terms of brain circuitry and systems. Environmental, genetic, metabolic, and behavioral factors that influence restitution of neurofunction have yet to be identified but are amenable to study with neuroimaging. With systematic longitudinal study and rigorous characterization of people with alcohol use disorders, neuroimaging in conjunction with neuropsychology can enable in vivo detection and tracking of brain systems affected by alcoholism, the functional relevance of identified neuropathology, the scope and limit of the brain's plasticity at different ages of alcohol exposure and withdrawal, and insight into neural mechanisms of insult and recovery. Still on the neuroscience research horizon are acknowledgment of the heterogeneity of expression of alcoholism's untoward effects, delineation of substrates of neural change with addiction and further change with alternating periods of drinking and sobriety, and viable approaches for curtailing drinking in alcohol abusers. ■

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