Neuropsychology and Substance Use: State-of-the-Art and Future Directions

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Preface

Ari Kalechstein and Wilfred van Gorp

Substance misuse continues to be a major public health problem, and the ramifications of this are manifold. For instance, at present, on a yearly basis, the total economic cost of substance misuse is literally hundreds of billions of dollars. These costs are related to a number of factors, including, but not limited to, treatment and prevention, reduced job productivity and/or absenteeism, interdiction by the criminal justice system, and incarceration.

The adverse effects of substance misuse can also be measured by calculating the number of treatment admissions for substance misuse. For example, in 2003 there were 1.7 million admissions to publicly funded substance abuse treatment programs. This does not take into account the number of admissions into private facilities. While the substance most likely to be misused was alcohol, there was marked misuse of other drugs, such as marijuana, opioids, cocaine, and amphetamine/methamphetamine. Thus, the issue does not appear to be specific to any particular substance.

There are many more psychosocial consequences of substance misuse, and these have been well documented over the past four to five decades; in contrast, with the exception of alcohol, the cognitive effects of substance misuse on the brain have received attention only in the past 10–15 years. An emerging body of literature has reported on the effects of various drugs on neuropsychological functioning, including benzodiazepines, cocaine, marijuana, MDMA, methamphetamine, nicotine, and opioids. Notably, there has been debate of whether certain drugs, such as MDMA, actually cause residual neuropsychological impairment. Furthermore, the co-occurrence of substance misuse and various medical and mental health disorders, such as schizophrenia and HIV, has received increased attention. Moreover, innovative researchers have sought to clarify the associations between these neuropsychological abnormalities and other indices of brain function, such as neuroimaging. Additionally, within the last two to three years, researchers have begun to document the relationship between neuropsychological profile and important functional outcomes, such as relapse to dependence.

Despite the fact that the neuropsychological consequences of many drugs of abuse are well documented, to our knowledge, no one has previously published an edited volume that focused exclusively on this issue involving

multiple substances of misuse. Based on this fact, we decided to create a volume that would review the available literature regarding this topic. For example, in order to highlight the incidence and prevalence of substance misuse, the first chapter of the volume focuses exclusively on epidemiology. The next eight chapters discuss the neuropsychological consequences of substances that are most likely to be misused. Three additional chapters focus on the co-occurrence of substance misuse in at-risk populations.

Astute readers may note that the neuropsychological consequences of certain drugs, such as PCP and LSD, were not reviewed. There are a number of reasons for this. First, and to our surprise, there were very few studies that examined the neuropsychological consequences of these drugs. Moreover, the prevalence rate of misuse of these substances was relatively low in comparison to that of other drugs. Because one of our goals was to maximize the relevance of this volume, it seemed most appropriate to include reviews on substances that are currently misused rather than those that might have been abused in decades past.

While we recognized the need to include thorough reviews of the literature for each topic, it was our intent to have chapters that were innovative and/or challenged current thinking in the field. For instance, one of the chapters focuses on an exciting new field, neuroeconomics, which addresses the link between neuropsychological functioning and cost/benefit analyses. Another chapter examines the manner in which context can influence brain structure and function, as well as behavior. These are exciting new fields of scientific endeavor.

Finally, to the extent that it was feasible, we asked authors to address ecologically valid questions related to the use of various drugs. For example, with respect to the use of benzodiazepines, it is clear that these medications are an effective treatment for various types of anxiety disorder; however, if individuals who take benzodiazepines are at risk to experience neuropsychological impairment, then what does that mean for the ability of these individuals to perform various day-to-day activities? Similarly, it has been demonstrated that marijuana can be used effectively as an analgesic and to counteract the anorectic effects of various medical disorders (e.g., HIV, cancer). Nonetheless, it is important to consider if there are potentially detrimental effects of controlled marijuana use that outweigh these benefits.

Before proceeding to the body of the volume, we wish to express our profound gratitude to each of the authors who contributed to this volume. Their dedication and hard work made this volume possible.

2 Alcohol

Marlene Oscar-Berman and Ksenija Marinkovic

Introduction

Alcoholism is a multidimensional disorder involving excessive ethanol ingestion. The course of the disease is influenced by an interaction of environmental factors with specific biological components, and manifests in the form of behavior abnormalities. In this chapter, we begin with an overview of the acute and residual effects of alcoholism, including its prevalence and the risk factors for developing neuropsychological deficits. Risk factors include genetics and family history, age, gender, and physical as well as mental health conditions. Next, we review the cognitive and emotional effects of intoxication. Examples of these effects are given for attentional, semantic, and psychomotor functions. We also consider the regions of the brain that are most vulnerable to the effects of alcoholism, i.e., the frontal lobes, the cerebellum, and the limbic system. Brain imaging techniques hold great promise for localizing brain areas most affected by intoxication. We suggest that these techniques be used in combination with other methodologies for maximal benefits in the treatment of alcoholism and in charting the course of recovery of function. Ideally, the collective methodologies will include neuropsychological testing, electromagnetic recordings (e.g., event-related potentials and magnetoencephalography), and brain scans (especially structural and functional magnetic resonance imaging).

Definitions and overview of acute and residual effects of alcoholism

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; APA, 1994) defines two alcohol use disorders, *alcohol abuse* and *alcohol dependence*. Abuse involves psychological, social, and work-related impairments or distress, causing problems with activities of daily living, in which alcohol consumption is implicated. Dependence stresses a disability (manifested by craving, tolerance, and physical dependence) in which drinking behaviors cannot be adequately restrained.

It is important to distinguish between the acute and the residual effects

of alcoholism. The most obvious acute effect of ethanol consumption is intoxication. Residual neurobehavioral effects are those that remain after a person has been abstinent for at least a month. Researchers interested in studying the residual effects will restrict patient enrollment to alcoholics who have been abstinent for a minimum of four weeks; this is important for obtaining stable levels of performance.

Scope of the problem: Prevalence of brain-related deficits associated with alcoholism

Approximately half of the nearly 20 million people in the United States who are problem drinkers have not been diagnosed with cognitive impairments. The remaining problem drinkers have neuropsychological difficulties that range from mild to very severe. For example, up to 2 million alcoholics develop permanent and debilitating conditions that require lifetime custodial care (Rourke & Løberg, 1996). Examples of such conditions include alcohol-induced persisting amnesic disorder (also called alcoholic Korsakoff's syndrome) (Butters, 1981), and alcohol-induced persisting dementia (APA, 1994) which seriously affects many mental functions in addition to memory (e.g., language, reasoning, and problem-solving abilities).

Most alcoholics with neuropsychological impairments show at least some improvement in brain structure and functioning within a year of abstinence. However, some alcoholics require additional time, and others have permanent deficits (Bates, Bowden, & Barry, 2002; Gansler et al., 2000; Sullivan, 2000). To date, little is known about the rate and extent to which people recover specific structural and functional processes after they stop drinking. In contrast, a number of studies have identified various factors that increase the likelihood that alcohol misuse will result in brain deficits.

Alcoholism's effects on the brain and behavior are diverse, and they are moderated and/or mediated by many factors (Oscar-Berman, 2000; Parsons, 1996). Consequently, no single measuring instrument can establish definitive criteria for alcoholism or the putative neurobehavioral sequelae of the disease. Among the numerous factors influencing the expression and course of alcoholism are: demographic variables (e.g., age, level of education, gender), genetic background, temperament, family history of alcoholism, alcohol exposure in the prenatal and perinatal periods, the social and ethnic surroundings during childhood, alcohol use patterns (e.g., the age of onset of alcohol consumption, the type and amount of alcohol consumed, severity and duration of the dependency, duration of abstinence, nutritional status during periods of consumption), and the use or abuse of other psychoactive substances. Additionally, overall physical and mental health are important factors, because comorbid medical, neurological, and psychiatric conditions can interact to aggravate alcoholism's effects on the brain and behavior (Petrakis, Gonzalez, Rosenheck, & Krystal, 2002). Examples of common comorbid conditions include:

- medical conditions such as malnutrition and diseases of the liver and the cardiovascular system;
- neurological conditions such as head injury, inflammation of the brain (i.e., encephalopathy), and fetal alcohol syndrome (or fetal alcohol effects); and
- psychiatric conditions such as depression, anxiety, post-traumatic stress disorder, schizophrenia, and the use of medicines or other drugs.

These conditions also can contribute to further drinking.

Risk factors and comorbid conditions that influence alcohol-related brain damage

The manner in which alcoholism leads to brain and behavior abnormalities is not surprising, because of the many different factors having an influence on the outcome measures used by clinicians and researchers (Grant, 1987; Parsons, 1996). In this section, we consider the following critical influences: genetic background and family history of alcoholism; age; gender; and health status.

Genetics and family history

In 1989, based on the results of twin, family, and adoption studies showing that hereditary factors influence vulnerability to alcoholism, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) funded Collaborative Studies on Genetics of Alcoholism (COGA). The goal of COGA is to identify specific genes that underlie this vulnerability. COGA investigators have successfully recruited over 3000 individuals from more than 300 extended families densely affected by alcoholism. The investigators have collected extensive clinical, neuropsychological, electrophysiological, biochemical, and genetic data. Evidence from these studies supports the idea that genes play an important role in alcoholism (e.g., see a review by Dick & Foroud, 2003).

At least 40% of the addictions to alcohol, tobacco, and other drugs have genetic influences (Bierut et al., 2002; Bowirrat & Oscar-Berman, 2005; McGue, 1999; Tsuang et al., 1998; Uhl & Grow, 2004). For example, offspring of monozygotic and dizygotic twins with a history of alcohol dependence were found to exhibit alcohol abuse or addiction more frequently than offspring of nonalcoholic fathers, and offspring of an alcohol-abusing monozygotic twin whose co-twin was alcohol dependent were more likely to be alcohol dependent than offspring of nonalcoholic twins (Jacob et al., 2003). However, in the absence of paternal alcoholism, offspring with high genetic risk (the unaffected father's co-twin is alcoholic) showed lower rates of alcoholism than children of alcoholics (Jacob et al., 2003). Genome scans have identified multiple addiction vulnerability loci but no regions that seem to contain genes of major effect in alcoholics (Foroud & Li, 1999; Harper, 1998).

The physiological basis of alcoholism is the subject of considerable

research, along with the possible genetic underpinnings of its effects on ion channels (Davies et al., 2003). A complete picture of the basic mechanisms of alcohol ingestion has been difficult to achieve partly because, unlike other psychoactive drugs, ethanol does not selectively bind to specific receptor sites. Instead, it affects the state of the membranes and thus modifies a variety of ion channels or receptors. As noted by Dick and Foroud (2003), sequencing of the human genome will facilitate the development of a catalog of human genes. Based on the findings from this catalog, researchers can identify candidate genes to determine the degree to which they are associated with alcoholism. Once replicable associations are established, the next step will be to identify the causative genetic variants responsible for the role of that gene in alcohol dependence.

Age

Neuropathological analyses provided some of the earliest insights into the relationship between alcoholism and aging. In *postmortem* specimens of brains of alcoholics, cerebral atrophy was found to resemble the brain shrinkage that occurs with normal chronological aging (Harper, 1998). The atrophy is most prominent in the frontal lobes, and it extends backwards to the parietal lobes. Other effects include ventricular enlargement and widening of the cerebral sulci of alcoholics in relation to increasing age (Fein et al., 2002; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Sullivan, 2000).

Given the observed morphological similarities in the brains of alcoholic and aging individuals, more recent studies sought to characterize parallels in functional decline associated with alcoholism and aging (Gansler et al., 2000). Some investigators proposed that alcoholism is associated with premature aging. The Premature Aging hypothesis has been put forth in two versions (reviewed by Ellis & Oscar-Berman, 1989; Oscar-Berman & Schendan, 2000). The initial model, the "accelerated aging" (or "cumulative effects") model, purported that alcoholism is accompanied by the precocious onset of neuroanatomical and behavioral changes typically associated with advancing age. Essentially, alcoholics become "cognitively old" before their time; thus, alcoholics at all ages are impaired compared to age-matched nonalcoholic controls. The second version places the timing of the changes somewhat differently. In this view (the "increased vulnerability" interpretation), an aging brain is more vulnerable to the influences of toxic substances, including ethanol, than is the brain of a younger person. This version proposes that only older alcoholics (over age 50) are impaired compared to age-matched controls, not younger alcoholics.

Taken together, most of the evidence from neuropathological and neuroradiological investigations supports the increased vulnerability model of premature aging. That is, certain brain structures show greater reduction in size (or blood flow) in older alcoholics than in younger alcoholics: the cerebral cortex (Di Sclafani et al., 1995; Harris et al., 1999; Pfefferbaum et al.,

1997), the corpus callosum (Pfefferbaum, Lim, Desmond, & Sullivan, 1996), the hippocampus (Laakso et al., 2000; Pfefferbaum et al., 1995), and the cerebellum (Harris et al., 1999; Sullivan, 2003). Although cortical changes have been reported throughout the brain, there is evidence that some cortical regions (especially the frontal lobes) are more consistently vulnerable to aging and alcoholism than other regions (e.g., Gansler et al., 2000; Gilman et al., 1996; Moselhy, Georgiou, & Kahn, 2001; Oscar-Berman & Hutner, 1993; Sullivan, 2000). Results of neurobehavioral investigations tend to support the view that aging increases one's vulnerability to alcohol-related decline (Gansler et al., 2000; Sullivan, 2000).

Gender

Until recently, research on gender differences in the biological effects of alcoholism had focused mainly on the reproductive system and hepatic injury rather than on the central nervous system. Evidence suggests that women alcoholics have increased menstrual disturbances, spontaneous abortions, and miscarriages, and women are more susceptible to alcoholic liver disease than men (NIAAA, 1997). Only in the last decade have gender differences been the focus of research on alcohol-related brain damage (Lancaster, 1995; NIAAA, 1997; Wuethrich, 2001), and the degree to which gender moderates the nature and extent of brain vulnerability remains controversial (Pfefferbaum, Rosenbloom, Serventi, & Sullivan, 2002; Sullivan, 2003). Parsons (1994) reported that although male and female alcoholics showed impaired performance on neuropsychological tests relative to same-sex controls, only the male alcoholics differed from their controls using event-related brain potentials (ERPs). Other investigators found that male and female alcoholics displayed similar electrophysiological abnormalities (Hill & Steinhauer, 1993).

Neuroimaging studies measuring gender differences in alcoholics' brain size and functioning have yielded contradictory evidence, with some studies showing women to be more susceptible than men to brain impairments, and other studies showing no such distinction. Using functional magnetic resonance imaging (fMRI), Tapert and colleagues (Tapert et al., 2001) found decreased activity in parietal and frontal cortex, particularly in the right hemisphere, in alcohol-dependent women during performance of a spatial working memory task. Using structural MRI, Kroft et al. (1991) found that the average ventricular volume in female alcoholics was within the typical range found in MRI studies of nonalcoholic females of similar ages. Using computerized tomography (CT) scans to measure brain atrophy, another group found evidence of a similar degree of brain shrinkage in men and women, despite shorter drinking histories in the women (Mann, Batra, Gunthner, & Schroth, 1992). Hommer et al. (1996) used structural MRI technology to measure the size of the corpus callosum in male and female alcoholics. The alcoholic women had smaller callosal areas than alcoholic

men and nonalcoholic controls; alcoholic men did not differ from nonalcoholic male controls. Abnormalities in the structure of the corpus callosum can occur as a consequence of diffuse cortical damage and subsequent degeneration of cortical axons. Interestingly, the size of the corpus callosum is notably reduced with age in alcoholic men (Pfefferbaum et al., 1996). In another study, Pfefferbaum and his group measured white matter brain macrostructure in women alcoholics to determine whether observed abnormalities interact with age (Pfefferbaum et al., 2002). Although the alcoholic women did not differ from controls in any brain measures, in the alcoholics, greater length of sobriety was associated with more cortical white matter (Pfefferbaum et al., 2002). Based on the results of a similar study employing Diffusion Tensor Imaging (a technique highly sensitive to microstructure damage) on separate subject groups, Pfefferbaum and Sullivan (2002b) suggested that alcohol use by women causes white matter microstructural disruption that is not detectable with grosser measures of white matter mass, and may antedate its appearance.

Physical and mental health

The medical conditions most likely to influence neurobiological function include liver disease, cardiovascular disease, and malnutrition. Common neurological conditions in alcoholics are head injury, encephalopathy (inflammation of the brain), and fetal alcohol syndrome (or fetal alcohol effects). Frequently occurring psychiatric conditions include depression, anxiety, post-traumatic stress disorder, schizophrenia, and the use of other drugs (Petrakis et al., 2002). Additionally, and apart from individual characteristics and vulnerabilities of the alcoholic, there are specific "outcome measures" (results of evaluations and tests performed by researchers and clinicians). Certain tests that are used to measure alcohol's effects on brain and behavior are more sensitive than others, and different tests are aimed at assessing very distinct functions or structures. Finally, it is important to consider each person's motivation to perform well on the tests, and expectations about failure.

Cognitive and emotional effects of intoxication

Whether considering the acute or the residual consequences of ethanol ingestion, its effects reach across various cognitive, emotional, psychomotor, and social abilities (Rourke & Løberg, 1996). The type and extent of the abnormalities are dependent upon factors such as those noted above. Although alcohol intoxication affects functioning at multiple levels of the central nervous system, cognitive abilities in situations of increased complexity are most likely to be disrupted. Alcohol may interfere with cognitive assessment of the environment and the capacity to inhibit impulsive responses. These impairments may contribute to socially important effects of acute

intoxication, as well as to the development of alcohol dependence itself. Indeed, in concert with studies on chronic alcoholics and populations at risk, studies using acute alcohol challenges are important as they may help to parse out the effects of alcohol neurotoxicity, genetic susceptibility, and environmental factors. An understanding of the dose- and task-related parameters of acute alcohol effects on the brain may offer insight into neural systems that are most susceptible to chronic alcohol abuse. Furthermore, studies of acute alcohol challenge are valuable, as they indicate the types of functions and the neural circuits that underlie impairments due to alcohol intoxication. The importance of such evidence derives from its direct applicability to driving situations, work-related hazards, and other societally relevant concerns.

Effects of alcohol depend on an individual's blood alcohol concentration (BAC), as low doses may have a stimulatory effect and higher levels may have depressant effects on behavior. In addition, effects can differ depending on the time lapsed since ingestion; the same BAC may result in different effects on the ascending versus descending limbs of the BAC curve. Furthermore, there are significant interindividual differences in tolerance to acute intoxication. Even when people are subjected to the same environmental conditions, their responses to a given dose of alcohol vary significantly on metabolic, physiological, subjective, cognitive, motor, and other measures (Reed, 1985). The pharmacokinetics (time course of absorption, distribution, metabolism, and excretion of ethanol) vary significantly when alcohol is administered orally, but much less so under intravenous administration conditions (Grant, Millar, & Kenny, 2000). Furthermore, there are marked *intra*individual differences (Nagoshi & Wilson, 1989) in the consistency of responses of the same individual when measured at different points across time. In general, effects of alcohol intoxication follow a biphasic time course as the initial feelings of relaxation and exuberance give way to hangover, exhaustion, and depression, or vomiting and loss of consciousness in cases of higher doses. Impairments in mental functions such as attention or vigilance can be detected at BAC levels much lower than the legal intoxication levels, such as 0.02–0.03% (Koelega, 1995). Furthermore, consistent with the evidence obtained from chronic alcoholics, acute intoxication results in a disproportionate impairment of the executive functions such as planning, working memory, or complex psychomotor control (Peterson, Rothfleisch, Zelazo, & Pihl, 1990). A more detailed picture of the neurophysiological basis of these effects emerges from neuroimaging studies.

Effects of alcohol on cognitive event-related potentials: Attentional Networks

Event-related potentials (ERPs) reflect moment-to-moment changes in the electrical activity of the brain as it relates to parameters of the stimuli occurring either in the environment or in internally generated thoughts. ERPs have been used extensively to investigate effects of acute intoxication as well as

chronic abuse of alcohol (Porjesz & Begleiter, 1985, 1996). A commonly used "oddball" paradigm consists of frequently presented standard stimuli and rarely occurring task-relevant target (oddball) stimuli such as tones or light flashes. In addition, a task-irrelevant, novel stimulus is presented in some versions of the task (Marinkovic, Halgren, Klopp, & Maltzman, 2000; Rodriguez Holguin, Porjesz, Chorlian, Polich, & Begleiter, 1999). Infrequently occurring stimuli elicit a large positive potential termed P3 with a latency of about 300 ms in simple tasks. P3 amplitude is smaller under alcohol intoxication (Pfefferbaum, Horvath, Roth, Clifford, & Kopell, 1980; Porjesz & Begleiter, 1985), suggesting a disruption of the central processing of novel, task-irrelevant stimuli even at very low BAC levels (Grillon, Sinha, & O'Malley, 1995; Jääskeläinen, Schroger, & Näätänen, 1999; Marinkovic, Halgren, & Maltzman, 2001). This effect is inversely related to the alcohol dose (Rohrbaugh et al., 1987; Teo & Ferguson, 1986) and is modulated by task difficulty (Campbell, Marois, & Arcand, 1984). Furthermore, it has been shown that the P3 is not a unitary component but a composite of at least two deflections (termed P3a and P3b) differing in task correlates, latency, scalp topography, and generating structures (Halgren, 1990). The P3a is evoked in the frontocentral parts of the brain by novel, unexpected stimuli (Courchesne, Hillyard, & Galambos, 1975). It is highly correlated with sympathetic arousal, and is selectively affected by acute intoxication (Marinkovic et al., 2001) (see Figure 2.1).

Inasmuch as the P3a reflects orienting to novelty, these results indicate high susceptibility of the attentional domain relevant for processing of the significant stimuli to alcohol intoxication. Conversely, P3b is the largest over the posterior scalp regions, it is elicited by task-relevant stimuli and may index cognitive closure of stimulus event processing (Knight, Grabowecky, & Scabini, 1995). Consistent with this evidence, irreversible

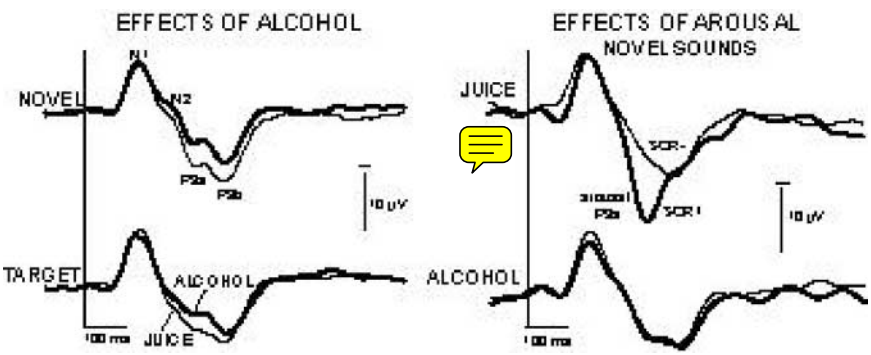

Figure 2.1 Group-average event-related potential waveforms recorded at frequency Fz. Alcohol (average BAC = 0.045%) decreases the late positive deflection to target and novel stimuli (left panel) and it selectively abolishes the P3a to novel sounds on trials with autonomic arousal (right panel). (Adapted from Marinkovic et al., 2001, with permission.)

amplitude attenuation and sometimes latency increase of the P3 deflection (Porjesz & Begleiter, 1985, 1996) have been observed in chronic alcoholics. Furthermore, the suspected role of genetics (Begleiter & Porjesz, 1999a; Goodwin, 1977; Schuckit, 1983) in increasing the risk for alcoholism has promoted the search for biological markers that could help to identify such individuals and could potentially allow for early diagnosis, focused prevention, and treatment of alcoholism. Attenuated P3 amplitude has been documented in individuals at high risk for alcoholism, such as offspring of alcoholics, and has given rise to a vulnerability marker hypothesis whereby attenuated P3 may suggest predisposition to an array of disinhibitory disorders including alcohol dependence (Begleiter & Porjesz, 1999b; Monteiro & Schuckit, 1988; Pfefferbaum, Ford, White, & Mathalon, 1991). Inasmuch as the commonly used "oddball" paradigm engages attentional brain circuits, this converging evidence also implicates their susceptibility to alcohol effects.

Semantic networks

Studies using semantic, more cognitively challenging tasks have explored alcohol effects on verbal, semantic, and memory brain networks. It has been established that the reaction speed and accuracy in word categorization and recognition tasks are impaired by acute alcohol intoxication (Haut, Beckwith, Petros, & Russell, 1989; Maylor, Rabbitt, & Kingstone, 1987). Some behavioral evidence suggests that alcohol impairs semantic processing (Maylor, Rabbitt, James, & Kerr, 1990). In light of this evidence, it is surprising to note that alcohol's effects on the brain during verbal cognitive processing have not been adequately studied, in spite of a proliferation of ERP studies of language processing. A negative ERP component with a latency of about 400–450 ms (N400 or N4) has been described (Kutas & Hillyard, 1980) which is sensitive to the semantic, but not orthographic, aspects of congruity with the preceding context. Novel words with an unexpected or incongruent meaning evoke a large N4 (such as "I like my tea with nails"). Conversely, semantic priming decreases N4 amplitude and latency (Nagy & Rugg, 1989; Smith & Halgren, 1987), suggesting its dependence on the ease of semantic contextual integration (Halgren, 1990; Holcomb, 1993). Recent studies indicate that alcohol intoxication affects verbal processing during early, prelexical, and late semantic stages, resulting in the increased difficulty of semantic access and integration (see Figure 2.2; Marinkovic, Halgren, & Maltzman, 2004). Neuroimaging studies indicate that the early, prelexical visual feature analysis is subserved by the ventrotemporal area, whereas the later stage of semantic and contextual integration relies on the distributed circuits that primarily encompass the left prefrontal and temporal regions (Buckner, Logan, Donaldson, & Wheeler, 2000; Marinkovic, 2004). Future studies will need to determine whether alcohol's effects on these stages of verbal processing are independent or merely cumulative, and to what degree they are modulated via attentional impairments.

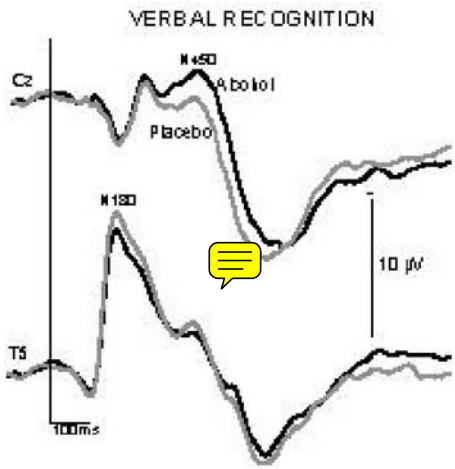

Figure 2.2 Alcohol affects the early (prelexical, peaking at 180 ms) and late (semantic, contextual, peaking at 450 ms) stages of verbal processing, as shown with group-average event-related potentials. (Adapted from Marinkovic et al., 2004, with permission.)

Psychomotor effects and impulsivity

Stimulus events evoke two seamlessly integrated brain-processing streams: one stream evaluates the stimulus ("input"), whereas the other prepares the response ("output"). Both of these aspects occur in parallel and form an integrated processing stream, but are rarely considered together. As outlined above, it has been shown that alcohol intoxication disrupts cognitive stimulus processing in the attentional and semantic domains. Research evidence suggests that alcohol impairs the psychomotor aspects of functioning as well.

It is a common belief that alcohol ingestion leads to impulsive or aggressive behavior. Indeed, laboratory research shows that alcohol intoxication increases the likelihood of aggressive behavior (Bushman & Cooper, 1990). However, careful examination of the doubtlessly complex interactions between alcohol intoxication and the multifaceted construct of aggression is still lacking. For instance, a behavior labeled as "aggressive" could include combinations of impulsivity, disinhibition, social or sexual inappropriateness, thought or decision-making impairments, or some other feature. Some evidence suggests that alcohol may have disinhibitory effects on behavior. Rather low alcohol doses (peak BAC of ~ 0.04%) decrease the latency of arousal to sexually explicit stimuli (Wilson & Niaura, 1984). Alcohol-induced disinhibition is also reflected in premature motor preparation based on incomplete stimulus evaluation (Marinkovic et al., 2000). The disinhibitory effects could result from the psychomotor stimulant properties of alcohol (Wise, 1988), or may reflect a disruption in the inhibitory control of behavior subserved by prefrontal regions (Peterson, Rothfleisch, Zelazo, & Pihl, 1990). Indeed,

alcohol decreases inhibitory control under the conditions of stop-signal imperative stimuli (Mulvihill, Skilling, & Vogel-Sprott, 1997) and a demanding continuous performance task (Dougherty et al., 1999), as moderately intoxicated subjects are impaired in withholding inappropriate responses.

Furthermore, these disinhibitory effects of alcohol are correlated with personality traits related to impulsivity and hyperactivity (Dougherty et al., 1999; Marinkovic et al., 2000). Impulsivity is negatively correlated with alcohol-induced motor impairment but positively correlated with drinking problems (Nagoshi, Wilson, & Rodriguez, 1991). Disinhibition and antisocial traits are associated with increased risk for early-onset alcoholism (Mazas, Finn & Steinmetz, 2000) and sensation/novelty seeking is associated with increased drinking (Finn, Sharkansky, Brandt, & Turcotte, 2000). Indeed, a cluster of traits termed "antisocial personality disorder," inclusive of hyperactivity and impulsivity, correlates highly with chronic alcohol use (Regier et al., 1990). Research has indicated that the shared neurochemical markers may underlie the commonalities between alcohol abuse and traits subsumed in "antisocial personality disorder" (Virkkunen & Linnoila, 1993). This may be suggestive of a preexisting neurochemical milieu in certain individuals that is associated with the impulsive, hyperactive, or aggressive behaviors and which, in turn, is susceptible to alcohol. Thus, impulsive behavior may be a premorbid trait predisposing individuals to a spectrum of disorders including alcohol dependence (Pihl, Peterson, & Lau, 1993).

In addition to the "input" and "output" processing streams, there are also "self-monitoring" functions such as error monitoring and error correction. An ERP component termed error-related negativity (ERN) is evoked when an error is made on a task trial and is presumed to be generated by the anterior cingulate cortex (Coles, Scheffers, & Fournier, 1995). It has been recently shown that moderate intoxication reduces the ERN amplitude (Ridderinkhof et al., 2002). Because errors are detected via a complex system involving multiple stages of stimulus processing, response monitoring, and feedback loops, future research will have to establish which stages are most impaired by alcohol intoxication (Holroyd & Yeung, 2003).

Overall, the ERP literature suggests that significant alterations in brain function can be detected in both semantic and attentional domains at rather low alcohol doses and that the measures of brain function are more sensitive to alcohol-induced impairments than behavioral measures alone. Because they reflect neural events with a millisecond temporal resolution, the electromagnetic methods (ERPs and MEG – magnetoencephalography) can delineate alcohol-induced changes in distinct waveform components, and can consequently indicate alterations in *stages* of processing. However, the underlying neural substrate cannot be inferred unambiguously from ERP/MEG. In contrast, methods relying on hemodynamic changes in brain activity (such as functional magnetic resonance imaging – fMRI, or positron emission tomography – PET) are temporally limited as they reflect the neural activity only indirectly. Nevertheless, they can provide millimeter spatial sampling and

can thus indicate reliably *where* in the brain alcohol-induced changes are occurring.

Effects of inebriation revealed with hemodynamic methods (fMRI and PET)

As previously noted, MRI technology, which has been used to investigate structural brain abnormalities due to chronic alcohol use, revealed the presence of frontal lobe atrophy (Jernigan et al., 1991; Pfefferbaum et al., 1992; Sullivan, 2000). Few studies have utilized newer technologies, such as fMRI, to study the neurobiological effects of alcohol. Functional MRI, which measures hemodynamic changes resulting from increased metabolic demands of an activated brain region, indirectly measures neural activity. This might be related to several factors, one being that the physiological basis defining the linkage between neural functioning and hemodynamics is not well understood. This linkage is complicated by the fact that alcohol is vasoactive. As a result, additional studies are required to delineate the basic physiological interactions between alcohol intoxication and the resulting hemodynamic changes.

The fMRI studies conducted thus far indicate a decrease in the activation levels (Levin et al., 1998; Seifritz et al., 2000), but the functional and regional specificity of these effects needs further investigation in view of alcohol's vasoactive properties. These results concur with PET, some studies showing that an alcohol-induced global decrease in glucose metabolism may be dose-related (Bonthius & West, 1990) and gender-specific (Wang et al., 2003). Another PET study (Volkow et al., 1988) reported decreased blood flow to cerebellum but increased blood flow to right temporal and prefrontal cortices at higher alcohol doses (1 g/kg). Other PET studies, however, reported a global increase in cerebral blood flow, but functionally- and regionally-specific blood flow reduction in the left prefrontal region during a verbal task (Wendt & Risberg, 2001). In a recent study using fMRI (Calhoun et al., 2004), two alcohol doses were administered to healthy subjects on separate occasions as they engaged in a visual perception task. In addition to a global activation decrease, there were dose-related changes in the prefrontal, insular, temporal, occipital, and parietal regions. Future fMRI studies of cognitive functions will reveal task-specific activation patterns and dose-related effects of alcohol intoxication with more precision.

PET also has been utilized successfully for the purpose of delineating the neural circuits of alcohol's reinforcing properties. For example, alcohol increases blood flow to the cerebral reward system, including the anterior cingulate and septum, medial temporal lobe, and lower brainstem (Ingvar et al., 1998). Moreover, a recent study showed that alcohol administration correlated with increased release of dopamine in the ventral striatum, which is similar to the effects observed during the administration of psychostimulants (Boileau et al., 2003). Future PET studies using alcohol challenge will reveal dose-specific changes in neurotransmitter function. They can be particularly

valuable in revealing the neural basis of the rewarding properties of intoxication (alcohol-induced "high") and delineating possible mechanisms of alcohol dependence (Bowirrat & Oscar-Berman, 2005).

In general, hemodynamic brain scanning techniques are highly sensitive to localization of brain function. Moreover, these techniques will be instrumental in the development of pharmacological treatments that will target brain areas activated during inebriation. Furthermore, they will be helpful in charting the course of recovery of brain functioning with abstinence.

Vulnerable brain structures

Results of research employing techniques from pathology, neuroimaging, electrophysiology, and behavioral neuroscience have determined that the brain structures most vulnerable to the effects of alcoholism are the neocortex (especially the frontal lobes), the limbic system (especially the hippocampus and hypothalamus), and the cerebellum (Gansler et al., 2000; Sullivan, 2000) (see Figure 2.3). Each of these is considered in turn.

The frontal lobes

The frontal lobes are connected with all of the other lobes of the brain, and they receive and send fibers to numerous subcortical structures as well

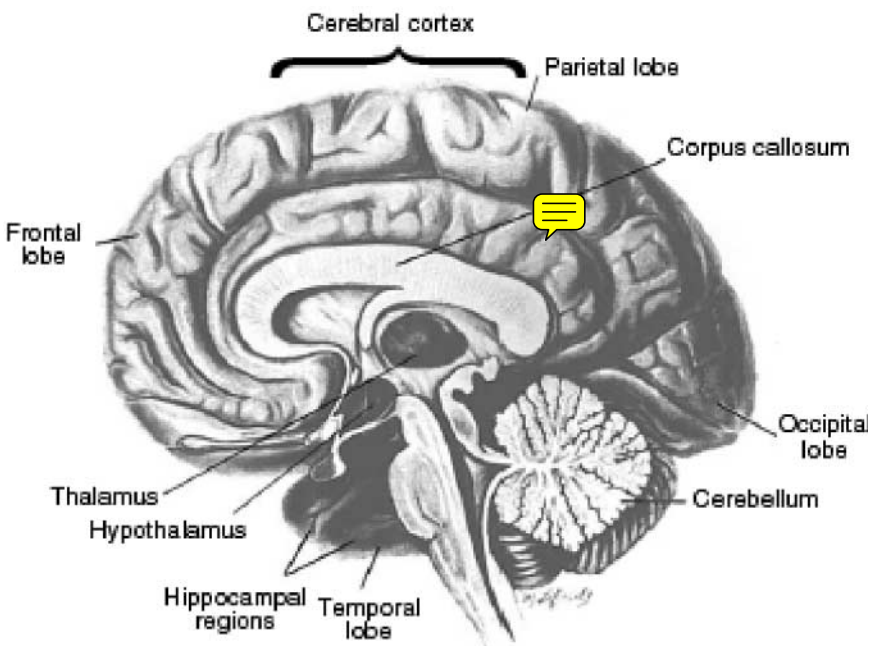

Figure 2.3 The human brain in cross-section.

(Fuster, 1997). While control of motor function takes place in the posterior region of the frontal lobes, the anterior region of the frontal lobes (prefrontal cortex) plays a kind of executive regulatory role within the brain (Goldberg, 2001; Lichter & Cummings, 2001). Executive functions (which depend upon many of our cognitive abilities, such as attention, perception, memory, and language) are defined differently by different theorists and researchers. Most agree, however, that executive functions are human qualities, including self-awareness, that allow us to be independent individuals with purpose and foresight about what we will do and how we behave. For example, executive abilities include judgment, problem-solving, decision-making, planning, and social conduct.

Damage to frontal brain systems consists of aberrations in personality, as well as cognitive changes such as those just mentioned. Frontal personality traits have been described in terms of "disinhibition" and lack of concern for the consequences of untoward behaviors. In comparison to dramatic personality changes, intellectual or cognitive changes are mild, but unmistakable. Frontal-system features have been only partially defined, but it is generally agreed that executive function deficits follow dorsolateral circuit damage, and that disinhibition and emotional changes follow orbitofrontal circuit lesions (Miller & Cummings, 1999).

Many studies have found the frontal lobes to be more susceptible to alcohol-related brain damage than other cerebral regions (Gansler et al., 2000; Moselhy et al., 2001; Ratti, Bo, Giardini, & Soragna, 2002; Sullivan, 2000). Studies of brain pathology at autopsy have revealed decreased neuron density in the frontal cortex of alcoholics (Harding, Wong, Svoboda, Kril, & Halliday, 1997). Harper (1998) and his collaborators established that 15–23% of cortical neurons are selectively lost from the frontal association cortex following chronic alcohol consumption. MRI studies have shown frontal lobe volume losses in alcoholic subjects (Pfefferbaum et al., 1997), and prefrontal neurobehavioral dysfunctioning has been frequently observed in alcoholics with and without the dense amnesia of Korsakoff's syndrome (Gansler et al., 2000; Oscar-Berman & Evert, 1997). Frontal abnormalities in alcoholics have been identified with fMRI scans (Tapert et al., 2001), reduced regional blood flow measurements (Melgaard et al., 1990), and with measurements of lower glucose metabolism throughout the brain (including prefrontal cortex) during alcohol intoxication (Volkow et al., 1995). Frontal lobe blood flow (Nicolás et al., 1993) and metabolism (Volkow et al., 1992) may decrease in alcoholics before significant shrinkage or major cognitive problems become detectable (Nicolás et al., 1993; Wang et al., 1993).

Cognitive functions and motor coordination may improve at least partially within three to four weeks of abstinence (Oscar-Berman & Evert, 1997; Sullivan, 2000), accompanied by at least partial reversal of brain shrinkage (O'Neill, Cardenas, & Meyerhoff, 2001; Pfefferbaum et al., 1995; Shear, Jernigan, & Butters, 1994) and some recovery of metabolic functions in the frontal lobes (Johnson-Greene, Adams, & Gilman, 1997) and cerebellum

(Martin, Nimmerrichter, Riddle, Welch, & Willcott, 1995; Seitz, Widmann, & Seeger, 1999). Frontal lobe blood flow continues to increase with abstinence, returning to approximately normal levels within four years (Gansler et al., 2000). Relapse to drinking leads to resumption of shrinkage (Pfefferbaum et al., 1995), continued declines in metabolism and cognitive function (Johnson-Greene et al., 1997), and evidence of neuronal cell damage (Martin et al., 1995).

The cerebellum

The cerebellum is a portion of the brain that coordinates movement of voluntary muscles, balance, and eye movements, and it also is essential to the neural circuitry subserving cognition and emotion (Schmahmann, 1997, 2000). The cerebellum contains about half of the brain's neurons, but the nerve cells are so small that the cerebellum accounts for only 10% of the brain's total weight. The cerebellum consists mainly of two large, tightly folded lobes, joined at the middle by the vermis. Also located anteriorly are the small flocculonodular lobes (flocculi). The cerebellum connects with the other brain structures through the cerebellar peduncles, located to the anterior of the cerebellum. Five different nerve cell types make up the cerebellum: stellate, basket, Purkinje, Golgi, and granule cells. The Purkinje cells are the only ones to send axons out of the cerebellum.

Atrophy of the cerebellum is commonly associated with alcoholism. White matter volume of the cerebellar vermis is significantly reduced (Baker, Harding, Halliday, Kril, & Harper, 1999; Pentney, Mullan, Felong, & Dlugos, 2002; Sullivan, 2003), and cerebellar vermian atrophy occurs in 25–40% of all alcoholics. Vermal white matter volume was reduced in ataxic alcoholics by 42%. It occurs even more often in people with additional thiamine deficiency, with 35–50% of those individuals showing evidence of superior vermian degeneration (Victor, 1992). Gross vermian atrophy is commonly seen *post-mortem* in alcoholics (Phillips, Harper, & Kril, 1987), and it also has been observed with *in vivo* neuroimaging techniques (Sullivan, 2003).

Over the past two decades, careful study has expanded the purview of the cerebellum to include influence on functions classically associated with frontal lobe functioning (Schmahmann, 2000; Sullivan, 2003). As noted in the previous section on frontal lobes, this part of the brain has executive control functions such as cognitive flexibility, speed in allocation of attentional resources, shifting ability, inhibition of perservative errors, abstractive and planning skills, and suppression of irrelevant information. Together, these observations suggest a functional role for frontocerebellar circuitry (Schmahmann, 1997). Thus, there is ample evidence for alcohol's untoward effects on the structure and function of the cerebellum and frontal lobes, and disruption of this circuitry is a potential mechanism underlying the behavioral impairment characteristic of alcoholism (Harris et al., 1999; Ilinsky & Kultas-Ilinsky, 2002; Sullivan et al., 2003).

Alcoholics with Korsakoff's syndrome have shown a significant decrease in Purkinje cell density in the cerebellar vermis and molecular layer volume (Baker et al., 1999). A 36% reduction in Purkinje cell numbers in the flocculi suggests disruption of vestibulocerebellar pathways. This is of particular interest given recent data showing the importance of cerebellum in the organization of higher order cerebral functions (Schmahmann, 2000).

The limbic system

The limbic system is responsible for monitoring internal homeostasis, mediating memory and learning, and contributing to emotions. The limbic system also drives important aspects of sexual behavior, motivation, and feeding behaviors. Primary areas of the limbic system include the hippocampus, amygdala, septal nuclei, hypothalamus, and anterior cingulate gyrus. For the purpose of this chapter, because numerous studies of alcoholics have reported abnormalities in the amygdala, hippocampus, and hypothalamus, the discussion is focused on those brain regions.

Amygdala

The amygdala is a small almond-shaped structure, deep inside the anteroinferior region of the temporal lobe. It is a heterogeneous brain area consisting of 13 nuclei and cortical regions and their subdivisions (Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000; Sah, Faber, Lopez De Armentia, & Power, 2003). It connects with prefrontal cortex, the hippocampus, the septal nuclei, and the medial dorsal nucleus of the thalamus. These connections make it possible for the amygdala to play its important role on the mediation and control of major affective states such as love, fear, rage, anxiety, and general negative affectivity (Aggleton, 2000; Amaral et al., 2003; Pitkänen et al., 2000). The amygdala, being a center for the identification of danger, is fundamental for self-preservation.

Neuroimaging studies in humans have shown that the amygdala responds to facial expressions of many emotions, especially those with negative affective qualities such as sadness, anger, and fear (Blair, Morris, Frith, Perrettand, & Dolan, 1999; Breiter & Rosen, 1999; Wang, McCarthy, Song, & LaBar, 2005; Winston, O'Doherty, & Dolan, 2003). In fact, facial expressions convey such strong emotional information that merely observing anger or fearful faces elicits visceral responses, including increased heart rate and sweating (Ohman & Soares, 1998). Neuroimaging studies (Davis & Whalen, 2001) have illustrated that these fearful responses to facial expressions are processed and largely mediated by the amygdala (having connections to both early sensory processing areas and autonomic reflex centers). Furthermore, amygdala responses to fearful faces have been observed even in the absence of conscious awareness of their presentation to subjects (Whalen et al., 1998).

A number of studies have linked the amygdala to the processing of motivational significance of stimuli and to the control of emotion (Breiter & Rosen, 1999; Everitt, Cardinal, Parkinson, & Robbins, 2003; LeDoux, 2003; Rolls, 2000). The amygdala is controlled in part by the brain's dopamine system (Delaveau, Salgado-Pineda, Wicker, Micallef-Roll, & Blin, 2005), the same system that responds to alcohol and produces feelings of pleasure when good things happen. In a recent study using fMRI in our laboratory, we observed clear evidence of differences between abstinent long-term alcoholics and nonalcoholic controls in amygdala activation to emotional materials. The subjects were scanned while viewing emotional words and emotional facial expressions. Subjects were given either shallow processing instructions ("Decide if the word [or the face] appears in color or black/white") or semantic deep processing instructions ("Decide if the word is abstract or concrete," or "if the person is intelligent or not"). After each of the four conditions, subjects were tested for recognition of the stimuli ("Have you seen this face/word before?"). Results indicated group differences in activation of mesial temporal brain regions, depending upon whether the materials were faces or words, and whether the processing level was deep or shallow. These differences were most apparent in the amygdala (and in the hippocampus to a lesser extent) with face stimuli. Thus, the alcoholic group showed significantly reduced activity during the deep processing of emotional faces. As can be seen in Figure 2.4, faces with negative and positive emotional expressions evoked stronger bilateral amygdala activity in the controls than in the alcoholics, whose responses were blunted. These results suggest that the alcoholics responded to the emotionally valenced stimuli in an undifferentiated manner. A similar lack of emotional differentiation by alcoholics also was observed in the hippocampus, although to a lesser degree than in the amygdala.

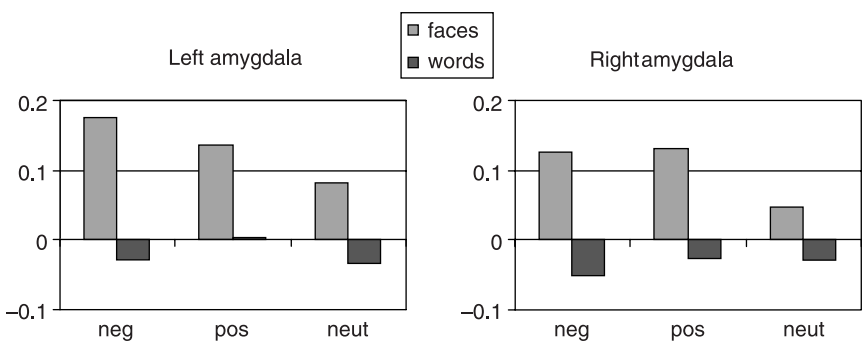

Figure 2.4 Group differences in amygdala activation to faces and words (controls minus alcoholics). Deep encoding of positive and negative faces evoked significantly more amygdala activity in the controls than in the alcoholics. However, this group difference was not observed during deep encoding of neutral faces (nor for word stimuli).

Hippocampus

The hippocampus is a horseshoe-shaped sheet of neurons located on the floor of each lateral ventricle within the temporal lobes and adjacent to the amygdala (Pitkänen et al., 2000). As part of the limbic system, it is intimately involved in motivation and emotion, and it also plays a central role in the formation of memories. The hippocampus consists of the complex interfolded layers of the dentate gyrus and Ammon's horn, which are continuous with the subiculum, which in turn merges with the parahippocampal gyrus. Although the idea that the hippocampus may play a role in brain mechanisms underlying anxiety is not new (Bannerman et al., 2002; Gray & McNaughton, 2000), there is now mounting evidence that the ventral hippocampus plays an important role in a brain system associated with fear and/or anxiety (Bannerman et al., 2002; Kjelstrup et al., 2002; McHugh, Deacon, Rawlins, & al, 2004). The anatomy of the hippocampus is closely associated with subcortical structures which contribute to the hypothalamic-pituitary-adrenal axis (Kjelstrup et al., 2002). A recent study also demonstrated that encoding of emotional memories depends on the hippocampus in conjunction with the amygdala, as well as their interaction with each other (Richardson, Strange, & Dolan, 2004).

The hippocampus is a target site for the teratogenic effects of ethanol (West & Pierce, 1986). Morphological changes in this brain region may play a critical role in the mental deficiency and behavioral abnormalities of individuals with fetal alcohol syndrome or alcohol-related neurodevelopmental disorder (Roebuck, Mattson, & Riley, 1998). There is evidence that certain hippocampal neuronal cell types are particularly sensitive to ethanol teratogenicity. For example, in nonhuman animals, chronic exposure of the developing hippocampus to ethanol can result in selective damage, such as a decrease in the number of CA1 pyramidal cells (Abdollah, Catlin, & Brien, 1993; Bonthius & West, 1990; Gibson, Reynolds, & Brien, 2000; Miller, 1995). One study of human alcoholics aged 45 years and under reported an early neuronal loss of the dentate gyrus and the ammonic fields CA1–CA4 (Bengochea & Gonzalo, 1990). Another study discovered glial cell loss (especially astrocytes and oligodendrocytes) in the hippocampus of alcoholics (Korbo, 1999).

The results of a recent study suggested that the effect of ethanol on the survival of newly formed neurons in the adult hippocampus could result in impairment of hippocampal-dependent cognitive functions, or, alternatively, the changes in cognition observed in alcoholism could lead to decreased neuronal survival (Herrera et al., 2003). Neurogenesis is primarily a developmental process that involves the proliferation, migration, and differentiation into neurons of primordial stem cells of the central nervous system. Neurogenesis declines until it ceases in the young adult mammalian brain, with two exceptions: The olfactory bulb and the hippocampus produce new neurons throughout adult life. The ethanol-induced reductions in

hippocampal neurogenesis can be attributed to two general mechanisms: an effect on cell proliferation or on cell survival. These changes in hippocampal structure could be part of the anatomical basis for cognitive deficits observed in alcoholism.

Structural neuroimaging studies have demonstrated a reduction of hippocampal volume in alcoholics (Agartz, Momenam, Rawlings, Kerich, & Hommer, 1999; Kurth et al., 2004; Pfefferbaum & Sullivan, 2002a). The loss of hippocampal volume has been attributed to changes in white matter (Harding et al., 1997), but the incorporation of newly formed neurons to the dentate gyrus could also be affected by alcohol. One MRI study measured hippocampus volume in late-onset alcoholics (Type I) and violent early-onset alcoholics (Type II), compared to nonalcoholic controls (Laakso et al., 2000). The right, but not left, hippocampus was significantly smaller in both alcoholic groups. While there was no correlation between the hippocampal volumes with age in the control subjects, there was tendency toward decreased volumes with aging and also with the duration of alcoholism in the Type I alcoholics. In a study of teens (aged 15–17 years) with alcohol use disorders, Nagel, Schweinsburg, Phan, and Tapert (2005) found reduced left – but not right – hippocampal volume compared to healthy age-equivalent controls. The groups were equivalent in right hippocampal, intracranial gray and white matter volumes, and memory performance. The authors suggested that premorbid volumetric differences might account for some of the observed group differences in hippocampal volume. Reduction of hippocampal volume in alcoholics is reversible after short periods of abstinence (White, Matthews, & Best, 2000). Similarly, hippocampal-dependent cognitive functions have also shown reversibility after comparable periods of abstinence.

Hypothalamus

The hypothalamus literally means "under the thalamus." It is a small structure nestled within the limbic system directly above the brainstem. The hypothalamus plays a role in many regulatory functions, such as eating and drinking, temperature control, hormone regulation, and emotional functions. The hypothalamus has connections with many other brain regions, and is involved in learning (Simonov, 1986).

Alcohol-related damage to the mammillary bodies of the hypothalamus is considered to lead to Korsakoff's syndrome (Oscar-Berman & Evert, 1997). Lesions of the mammillary bodies or to other regions of the brain (basal forebrain, hippocampus, fornix, medial and anterior nuclei of the thalamus) are associated with memory impairments (Butters, 1981; Mesulam, 2000). The specific memory impairments include severe anterograde amnesia for recent events, and some retrograde amnesia, i.e., loss of memory for events that happened long ago (prior to the appearance of obvious symptomatology). Damage to basal forebrain structures (important in the production of

neurotransmitters, which are needed for normal memory functions) may also be involved.

Amnesia, especially anterograde amnesia, or memory loss for recent events, is an intriguing and serious disorder. When amnesia occurs as a consequence of long-term alcoholism, it is referred to as alcohol-induced persisting amnestic disorder (APA, 1994), or alcoholic Korsakoff's syndrome. Patients with Korsakoff's syndrome are permanently unable to remember new information for more than a few seconds. Because new events are forgotten a few seconds after they occur, virtually nothing new is learned, and patients with Korsakoff's syndrome live perpetually in the past. However, in contrast to patients with alcoholic dementia, who have generalized cognitive decline (including widespread memory loss), patients with Korsakoff's syndrome retain old memories formed prior to the onset of alcohol-related brain damage.

Although anterograde amnesia is the most obvious presenting symptom in Korsakoff patients, these individuals have other cognitive impairments as well. Like patients with bilateral prefrontal cortical lesions, Korsakoff patients are abnormally sensitive to distractions (proactive interference). This sensitivity may be due to alcoholism-related prefrontal dysfunction, which impairs the ability to counteract the effects of cognitive interruptions. In addition to their memory problems and their sensitivity to interference, Korsakoff patients also tend to repeat unnecessary behaviors (perseverative responding), have restricted attention, retarded perceptual processing abilities, ataxia, and decreased sensitivity to reward contingencies (Oscar-Berman & Evert, 1997). These additional abnormalities reflect widespread cerebral atrophy accompanying sustained alcohol abuse. Thus, consideration should be given to sensory and cognitive deficits that may be integral to the disease process caused by chronic alcoholism.

Implications for treatment and recovery

Clinicians must consider a variety of treatment methods to promote cessation of drinking, maintenance of sobriety, and recovery of impaired functioning. Because alcoholism is associated with diverse changes to the brain and behavior, treatment professionals might find it most helpful to use a combination of neuropsychological observations and structural and functional brain imaging results in developing predictors of abstinence versus relapse, with the purpose of tailoring treatment methods to each individual patient. For example, the development of effective medications for controlling alcoholism relies upon knowledge about the neuroanatomical origins of neurotransmitters involved in craving, intoxication, and addiction. Neuroimaging methods have already provided significant insight into the nature of brain damage caused by heavy alcohol use, and the integration of results from different methods of neuroimaging will spur further advances in the diagnosis and treatment of alcoholism-related damage. Clinicians also can use brain imaging

techniques to monitor the course of treatment because these techniques can reveal structural, functional, and biochemical changes in patients across time as a result of abstinence, therapeutic interventions, withdrawal, or relapse. Neuroimaging research already has shown that abstinence of less than a month can result in an increase in cerebral metabolism, particularly in the frontal lobes, and that continued abstinence can lead to at least partial reversal in loss of brain tissue (Gansler et al., 2000; Sullivan, 2000). Thus, through the combined efforts of scientists and clinicians, important strides already have been made in the diagnosis, prevention, and treatment of alcoholism, and hopefully there will be continued advances in the future.

Conclusions

Alcoholics are a diverse group. They experience different subsets of symptoms, and the disease has different origins and modulating influences for different people. Therefore, to understand the effects of alcoholism, it is important to consider the influence of a wide range of variables on a particular behavior or set of behaviors. The underpinnings of alcohol-induced brain defects are multivariate; to date, the available literature does not support the assertion that any one variable can consistently and completely account for these impairments.

The most plausible conclusion is that neurobehavioral deficits in some alcoholics result from prolonged ingestion of alcohol, which impairs the way the brain normally works, by people who are vulnerable to some forms of brain damage. The identification of these vulnerabilities is a primary focus of current research. In the search for answers, it is necessary to use as many kinds of tools as possible, keeping in mind that specific deficits can be observed only with certain methods, with specific paradigms, and with particular types of people with distinct risk factors. Such confluence of information can provide evidence linking structural damage, functional alterations, and the specific behavioral and neuropsychological effects of alcoholism. These measures also can determine the degree to which abstinence and treatment result in the reversal of atrophy and dysfunction.

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References

Abdollah, S., Catlin, M. C., & Brien, J. F. (1993). Ethanol neuro-behavioural teratogenesis in the guinea pig: Behavioural dysfunction and hippocampal morphological change. *Canadian Journal of Physiology and Pharmacology*, *71*, 776–782.

Agartz, I., Momenam, R., Rawlings, R. R., Kerich, M. J., & Hommer, D. W. (1999). Hippocampal volume in patient with alcohol dependence. *Archives of General Psychiatry*, *56*, 356–363.

Aggleton, J. P. (2000). *The amygdala: a functional analysis* (2nd ed.). Oxford: Oxford University Press.

Amaral, D. G., Bauman, M. D., Capitanio, J. P., Lavenex, P., Mason, W. A., Mauldin-Jourdain, M. L., et al. (2003). The amygdala: is it an essential component of the neural network for social cognition? *Neuropsychologia*, *41*, 517–522.

APA (1994). *Diagnostic and statistical manual of mental disorders (DSM-IV)*. Washington, DC: American Psychiatric Association.

Baker, K. G., Harding, A. J., Halliday, G. M., Kril, J. J., & Harper, C. G. (1999). Neuronal loss in functional zones of the cerebellum of chronic alcoholics with and without Wernicke's encephalopathy. *Neuroscience*, *19*, 429–438.

Bannerman, D. M., Deacon, R. M. J., Offen, S., Friswell, J., Grubb, M., & Rawlins, J. N. P. (2002). A double dissociation of function within the hippocampus: Spatial memory and hyponeophagia. *Behavioral Neuroscience*, *116*, 884–901.

Bates, M. E., Bowden, S. C., & Barry, D. (2002). Neurocognitive impairment associated with alcohol use disorders: Implications for treatment. *Experimental and Clinical Psychopharmacology*, *10*, 193–212.

Begleiter, H., & Porjesz, B. (1999a). What is inherited in the predisposition toward alcoholism? A proposed model. *Alcoholism: Clinical and Experimental Research*, *23*, 1125–1135.

Begleiter, H., & Porjesz, B. (1999b). What is inherited in the predisposition toward alcoholism? A proposed model [see comments]. *Alcoholism Clinical and Experimental Research*, *23*, 1125–1135.

Bengochea, O., & Gonzalo, L. M. (1990). Effect of chronic alcoholism on the human hippocampus. *Histology and Histopathology*, *5*, 349–357.

Bierut, L. J., Saccone, N. L., Rice, J. P., Goate, A., Foroud, T., Edenberg, H., et al. (2002). Defining alcohol-related phenotypes in humans. The collaborative study on the genetics of alcoholism. *Alcohol Research and Health*, *26*, 208–213.

Blair, R. J. R., Morris, J. S., Frith, C. D., Perrettand, D. I., & Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain*, *122*, 883–893.

Boileau, I., Assaad, J. M., Pihl, R. O., Benkelfat, C., Leyton, M., Diksic, M., et al. (2003). Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse*, *49*, 226–231.

Bonthius, D. J., & West, J. R. (1990). Alcohol-induced neuronal loss in developing rats: Increased brain damage with binge exposure. *Alcoholism: Clinical and Experimental Research*, *14*, 107–118.

Bowirrat, A., & Oscar-Berman, M. (2005). Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, *118*, 29–37.

Breiter, H. C., & Rosen, B. R. (1999). Functional magnetic resonance imaging of brain reward circuitry in the human. In J. F. McGinty (Ed.), *Advancing from the ventral striatum to the extended amygdala* (Vol. 877, pp. 523–547). New York: New York Academy of Sciences.

Buckner, R. L., Logan, J., Donaldson, D. I., & Wheeler, M. E. (2000). Cognitive neuroscience of episodic memory encoding. *Acta Psychologica (Amsterdam)*, *105*, 127–139.

Bushman, B. J., & Cooper, H. M. (1990). Effects of alcohol on human aggression: An integrative research review. *Psychological Bulletin*, *107*, 341–354.

Butters, N. (1981). The Wernicke-Korsakoff syndrome: a review of psychological, neuropathological and etiological factors. *Current Topics in Alcoholism*, *8*, 205–232.

Calhoun, V. D., Altschul, D., McGinty, V., Shih, R., Scott, D., Sears, E., et al. (2004). Alcohol intoxication effects on visual perception: An fMRI study. *Human Brain Mapping*, *21*, 298–299.

Campbell, K., Marois, R., & Arcand, L. (1984). Ethanol and the event-related evoked potentials. Effects of rate of stimulus presentation and task difficulty. *Annals of the New York Academy of Sciences*, *425*, 551–555.

Coles, M. G., Scheffers, M. K., & Fournier, L. (1995). Where did you go wrong? Errors, partial errors, and the nature of human information processing. *Acta Psychologica (Amsterdam)*, *90*, 129–144.

Courchesne, E., Hillyard, S. A., & Galambos, R. (1975). Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalography and Clinical Neurophysiology*, *39*, 131–143.

Davies, A. G., Pierce-Shimomura, J. T., Kim, H., VanHoven, M. K., Thiele, T. R., Bonci, A., et al. (2003). A central role of the BK potassium channel in behavioral responses to ethanol in C. elegans. *Cell*, *115*, 655–666.

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry*, *6*, 13–34.

Delaveau, P., Salgado-Pineda, P., Wicker, B., Micallef-Roll, J., & Blin, O. (2005). Effect of levodopa on healthy volunteers' facial emotion perception: an FMRI study. *Clinical Neuropharmacology*, *28*, 255–261.

Di Sclafani, V., Ezekiel, F., Meyerhoff, D. J., MacKay, S., Dillon, W. P., Weiner, M. W., et al. (1995). Brain atrophy and cognitive function in older abstinent alcoholic men. *Alcoholism: Clinical and Experimental Research*, *19*, 1121–1126.

Dick, D. M., & Foroud, T. (2003). Candidate genes for alcohol dependence: A review of genetic evidence from human studies. *Alcoholism: Clinical and Experimental Research*, *27*, 868–879.

Dougherty, D. M., Moeller, F. G., Steinberg, J. L., Marsh, D. M., Hines, S. E., & Bjork, J. M. (1999). Alcohol increases commission error rates for a continuous performance test. *Alcoholism: Clinical and Experimental Research*, *23*, 1342–1351.

Ellis, R. J., & Oscar-Berman, M. (1989). Alcoholism, aging, and functional cerebral asymmetries. *Psychological Bulletin*, *106*, 128–147.

Everitt, B. J., Cardinal, R. N., Parkinson, J. A., & Robbins, T. W. (2003). Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Annals of the New York Academy of Sciences*, *985*, 233–250.

Fein, G., Di Sclafani, V., Cardenas, V. A., Goldmann, H., Tolou-Shams, M., & Meyerhoff, D. J. (2002). Cortical gray matter loss in treatment-naive alcohol dependent individuals. *Alcoholism: Clinical and Experimental Research*, *26*, 558–564.

Finn, P. R., Sharkansky, E. J., Brandt, K. M., & Turcotte, N. (2000). The effects of familial risk, personality, and expectancies on alcohol use and abuse. *Journal of Abnormal Psychology*, *109*, 122–133.

Foroud, T., & Li, T. K. (1999). Genetics of alcoholism: A review of recent studies in human and animal models. *American Journal of the Addictions*, *8*, 261–278.

Fuster, J. M. (1997). *The prefrontal cortex* (3rd ed.). New York: Lippincott-Raven.

Gansler, D. A., Harris, G. J., Oscar-Berman, M., Streeter, C., Lewis, R. F., Ahmed, I.,

et al. (2000). Hypoperfusion of inferior frontal brain regions in abstinent alcoholics: A pilot SPECT study. *Journal of Studies on Alcohol*, *61*, 32–37.

Gibson, M. A., N.S., B., Reynolds, J. N., & Brien, J. F. (2000). Effects of chronic prenatal ethanol exposure on locomotor activity, and hippocampal weight, neurons, and nitric oxide synthase activity of the young postnatal guinea pig. *Neurotoxicology and Teratology*, *22*, 183–192.

Gilman, S., Adams, K. M., Johnsongreene, D., Koeppe, R. A., Junck, L., Kluin, K. J., et al. (1996). Effects of disulfiram on positron emission tomography and neuropsychological studies in severe chronic alcoholism. *Alcoholism: Clinical and Experimental Research*, *20*, 1456–1461.

Goldberg, E. (2001). *The executive brain: Frontal lobes and the civilized mind*. New York: Oxford University Press.

Goodwin, D. W. (1977). Genetic and experiential antecedents of alcoholism: a prospective study. *Alcoholism: Clinical and Experimental Research*, *1*, 259–265.

Grant, I. (1987). Alcohol and the brain: Neuropsychological correlates. *Journal of Consulting and Clinical Psychology*, *55*, 310–324.

Grant, S. A., Millar, K., & Kenny, G. N. (2000). Blood alcohol concentration and psychomotor effects. *British Journal of Anaesthesiology*, *85*, 401–406.

Gray, J. A., & McNaughton, N. (2000). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system* (2nd ed.). Oxford, UK: Oxford University Press.

Grillon, C., Sinha, R., & O'Malley, S. S. (1995). Effects of ethanol on the processing of low probability stimuli: an ERP study. *Psychopharmacology (Berlin)*, *119*, 455–465.

Halgren, E. (1990). Human evoked potential. In A. A. Boulton, G. B. Baker, & C. Vanderwolf (Eds.), *Neuropsychological techniques: Applications to neural systems* (Vol. 15, pp. 147–275). Clifton, NJ: Humana.

Harding, A. J., Wong, A., Svoboda, M., Kril, J. J., & Halliday, G. M. (1997). Chronic alcohol consumption does not cause hippocampal neuron loss in humans. *Hippocampus*, *7*, 78–87.

Harper, C. (1998). The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *Journal of Neuropathology and Experimental Neurology*, *57*, 101–110.

Harris, G. J., Oscar-Berman, M., Gansler, D. A., Streeter, C., Lewis, R. F., Ahmed, I., et al. (1999). Hypoperfusion of cerebellum and aging effects on cerebral cortex blood flow in abstinent alcoholics: A SPECT study. *Alcoholism: Clinical and Experimental Research*, *23*, 1219–1227.

Haut, J. S., Beckwith, B. E., Petros, T. V., & Russell, S. (1989). Gender differences in retrieval from long-term memory following acute intoxication with ethanol. *Physiology and Behavior*, *45*, 1161–1165.

Herrera, D. G., Yague, A. G., Johnsen-Soriano, S., Bosch-Morell, F., Collado-Morente, L., Muriach, M., et al. (2003). Selective impairment of hippocampal neurogenesis by chronic alcoholism: Protective effects of an antioxidant. *Proceedings of the National Academy of Sciences*, *100*, 7919–7924.

Hill, S. Y., & Steinhauer, S. R. (1993). Event-related potentials in women at risk for alcoholism. *Alcohol*, *10*, 349–354.

Holcomb, P. J. (1993). Semantic priming and stimulus degradation: implications for the role of the N400 in language processing. *Psychophysiology*, *30*, 47–61.

Holroyd, C. B., & Yeung, N. (2003). Alcohol and error processing. *Trends in Neuroscience*, *26*, 402–404.

Hommer, D., Momenan, R., Rawlings, R., Ragan, P., Williams, W., Rio, D., et al. (1996). Decreased corpus callosum size among alcoholic women. *Archives of Neurology*, *53*, 359–363.

Ilinsky, I. A., & Kultas-Ilinsky, K. (2002). Motor thalamic circuits in primates with emphasis on the area targeted in treatment of movement disorders. *Movement Disorders*, *17*, S9–S14.

Ingvar, M., Ghatan, P. H., Wirsen-Meurling, A., Risberg, J., Von Heijne, G., Stone-Elander, S., et al. (1998). Alcohol activates the cerebral reward system in man. *Journal of Studies on Alcohol*, *59*, 258–269.

Jacob, T., Waterman, B., Heath, A., True, W., Bucholz, K. K., Haber, R., et al. (2003). Genetic and environmental effects on offspring alcoholism: new insights using an offspring-of-twins design. *Archives of General Psychiatry*, *60*, 1265–1272.

Jernigan, T. L., Butters, N., DiTraglia, G., Schafer, K., Smith, T., Irwin, M., et al. (1991). Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. *Alcoholism: Clinical and Experimental Research*, *15*, 418–427.

Johnson-Greene, D., Adams, K. M., & Gilman, S. (1997). Effects of abstinence and relapse upon neuropsychological function and cerebral glucose metabolism in severe chronic alcoholism. *Journal of Clinical and Experimental Neuropsychology*, *19*, 378–385.

Jääskeläinen, I. P., Schroger, E., & Näätänen, R. (1999). Electrophysiological indices of acute effects of ethanol on involuntary attention shifting. *Psychopharmacology (Berlin)*, *141*, 16–21.

Kjelstrup, K. G., Tuvnes, F. A., Steffenach, H. A., Murison, R., Moser, E. I., & Moser, M. B. (2002). Reduced fear expression after lesions of the ventral hippocampus. *Proceedings of the National Academy of Sciences*, *99*, 10825–10830.

Knight, R. T., Grabowecky, M. F., & Scabini, D. (1995). Role of human prefrontal cortex in attention control. In H. H. Jasper, S. Riggio, & P. S. Goldman-Rakic (Eds.), *Epilepsy and the functional anatomy of the frontal lobe* (pp. 21–36). New York: Raven Press.

Koelega, H. S. (1995). Alcohol and vigilance performance: a review. *Psychopharmacology (Berlin)*, *118*, 233–249.

Korbo, L. (1999). Glial cells in the hippocampus of alcoholics. *Alcoholism: Clinical and Experimental Research*, *23*, 164–168.

Kroft, C. L., Gescuk, B., Woods, B. T., Mello, N. K., Weiss, R. D., & Mendelson, J. H. (1991). Brain ventricular size in female alcoholics: An MRI study. *Alcoholism: Clinical and Experimental Research*, *8*, 31–34.

Kurth, C., Wegerer, V., Reulbach, U., Lewczuk, P., Kornhuber, J., Steinhoff, B. J., et al. (2004). Analysis of hippocampal atrophy in alcoholic patients by a Kohonen feature map. *Neuroreport*, *15*, 367–371.

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: brain potentials reflect semantic incongruity. *Science*, *207*, 203–205.

Laakso, M. P., Vaurio, O., Savolainen, L., Repo, E., Soininen, H., Aronen, H. J., et al. (2000). A volumetric MRI study of the hippocampus in type 1 and 2 alcoholism. *Behavioral Brain Research*, *109*, 177–186.

Lancaster, F. E. (1995). Gender differences in animal studies. Implications for the study of human alcoholism. *Recent Developments in Alcoholism*, *12*, 209–215.

LeDoux, J. E. (2003). The emotional brain, fear, and the amygdala. *Cell and Molecular Neurobiology*, *23*, 727–738.

Levin, J. M., Ross, M. H., Mendelson, J. H., Kaufman, M. J., Lange, N., Maas, L. C.,

et al. (1998). Reduction in BOLD fMRI response to primary visual stimulation following alcohol ingestion. *Psychiatry Research*, *82*, 135–146.

Lichter, D. G., & Cummings, J. L. (2001). *Frontal-subcortical circuits in psychiatric and neurological disorders*. New York: The Guilford Press.

Mann, K., Batra, A., Gunthner, A., & Schroth, G. (1992). Do women develop alcoholic brain damage more readily than men? *Alcoholism: Clinical and Experimental Research*, *16*, 1052–1056.

Marinkovic, K. (2004). Spatiotemporal dynamics of word processing in the human cortex. *Neuroscientist*, *10*, 142–152.

Marinkovic, K., Halgren, E., Klopp, J., & Maltzman, I. (2000). Alcohol effects on movement-related potentials: a measure of impulsivity? *Journal of Studies on Alcohol*, *61*, 24–31.

Marinkovic, K., Halgren, E., & Maltzman, I. (2001). Arousal-related P3a to novel auditory stimuli is abolished by moderately low alcohol dose. *Alcohol and Alcoholism*, *36*, 529–539.

Marinkovic, K., Halgren, E., & Maltzman, I. (2004). Effects of alcohol on verbal processing: An ERP study. *Alcoholism: Clinical and Experimental Research*, *28*, 415–423.

Martin, P. R., Nimmerrichter, A., Riddle, W. R., Welch, L. W., & Willcott, M. R. (1995). Brain proton magnetic resonance spectroscopy studies in recently abstinent alcoholics. *Alcoholism: Clinical and Experimental Research*, *19*, 1078–1082.

Maylor, E. A., Rabbitt, P. M., James, G. H., & Kerr, S. A. (1990). Comparing the effects of alcohol and intelligence on text recall and recognition. *British Journal of Psychology*, *81*, 299–313.

Maylor, E. A., Rabbitt, P. M., & Kingstone, A. (1987). Effects of alcohol on word categorization and recognition memory. *British Journal of Psychology*, *78*, 233–239.

Mazas, C. A., Finn, P. R., & Steinmetz, J. E. (2000). Decision-making biases, antisocial personality, and early-onset alcoholism. *Alcoholism: Clinical and Experimental Research*, *24*, 1036–1040.

McGue, M. (1999). The behavioral genetics of alcoholism. *Current Direction in Psychological Science*, *8*, 109–115.

McHugh, S. B., Deacon, R. M. J., Rawlins, J. N. P., et al. (2004). Amygdala and ventral hippocampus contribute differentially to mechanisms of fear and anxiety. *Behavioral Neuroscience*, *118*, 63–78.

Melgaard, B., Henriksen, L., Ahlgren, P., Danielsen, U. T., Sorensen, H., & Paulson, O. B. (1990). Regional cerebral blood flow in chronic alcoholics measured by single photon emission computerized tomography. *Acta Neurologica Scandinavica*, *82*, 87–93.

Mesulam, M.-M. (2000). Behavioral neuroanatomy. Large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specialization. In M.-M. Mesulam (Ed.), *Principles of behavioral and cognitive neurology* (pp. 1–120). New York: Oxford.

Miller, B. L., & Cummings, J. L. (1999). *The human frontal lobes: Functions and disorders*. New York: Guilford Press.

Miller, M. W. (1995). Generation of neurons in the rat dentate gyrus and hippocampus: Effects of prenatal and postnatal treatment with ethanol. *Alcoholism: Clinical and Experimental Research*, *19*, 1500–1509.

Monteiro, M. G., & Schuckit, M. A. (1988). Populations at high alcoholism risk: recent findings. *Journal of Clinical Psychiatry*, *49*, 3–7.

Moselhy, H. F., Georgiou, G., & Kahn, A. (2001). Frontal lobe changes in alcoholism: A review of the literature. *Alcohol and Alcoholism*, *36*, 357–368.

Mulvihill, L. E., Skilling, T. A., & Vogel-Sprott, M. (1997). Alcohol and the ability to inhibit behavior in men and women. *Journal of Studies on Alcohol*, *58*, 600–605.

Nagel, B. J., Schweinsburg, A. D., Phan, V., & Tapert, S. F. (2005). Hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Reseearch: Neuroimaging*, *139*, 181–190.

Nagoshi, C. T., & Wilson, J. R. (1989). Long-term repeatability of human alcohol metabolism, sensitivity and acute tolerance. *Journal of Studies on Alcohol*, *50*, 162–169.

Nagoshi, C. T., Wilson, J. R., & Rodriguez, L. A. (1991). Impulsivity, sensation seeking, and behavioral and emotional responses to alcohol. *Alcoholism: Clinical and Experimental Research*, *15*, 661–667.

Nagy, M. E., & Rugg, M. D. (1989). Modulation of event-related potentials by word repetition: the effects of inter-item lag. *Psychophysiology*, *26*, 431–436.

NIAAA. (1997). *Ninth special report to the US Congress on alcohol and health*. Bethesda, MD: NIAAA.

Nicolás, J. M., Catafau, A. M., Estruch, R., Lomeña, F. J., Salamero, M., Herranz, R., et al. (1993). Regional cerebral blood flow-SPECT in chronic alcoholism: Relation to neuropsychological testing. *Journal of Nuclear Medicine*, *34*, 1452–1459.

O'Neill, J., Cardenas, V. A., & Meyerhoff, D. J. (2001). Effects of abstinence on the brain: quantitative magnetic resonance imaging and magnetic resonance spectroscopic imaging in chronic alcohol abuse. *Alcoholism: Clinical and Experimental Research*, *25*, 1673–1682.

Ohman, A., & Soares, J. J. (1998). Emotional conditioning to masked stimuli: expectancies for aversive outcomes following nonrecognized fear-relevant stimuli. *Journal of Experimental Psychology: General*, *127*, 69–82.

Oscar-Berman, M. (2000). Neuropsychological vulnerabilities in chronic alcoholism. In A. Noronha, M. J. Eckardt & K. Warren (Eds.), *Review of NIAAA's neuroscience and behavioral research portfolio* (Vol. 34, pp. 437–471). Bethesda, MD: US Department of Health and Human Services.

Oscar-Berman, M., & Evert, D. L. (1997). Alcoholic Korsakoff's syndrome. In P. D. Nussbaum (Ed.), *Handbook of neuropsychology and aging* (pp. 201–215). New York: Plenum Press.

Oscar-Berman, M., & Hutner, N. (1993). Frontal lobe changes after chronic alcohol ingestion. In W. A. Hunt & S. J. Nixon (Eds.), *Alcohol-induced brain damage* (Vol. 22, pp. 121–156). Rockville, MD: NIAAA.

Oscar-Berman, M., & Schendan, H. E. (2000). Asymmetries of brain function in alcoholism: Relationship to aging. In L. Obler & L. T. Connor (Eds.), *Neurobehavior of language and cognition: Studies of normal aging and brain damage* (pp. 213–240). New York: Kluwer Academic.

Parsons, O. A. (1994). Neuropsychological measures and event-related potentials in alcoholics: Interrelationships, long-term reliabilities, and prediction of resumption of drinking. *Journal of Clinical Psychology*, *50*, 37–46.

Parsons, O. A. (1996). Alcohol abuse and alcoholism. In R. L. Adams, O. A. Parsons, J. L. Culbertson & S. J. Nixon (Eds.), *Neuropsychology for clinical practice* (pp. 175–201). Washington, DC: American Psychological Press.

Pentney, R. J., Mullan, B. A., Felong, A. M., & Dlugos, C. A. (2002). The total numbers of cerebellar granule neurons in young and aged Fischer 344 and

Wistar-Kyoto rats do not change as a result of lengthy ethanol treatment. *Cerebellum*, *1*, 79–89.

Peterson, J. B., Rothfleisch, J., Zelazo, P. D., & Pihl, R. O. (1990). Acute alcohol intoxication and cognitive functioning. *Journal of Studies on Alcohol*, *51*, 114–122.

Petrakis, I. L., Gonzalez, G., Rosenheck, R., & Krystal, J. H. (2002). Comorbidity of alcoholism and psychiatric disorders. *Alcohol Research and Health*, *26*, 81–89.

Pfefferbaum, A., Ford, J. M., White, P. M., & Mathalon, D. (1991). Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcoholism: Clinical Experimental Research*, *15*, 839–850.

Pfefferbaum, A., Horvath, T. B., Roth, W. T., Clifford, S. T., & Kopell, B. S. (1980). Acute and chronic effects of ethanol on event-related potentials. *Advvances in Experimental and Medical Biology*, *126*, 625–639.

Pfefferbaum, A., Lim, K. O., Desmond, J. E., & Sullivan, E. V. (1996). Thinning of the corpus callosum in older alcoholic men: A magnetic resonance imaging study. *Alcoholism: Clinical and Experimental Research*, *20*, 752–757.

Pfefferbaum, A., Lim, K. O., Zipursky, R. B., Mathalon, D. H., Rosenbloom, M. J., Lane, B., et al. (1992). Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcoholism: Clinical and Experimental Research*, *16*, 1078–1089.

Pfefferbaum, A., Rosenbloom, M., Serventi, K. L., & Sullivan, E. V. (2002). Corpus callosum, pons, and cortical white matter in alcoholic women. *Alcoholism: Clinical and Experimental Research*, *26*, 400–406.

Pfefferbaum, A., & Sullivan, E. V. (2002a). Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *NeuroImage*, *15*, 708–718.

Pfefferbaum, A., & Sullivan, E. V. (2002b). Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *NeuroImage*, *15*, 708–718.

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., & Lim, K. O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism: Clinical and Experimental Research*, *21*, 521–529.

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., Shear, P. K., Rosenbloom, M. J., & Lim, K. O. (1995). Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcoholism: Clinical and Experimental Research*, *19*, 1177–1191.

Phillips, S. C., Harper, C. G., & Kril, J. (1987). A quantitative histological study of the cerebellar vermis in alcoholic patients. *Brain*, *110*, 301–314.

Pihl, R. O., Peterson, J. B., & Lau, M. A. (1993). A biosocial model of the alcohol-aggression relationship. *Journal of Studies on Alcohol (Supplement)*, *11*, 128–139.

Pitkänen, A., Pikkarainen, M., Nurminen, N., & Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampus formation, perirhinal cortex, and postrhinal cortex in rat. A review. In H. E. Scharfman, R. Schwarcz, & M. P. Witter (Eds.), *The parahippocampal region: Implications for neurological and psychiatric diseases* (Vol. 911, pp. 369–391). New York: New York Academy of Sciences.

Porjesz, B., & Begleiter, H. (1985). Human brain electrophysiology and alcoholism. In R. E. Tarter & D. H. Van Thiel (Eds.), *Alcohol and the brain* (pp. 139–182). New York: Plenum Press.

Porjesz, B., & Begleiter, H. (1996). Effects of alcohol on electrophysiological activity

of the brain. In H. Begleiter & B. Kissin (Eds.), *The pharmacology of alcohol and alcohol dependence* (pp. 207–247). New York: Oxford University Press.

Ratti, M. T., Bo, P., Giardini, A., & Soragna, D. (2002). Chronic alcoholism and the frontal lobe: Which executive functions are impaired? *Acta Neurologica Scandinavica*, *105*, 276–281.

Reed, T. E. (1985). The myth of "the average alcohol response". *Alcohol*, *2*, 515–519.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., et al. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association*, *264*, 2511–2518.

Richardson, M. P., Strange, B. A., & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interactions. *Nature Neuroscience*, *7*, 278–285.

Ridderinkhof, K. R., de Vlugt, Y., Bramlage, A., Spaan, M., Elton, M., Snel, J., et al. (2002). Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science*, *298*, 2209–2211.

Rodriguez Holguin, S., Porjesz, B., Chorlian, D. B., Polich, J., & Begleiter, H. (1999). Visual P3a in male alcoholics and controls. *Alcoholism: Clinical and Experimental Research*, *23*, 582–591.

Roebuck, T. M., Mattson, S. N., & Riley, E. P. (1998). A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcoholism: Clinical and Experimental Research*, *22*, 339–344.

Rohrbaugh, J. W., Stapleton, J. M., Parasuraman, R., Zubovic, E. A., Frowein, H. W., Varner, J. L., et al. (1987). Dose-related effects of ethanol on visual sustained attention and event-related potentials. *Alcohol*, *4*, 293–300.

Rolls, E. T. (2000). Precis of the brain and emotion. *Behavioral and Brain Sciences*, *23*, 177–234.

Rourke, S. B., & Løberg, T. (1996). The neurobehavioral correlates of alcoholism. In I. Grant & S. J. Nixon (Eds.), *Neuropsychological assessment of neuropsychiatric disorders* (2nd ed., pp. 423–485). New York: Oxford University Press.

Sah, P., Faber, E. S., Lopez De Armentia, M., & Power, J. (2003). The amygdaloid complex: anatomy and physiology. *Physiological Review*, *83*, 803–834.

Schmahmann, J. D. (1997). *The cerebellum and cogniton* (Vol. 41). San Diego: Academic Press.

Schmahmann, J. D. (2000). The role of the cerebellum in affect and psychosis. *Journal of Neurolinguistics*, *13*, 189–214.

Schuckit, M. A. (1983). The genetics of alcoholism. In B. Tabakoff, P. B. Sutker, & C. L. Randall (Eds.), *Medical and social aspects of alcohol abuse* (pp. 31–46). New York: Plenum Press.

Seifritz, E., Bilecen, D., Hanggi, D., Haselhorst, R., Radu, E. W., Wetzel, S., et al. (2000). Effect of ethanol on BOLD response to acoustic stimulation: implications for neuropharmacological fMRI. *Psychiatry Research*, *99*, 1–13.

Seitz, D., Widmann, U., & Seeger, U. (1999). Localized protein magnetic resonance spectroscopy of the cerebellum in detoxifying alcoholics. *Alcoholism: Clinical and Experimental Research*, *23*, 158–163.

Shear, P. K., Jernigan, T. L., & Butters, N. (1994). Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics. *Alcoholism: Clinical and Experimental Research*, *18*, 172–176.

Simonov, P. V. (1986). *The emotional brain*. New York: Plenum Press.

Smith, M. E., & Halgren, E. (1987). Event-related potentials during lexical decision: effects of repetition, word frequency, pronounceability, and concreteness. *Electroencephalography and Clinical Neurophysiology (Supplement)*, *40*, 417–421.

Sullivan, E. V. (2000). Neuropsychological vulnerability to alcoholism: Evidence from neuroimaging studies. In A. Noronha, M. Eckardt, & K. Warren (Eds.), *Review of NIAAA's neuroscience and behavioral research* (Vol. 34, pp. 473–508). Bethesda, MD: NIAAA.

Sullivan, E. V. (2003). Compromised pontocerebellar and cerebellothalamocortical systems: Speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. *Alcoholism: Clinical and Experimental Research*, *27*, 1409–1419.

Sullivan, E. V., Harding, A. J., Pentney, R., Dlugos, C., Martin, P. R., Parks, M. H., et al. (2003). Disruption of frontocerebellar circuitry and function in alcoholism. *Alcoholism: Clinical and Experimental Research*, *27*, 301–309.

Tapert, S. F., Brown, G. G., Kindermann, S. S., Cheung, E. H., Frank, L. R., & Brown, S. A. (2001). fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clinical and Experimental Research*, *21*, 236–245.

Teo, R. K., & Ferguson, D. A. (1986). The acute effects of ethanol on auditory event-related potentials. *Psychopharmacology*, *90*, 179–184.

Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., et al. (1998). Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, *55*, 967–972.

Uhl, G. R., & Grow, R. W. (2004). The burden of complex genetics in brain disorders. *Archives of General Psychiatry*, *61*, 223–229.

Victor, M. (1992). The effects of alcohol on the nervous system. In C. S. Lieber (Ed.), *Medical and nutritional complications of alcoholism: Mechanisms and management* (pp. 413–457). New York: Plenum Press.

Virkkunen, M., & Linnoila, M. (1993). Brain serotonin, type II alcoholism and impulsive violence. *Journal of studies on Alcohol (Supplement)*, *11*, 163–169.

Volkow, N. D., Hitzemann, R., Wang, G. J., Fowler, J. S., Burr, G., Pascani, K., et al. (1992). Decreased brain metabolism in neurologically intact healthy alcoholics. *American Journal of Psychiatry*, *149*, 1016–1022.

Volkow, N. D., Hitzemann, R., Wang, G. J., Fowler, J. S., Burr, G., Pascani, K., et al. (1995). Monitoring the brain's response to alcohol with positron emission tomography. *Alcohol Health and Research World*, *19*, 296–299.

Volkow, N. D., Mullani, N., Gould, L., Adler, S. S., Guynn, R. W., Overall, J. E., et al. (1988). Effects of acute alcohol intoxication on cerebral blood flow measured with PET. *Psychiatry Research*, *24*, 201–209.

Wang, G. J., Volkow, N. D., Fowler, J. S., Franceschi, D., Wong, C. T., Pappas, N. R., et al. (2003). Alcohol intoxication induces greater reductions in brain metabolism in male than in female subjects. *Alcoholism: Clinical and Experimental Research*, *27*, 909–917.

Wang, G. J., Volkow, N. D., Roque, C. T., Cestaro, V. L., Hitzemann, R. J., Cantos, E. L., et al. (1993). Functional importance of ventricular enlargement and cortical atrophy in healthy subjects and alcoholics as assessed with PET, MR imaging, and neuropsychologic testing. *Radiology*, *186*, 59–65.

Wang, L., McCarthy, G., Song, A. W., & LaBar, K. S. (2005). Amygdala activation to sad pictures during high-field (4 tesla) functional magnetic resonance imaging. *Emotion*, *5*, 12–22.

West, J. R., & Pierce, D. R. (1986). Perinatal alcohol exposure and neuronal damage. In J. R. West (Ed.), *Alcohol and brain development* (pp. 120–157). New York: Oxford University Press.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience*, *18*, 411–418.

White, A. M., Matthews, D. B., & Best, P. J. (2000). Ethanol, memory, and hippocampal function: A review of recent findings. *Hippocampus*, *10*, 88–93.

Wilson, G. T., & Niaura, R. (1984). Alcohol and the disinhibition of sexual responsiveness. *Journal of Studies on Alcohol*, *45*, 219–224.

Winston, J. S., O'Doherty, J., & Dolan, R. J. (2003). Common and distinct neural responses during direct and incidental processing of multiple facial emotions. *Neuroimage*, *20*, 84–97.

Wise, R. A. (1988). Psychomotor stimulant properties of addictive drugs. *Annals of the New York Academy of Sciences*, *537*, 228–234.

Wuethrich, B. (2001). Does alcohol damage female brains more? *Science*, *291*, 2077–2079.