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Commentary on "Increased MCP-1 and Microglia in Various regions of Human Alcoholic Brain"

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Alcoholism–the chronic and excessive consumption of alcohol–is a syndrome characterized by untoward somatic and nervous system sequelae. Often unrecognized is the extent of the neurobehavioral deficits of alcoholism and their impact on the well-being of the individual. Further, the mechanism of alcoholism-induced neuropathology is not fully understood. Among possible causative factors are neurotoxicity of the ethanol molecule itself or its metabolic products (e.g., acetaldehyde), nutritional deficiencies (e.g., B vitamins), head trauma, and repeated withdrawals. The article by He and Crews poses yet another mechanism – alcohol-induced neuroinflammation.

This review of chronic alcohol consumption as a substrate of neurodegeneration provides a context for our commentary on the clinical and basic neuroscience significance of the postmortem study of human alcoholic brains by He and Crews (this issue). Toward this end, we review brain structure, function, and chemistry studies that have led to the common belief of the neurodegenerative effects of alcoholism. We attempt to distinguish between evidence for clinically detected abnormalities as attributable to permanent or transient neural damage and whether such damage is pervasive or restricted. Finally, we proffer ideas for further neuropathological studies to explicate findings from in vivo longitudinal studies conducted in human alcoholism and animal models.

A perspective on the clinical significance of alcohol-induced neuroinflammation as a potential mechanism of alcohol-induced neuropathology requires an appreciation of the terms used (or misused). According to Adams and Victor (Adams and Victor, 1993), "*Atrophy* specifies a gradual decay and loss of neurons, leaving in their wake no degradative products and only a sparsely cellular, fibrous gliosis while *degeneration* refers to a more rapid process of neuronal, myelin or tissue breakdown with resulting degradative products that evoke a more vigorous reaction of phagocytosis and cellular gliosis" (page 921). Evidence for permanent loss of neurons in alcoholism is sparse, and alcohol-induced damage to brain tissue can usually be attributable to neurodegenerative rather than atrophic processes. When neuronal death does occur, it is usually considered to be necrosis, which "occurs when neurons are damaged by a trauma or metabolic injury and typically involves the concurrent death of groups of adjacent cells. Cells undergoing necrosis initially swell and their internal components, or orgenelles, break down. The cells eventually rupture and spill debris that leads to local inflammation" (page 177) (Goodlett and Horn, 2001). Figure 1 present examples of presumed acute edematous and

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chronic necrotic mammillary bodies of two men diagnosed with Wernicke's encephalopathy (Sullivan and Pfefferbaum, 2008) and a rat model of pyrithiamine-induced WE (Pfefferbaum, et al., 2007).

A potential mechanism of the neurotoxic effects of chronic excessive alcohol consumption

The study by He and Crews (2008) is an hypothesis-driven work with the objective of isolating a potential mechanism of neural damage caused by extensive, chronic alcohol consumption. To this end, the authors obtained human brain tissue of alcoholics and moderate drinking controls from the New South Wales Tissue Resource Center, which provided a clinical characterization through systematic postmortem "interview" (Harper, et al., 2003). Markers of inflammation sought were proinflammatory cytokines, specifically, monocyte chemoattractant protein 1 (MCP-1, also known as CCL2) and microglia. MCP-1 is a particularly promising candidate because it has been shown to regulate alcohol consumption in mice (Blednov, et al., 2005). Perhaps relevant to the human condition, the regulation of drinking was limited to female rats; although controversial (c.f., Hommer, et al., 2001; Pfefferbaum, et al., 2001), some studies have found that women have radiological evidence for great brain damage from chronic alcoholism than men (e.g., Hommer, 2003; Mann, et al., 2005; for review of sex differences in alcohol use disorders Witt, 2007). MCP-1 is also involved in demyelination in a variety of experimental animal models (Kim and Perlman, 2005). MCP-1 protein levels were measured in brain homogenate in the ventral tegmental area (VTA), substantia nigra (SN), hippocampus, and amygdala and found to be elevated in alcoholics relative to controls. Thus, in all regions examined, albeit not the entire brain, MCP-1 levels were abnormally high in alcoholics. In their immunohistochemistry analysis seeking microglial markers of inflammation in cingulate cortex, amygdala, VTA, and brainstem, the authors found differential regional patterns depending on marker type: ionized calcium binding adaptor protein-1 (Iba-1) and Glucose transporter-5 ($GluT_5$). Both markers have a microglial-restricted expression confirmed with RNA analysis of rat brain-derived primary-cultured cells (Imai, et al., 1996) and immunocytochemistry of adult rat brain sections for Iba-1 (Ito, et al., 1998) and immunocytochemistry of human tissue for $GluT_5$ (Horikoshi, et al., 2003; Payne, et al., 1997; Sasaki, et al., 2003). Enhanced expression of Iba-1 in neuroinflammatory processes has been demonstrated in models of ischemia (Ito, et al., 2001), hippocampal denervation (Babcock, et al., 2003), Parkinson's disease (Wada, et al., 2006), stress (Frank, et al., 2007), and aging (Choi, et al., 2007; Hwang, et al., 2008). In the He and Crews study, although neither marker detected greater microglial density in the alcoholics than the controls in the amygdala, both markers revealed signs of greater microglial presence in the alcoholic cingulate cortex, and $GluT_5$ detected such presence in VTA and midbrain structures. These positive signs of neuroinflammation provide cross-sectional support for their mechanistic role in alcoholism-related neurodegeneration. That the neurodegenerative effects had a profile of action suggests that selective brain structures carry a special vulnerability to the throes of alcoholism.

As most worthy research endeavors do, this study raises as many questions as it answers. To wit: What other brain regions might be vulnerable or resilient? Why should alcohol excesses have differential regional effects? Can identification of steps in the neurodegenerative cascade to cell death (which was not examined by He and Crews) lead to mechanisms of arrest or reversal of damage prior to neural death? Can this cascade of events, associated with very high doses of alcohol, whether consumed in massive binges or chronically over a lifetime, contribute to remodeling brain systems to be dependent on alcohol? What roles do genetics, family history, or historical events (e.g., age of alcoholism onset, bouts of nutritional deficiency, number of withdrawals) play in the ultimate outcome observed postmortem? Given that neuroinflammatory processes are capable of insulting both gray and white matter, are clinically

significant sequelae of alcoholism necessarily a result of neuronal death, or alternatively, can they arise from “incomplete” lesions of white matter or cell processes?

Alcohol-induced neurodegeneration: Evidence from neuropathological, neuroelectrophysiological, neuropsychological, and neuroradiological human studies

Neuropathological evidence

Neuropathological studies of chronic alcoholism indicate that loss of neurons is selective to frontal cortex (Courville, 1955; Harper and Kril, 1990) with little evidence for widespread cell loss (Harper, 1998; Harper, et al., 1987; Kril and Harper, 1989). Although more recent work using TUNEL staining, an indicator of damaged DNA and potentially indicative of apoptosis, reveals TUNEL-positive cells in the superior frontal cortex of human alcoholics, rarely observed in control brains, morphological and immunohistochemical evidence suggests that the majority of TUNEL-stained cells were glial, not neuronal (Ikegami, et al., 2003).

Subcortical gray matter has also been examined. Although neuronal dysmorphology can be present in hippocampus (Harding, et al., 1997; Kril, et al., 1997), thalamus (Harding, et al., 2000), and cerebellum (Pentney, 1993; Phillips, et al., 1987; Torvik and Torp, 1986), neuronal loss is rarely reported in postmortem human tissue. “Atrophy” of the anterior vermis and adjoining portions of the anterior lobes of the cerebellum was described in alcoholic human patients as early as the 1950's (Victor, et al., 1959), and reduced Purkinje cell density was reported with histopathological examination of the anterior superior segment of the cerebellar vermis of human alcoholics (Phillips, et al., 1987; Torvik and Torp, 1986). More recent work, however, suggests that Purkinje cell loss in the vermis occurs only in chronic alcoholics with cerebellar dysfunction (Baker, et al., 1999).

With the exception of the frontal lobes, evidence for neuronal loss in response to chronic alcoholism is scarce. By contrast, postmortem studies of brains of human alcoholics often report that white matter is especially affected (Badsberg-Jensen and Pakkenberg, 1993; De la Monte, 1988; Harper and Kril, 1991; Harper and Kril, 1994) regardless of sex (Harper, et al., 1990). Abnormalities identified in white matter on postmortem examination include volume shrinkage, demyelination, loss of myelinated fibers, and axonal deletion possibly arising from regional neuronal loss (Alling and Bostrom, 1980; Harper, et al., 1988; Harper and Kril, 1989; Kril, et al., 1997). The corpus callosum is also affected (Harper and Kril, 1988; Tarnowska-Dziduszko, et al., 1995), especially in alcoholics who have experienced nutritional deficiencies. In their most extreme forms, these white matter conditions can be life-threatening and are associated with Marchiafava-Bignami disease and central pontine myelinolysis (Charness, 1993; Victor, et al., 1989).

Neuroelectrophysiological evidence

The P300 component of the event-related potential (ERP) elicited in behavioral paradigms requiring response inhibition to prepotent stimuli (e.g., NOGO stimuli in the GO/NOGO paradigm) is commonly diminished in recovering alcoholics (Ceballos, et al., 2003; Cohen, et al., 1997; Ford, et al., 1991; Hada, et al., 2000; Rodriguez Holguin, et al., 1999) and also nonalcoholic children of alcoholic fathers (Cohen, et al., 1997; Rodriguez Holguin, et al., 1999). This electrophysiological measure of response inhibition has a frontal scalp distribution and suggests a focal eminence of the alcoholism-related impairment (Bokura, et al., 2001; Filipovic, et al., 1999; Pfefferbaum and Ford, 1988; Pfefferbaum, et al., 1985; Shibata, et al., 1997; Shibata, et al., 1998). Given that response inhibition is controlled by frontal systems, appropriate response inhibition to a NOGO stimulus requires functionally intact frontally-

based corticocortical pathways, which are affected in alcoholics and may even sustain neuronal loss (Harper, et al., 2003).

Neuropsychological evidence

The acute behavioral effects of alcohol intoxication are well-known and recognized as ataxia of gait, slurred speech, prolonged reaction time, poor memory consolidation, impaired emotional modulation, and compromised judgment. Chronic alcoholics can continue to exhibit a subset of this constellation of cognitive and motor impairment, often in a milder form, even after a month's abstinence from alcohol and without alcohol on board. Functions tend to be impaired but not completely lost in sober “uncomplicated” alcoholics (Victor, et al., 1989). Typically, the processes affected are visuospatial abilities, executive functions, and gait and balance (for reviews, Fein, et al., 1990; Moselhy, et al., 2001; Oscar-Berman, 2000; Oscar-Berman, et al., 2004; Sullivan, 2000), evidenced in both alcoholic men (Sullivan, et al., 2000) and women (Sullivan, et al., 2002). Executive functions affected include working memory, problem solving, temporal ordering, response inhibition, and psychomotor speed (Johnson-Greene, et al., 1997; Nixon, et al., 2002; Oscar-Berman and Hutner, 1993; Sullivan, 2000). These symptoms characterize impairment arising from lesions of cerebellum, frontostriatal circuitry (Sullivan, et al., 2003), and frontolimbic circuitry and occasionally have been formally correlated with measurements of local brain structure (Rosenbloom, et al., 2007), metabolite concentrations (Bendszus, et al., 2001; Meyerhoff, et al., 2004), or glucose metabolism (Adams, et al., 1993; Gilman, et al., 1996; Wang, et al., 1993).

Neuroradiological evidence

CT and MRI

Early observations using computerized tomography (CT) identified “shrinkage” in the brains of chronic alcoholics (Cala, et al., 1981) that were later verified with higher resolution imaging based on magnetic resonance (MR) techniques. Cross-sectional MR imaging (MRI) studies of chronically dependent alcoholic human adults, without obvious complications from nutritional deficiencies or hepatic disorders, demonstrated a comprised cortical mantle with thinner gyri and wider sulci than controls (for reviews Oscar-Berman and Marinkovic, 2007; Sullivan and Pfefferbaum, 2005). Specific brain regions affected by chronic alcohol exposure and described by structural MRI include cortical gray and white matter (Jernigan, et al., 1991; Pfefferbaum, et al., 1992), particularly prefrontal areas in older alcoholic individuals (Cardenas, et al., 2007; Pfefferbaum, et al., 1997), mammillary bodies (Davila, et al., 1994; Shear, et al., 1996; Sullivan, et al., 2000), anterior hippocampus (Agartz, et al., 1999; Sullivan and Marsh, 2003; Sullivan, et al., 1995), thalamus (De Bellis, et al., 2005; Sullivan, et al., 2003), pons (Pfefferbaum, et al., 2002; Sullivan, 2003), and cerebellum (De Bellis, et al., 2005; Sullivan, et al., 2000). A subset of these and other studies have tested the relationship between regional brain volume and performance on specific neuropsychological tests and have been successful in demonstrating associations or even double dissociations, for example, between olfactory discrimination and thalamic volume (Shear, et al., 1992), postural stability and cerebellar vermis (Sullivan, et al., 2000; Sullivan, et al., 2006), and perseverative errors in problem solving and prefrontal cortical volume (Chanraud, et al., 2007).

In search of clues to factors that either cause or exacerbate the untoward effect of chronic alcohol consumption, we noted a graded effect in ostensibly “uncomplicated” alcoholics, that is, those without clinically obvious symptoms of any of the serious medical conditions commonly associated with alcoholism (e.g., Wernicke's Encephalopathy (WE), Korsakoff's Syndrome (KS), alcoholic dementia, hepatic encephalopathy, cirrhosis). When compared with healthy controls, uncomplicated alcoholics had mild to moderate volume deficits and alcoholics with KS and historical evidence for WE had moderate to severe volume deficits in

the mammillary bodies, hippocampus, thalamus, cerebellum, and pons (Sullivan and Pfefferbaum, 2008). That the uncomplicated alcoholics showed the same pattern of focal brain volume deficits as did the KS alcoholics but in a milder form implicates a nutritional deficiency component, likely thiamine, as contributing to the constellation of brain regions affected (Butters, 1981; Thomson, 2000). Whether bouts of subclinical vitamin deficiencies fully account for or simply contribute to regional brain volume shrinkage in alcoholism remains controversial (Impeduglia, et al., 1987; Martin, et al., 2003; Pfefferbaum, et al., 2007; Thomson, 2000).

MR Spectroscopy (MRS)

MRS enables in vivo investigation of the biochemical composition of the brain and how the brain's principal proton metabolites are altered by chronic alcohol exposure. The proton spectrum provides quantitative measures of vital brain metabolites: N-acetyl compounds primarily N-acetyl-aspartate (NAA), a marker of living, mature neurons; creatine +phosphocreatine (Cr), a reflection of high-energy phosphate metabolism; choline (Cho), an index of membrane turnover; myo-inositol (mI), an index of gliosis; and the neurotransmitter glutamate. An assumption, then, is that decline or deficits in gray matter NAA should reflect neuronal damage or loss, as it apparently does in conditions like Alzheimer's disease (Adalsteinsson, et al., 1998), which is marked by known neuronal death (Braak and Braak, 1994). Other metabolites, including Cho and mI, may reflect neuroinflammatory processes.

Exemplary studies report abnormally low levels of NAA in frontal (Bendszus, et al., 2001; Fein, et al., 1994; Jagannathan, et al., 1996) and cerebellar (Bendszus, et al., 2001; Jagannathan, et al., 1996; Mann, et al., 1998) regions in alcoholics than controls, suggesting neuronal loss. A comparison between currently drinking and recently abstinent (3 week) alcoholics found only a volume deficit in frontal white matter in the former, but no difference in levels of NAA, Cr, or Cho (O'Neill, et al., 2001). Another group reported that NAA was nearly 15% lower in a frontal white matter region and mI was higher in frontal and parietal regions in recently abstinent (4 weeks) alcoholics than controls (Schweinsburg, et al., 2000). An NAA deficit in frontal white matter and elevated parietal gray matter Cr and mI was observed to be especially strong in older alcoholics (Meyerhoff, et al., 2004).

MR Diffusion Tensor Imaging (DTI)

Rigorous study of white matter integrity is enhanced by examination with DTI, which permits characterization of myelin integrity and axon density (Basser and Jones, 2002; Le Bihan, 2003; Moseley, et al., 1990). In alcoholism, microstructural white matter abnormalities involve callosal and pericallosal degradation that occur in men (Pfefferbaum and Sullivan, 2005; Pfefferbaum, et al., 2000) and women (Pfefferbaum and Sullivan, 2002). These abnormalities correlate with working memory, visuospatial ability, and gait and balance (Pfefferbaum, et al., 2006) and demonstrated an age-alcohol interaction (Pfefferbaum, et al., 2006). More recently, we showed that FA deficits are widespread throughout left and right hemispheres in men and women (Pfefferbaum, et al., 2006). This widespread distribution of white matter microstructural compromise contrasts with the regional-specific deficits seen in nutritional deficiency syndromes that can accompany alcoholism. Results from rodent models of alcoholism and thiamine deficiency suggest that some white matter pathology in alcoholism is due to the neurotoxicity of alcohol per se (He, et al., 2007; Langlais and Savage, 1995; Pfefferbaum, et al., 2006; Zimatkin and Zimatkina, 1996).

Evidence for recovery with abstinence from alcohol

From the earliest CT studies to current MRI studies aimed at tracking evidence for brain structural recovery, positive support for at least partial reversal of brain tissue shrinkage with

abstinence from alcohol (CT: Cala, et al., 1983; Carlen, et al., 1986; Carlen, et al., 1984) (MRI: Cardenas, et al., 2007; Pfefferbaum, et al., 1995; Pfefferbaum, et al., 1998). We assume that the shrinkage with drinking does not necessarily reflect "loss," nor does the tissue expansion with abstinence reflect neurogenesis. Rather, the controlled longitudinal structural imaging studies likely reflect non-neuronal loss and neuronal cell body and process shrinkage.

To account for changes in brain tissue volume over the course of alcoholism, through bouts of drinking and abstinence, Carlen posed a two factor process, whereby one process reflected shrinkage without cell death thereby permitting volume change (up or down), and the other reflected true, irreversible neuronal cell death (Carlen, et al., 1984). That brain volume can increase and that this increase predicts improvement on neuropsychological test performance (Rosenbloom, et al., 2007; Sullivan, et al., 2000) again supports the contention that little neuronal death occurs with alcoholism. Recovery of NAA, the spectroscopic marker of neuronal integrity, can also occur and has been documented in frontal lobes over short-term supervised abstinence (Bendszus, et al., 2001) and in cerebellum over longer-term abstinence (Parks, et al., 2002) with complementary improvement in cognitive and motor performance. Higher mI, the spectroscopic marker of glia, observed in the anterior cingulate gyrus of recently detoxified alcoholics is not observed in longer-term sober alcoholics or controls (Schweinsburg, et al., 2001). Probably, low NAA levels reflect neurodegeneration without cell death, and increases with abstinence may reflect healing without cell generation. Further, alcohol-related increases in mI together with perturbation of NAA levels prominent in white matter support the possibility that white matter even more than gray matter is affected by alcoholism, a conclusion embraced in human neuropathological studies (De la Monte, 1988; Harper, et al., 2003).

Axonal (Wallerian) degeneration can lead to a permanent reduction in white matter volume. Consistent with these results are molecular studies of human brains that report expression of genes encoding myelin proteins (Lewohl, et al., 2000; Mayfield, et al., 2002) and actual levels of myelin-associated proteins as being low in alcoholic relative to control cases (Hasin, et al., 2006; Lewohl, et al., 2005). Frequent withdrawals from alcohol may also contribute to disruption of white matter integrity (Phillips, et al., 1987; Sullivan, et al., 1996). Specific white matter structures of the brain, such as the corpus callosum, are particularly affected by alcoholism (Harper and Kril, 1988; Hommer, et al., 1996; Pfefferbaum, et al., 1996). The precise structural changes underlying the white matter volume shrinkage, restoration with alcohol abstinence, and disruption of microstructural integrity remain unclear, but in vivo DTI studies (Pfefferbaum, et al., 2006; Pfefferbaum, et al., 2006; Pfefferbaum and Sullivan, 2002; Pfefferbaum and Sullivan, 2005; Pfefferbaum, et al., 2000) implicate compromise of both myelin and axonal integrity and may explain why tissue volume recovery appears incomplete with abstinence. Definitive pathology accounting for reversible brain shrinkage remains unidentified, indicating the need for further investigation of the potential interaction of alcohol exposure pattern, withdrawal experience, and nutritional deficiency in white matter pathology.

How He and Crews fill a lacuna of evidence for alcoholism neurotoxicity

The hypothesis tested by He and Crews was that alcohol induces inflammatory processes in the brain leading to neurodegeneration. To the extent that He and Crews sought to demonstrate an overly active immune response in the brains of alcoholics compared with controls, they were successful. Greater expression of MCP-1, Iba-1, or $GluT_5$ in several brain regions of alcoholics relative to controls supports the concept that neuroinflammation occurs in response to chronic and excessive alcohol consumption.

That neuroinflammation may lead to neurodegeneration is supported by several converging lines of evidence. Neuroinflammation is a feed-forward/feed-back process. For example, an immune reaction primes microglia to activate proinflammatory cytokines (e.g., IL1β and TNFα), which in turn stimulate microglia to produce MCP-1, which in turn leads to excessive production of proinflammatory cytokines, and potentially neurodegeneration (Qin, et al., 2007). Systemic cytokines, particularly TNFα, may enter the brain to initiate the inflammatory process (Qin, et al., 2007) and lead to neuronal loss by increasing brain glutamate levels (Zou and Crews, 2005). Alcohol may also modify the glutamatergic system (Krystal, et al., 2003; Melendez, et al., 2005), but direct evidence for a hyperglutamatergic state in chronic alcoholism is lacking. Significant clues to the conditions sufficient to produce a hyperglutamatergic state derives from animal studies, indicating a dramatic increase in extracellular glutamate in the striatum during withdrawal from alcohol in chronically treated rats but not during alcohol treatment itself (Rossetti and Carboni, 1995). Whether withdrawal with related neurological signs is a necessary condition for the change in glutamatergic state remains to be established. Future in vivo MRS studies focusing on additional excitotoxic and inflammatory markers, notably glutamate, may be revealing of locus and mechanism of alcohol neurotoxicity and even neuronal death.

Another untoward outcome of excessive alcohol consumption on the brain is compromise of neurovascular health (Hillbom and Kaste, 1990; Regan, 1990). Epidemiological studies in Europe, China, and the U.S. indicate an undeniable increased risk of ischemic or hemorrhagic stroke in men and women who declare drinking, on average, more than 21 drinks per week or more than 3 drinks per day. Although some reports suggest a protective effect of low drinking (no more that 1 drink per day for women and no more than 2 drinks per day for men) from ischemic stroke (Elkind, et al., 2006; Reynolds, et al., 2003), a 10-year prospective study of 64,338 Chinese men found little evidence for such protection but did note a linear relation between greater number of drinks consumed and higher relative risk for stroke and mortality from stroke (Bazzano, et al., 2007). It has been speculated that alcohol-induced stroke and inflammation may be stimulated or exacerbated by alcohol-induced injury to the blood brain barrier (BBB), which includes brain microvascular endothelial cells (BMVEC) and astrocytes (Haorah, et al., 2007). To examine this possibility, BMVEC, harvested from human epileptics during temporal lobe tissue resection, were exposed to alcohol for 2-48 hours (Haorah, et al., 2008). Through astrocytic secretion (Haorah, et al., 2008) or oxidative stress (Haorah, et al., 2007), alcohol treatment increased metalloproteinase activity; also observed was a parallel decrease in the collagen content of the BMVEC's basement membrane, the essential component of the BBB. This experiment indicates either oxidative stress or glial activation as contributing to BBB injury, which in turn could be a potential cause of stroke in alcoholism.

The in vivo, postmortem, and animal studies of chronic alcohol consumption indicate the importance of pursuing evidence for alcohol's neurotoxic effect on white matter, which can also sustain damage through neuroinflammatory processes. Although not yet established in alcoholism, there is evidence that neuroinflammation can selectively harm white matter. The “Father of Microglia,” Pio del Rio-Hortega, characterized microglial response to brain lesions describing “fountains of microglia” in the corpus callosum and other perinatal white matter (del Rio-Hortega and Penfield, 1892). Additionally, the extent of axonal damage in the primary demyelinating lesion of multiple sclerosis patients is associated with the number of activated microglia (Neumann, 2003). Potential microglial-mediated vehicles of damage to white matter include MCP-1, shown to be involved in demyelination in a variety of experimental animal models (Kim and Perlman, 2005); cytokines, such as IL-1, which result in reversible demyelination of axons (Ferrari, et al., 2004; Hartung, et al., 1992); and potentiation of glutamate release through impairment of glutamate uptake and reduction in the expression of glutamate transporters (Matute, et al., 2007; Matute, et al., 2006). These leads should serve to

generate testable hypotheses about alcohol's role in mediating neuroinflammation-induced white matter degeneration.

Significance of basic research on alcoholism to medicine and society

According to the 2001-2 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) survey, more than 20% of men, age 18 to 29, met criteria for a diagnosable alcohol use disorder (AUD): 9.3% Alcohol Abuse and 13% Alcohol Dependence. The lower prevalence in women and a declining prevalence with older age reduce the population-wide mean prevalence of an AUD in the past year to less than 10% (Grant, et al., 2004). The socioeconomic, health, and mortality costs of alcohol use in the US, whether diagnosed as an AUD or not, exceed $184 billion and have increased by 25% over estimates made for 1992 (Harwood, 2000). Alcoholism is pervasive in medical settings, estimated as upwards of 30% in university hospitals and 50% in Veterans hospitals (Beresford, et al., 1990), and often undetected, ignored, and under-treated despite its being a treatable condition. Surely, isolating specific mechanisms of alcoholism neurotoxicity is essential and carries the hope of stemming its adverse affects on brain structure and function and identifying targets for pharmacological therapy, whether for arrest, amelioration, or reversal of damage or for reduction of craving or of dependency.

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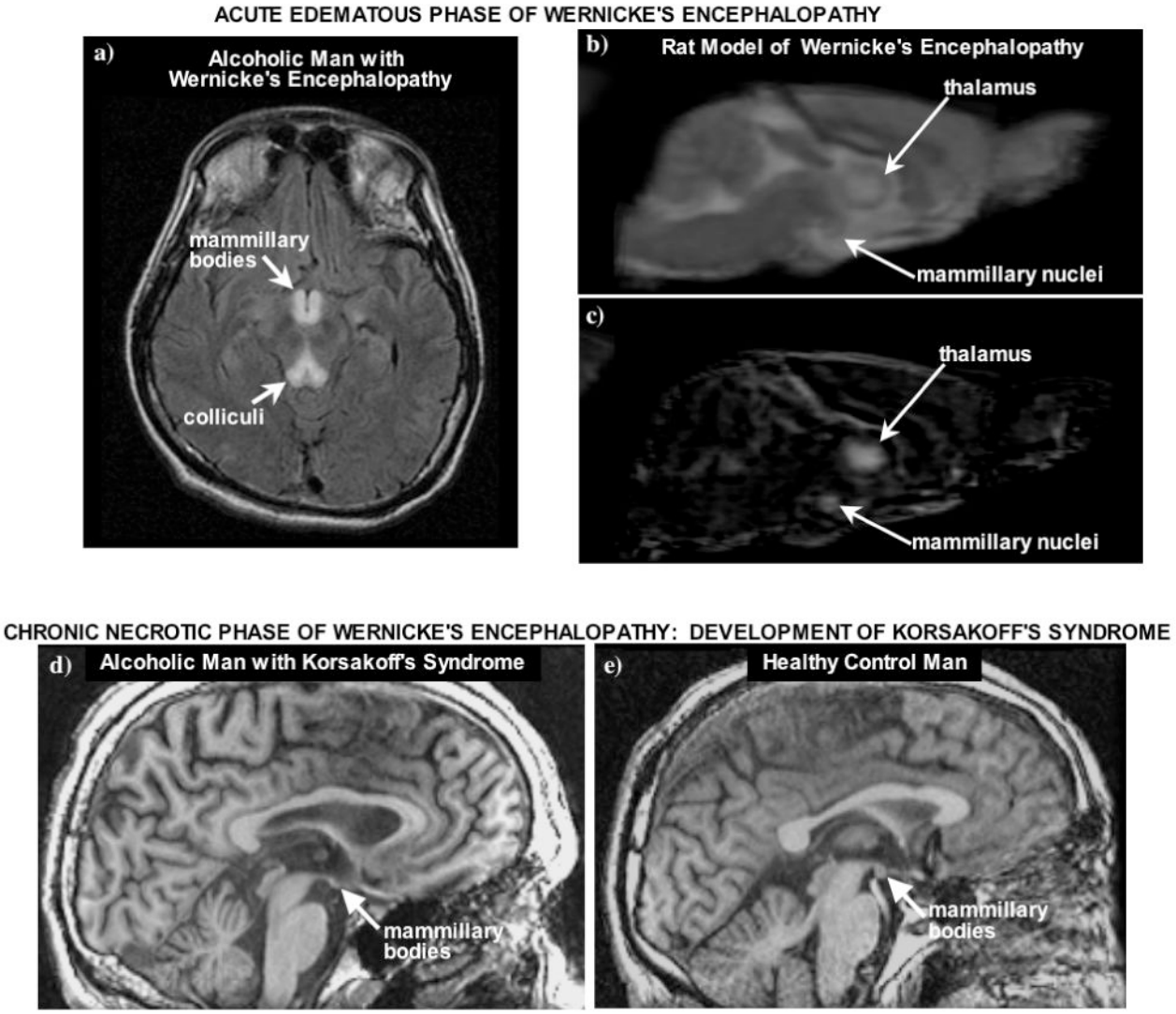

Figure 1.

a) Axial MR fluid attenuated inversion recovery (FLAIR) image of an acute a 35 year-old man with schizophrenia and acute nutritional deficiency-induced Wernicke's Encephalopathy (WE). Prominent are the hyperintense signals in the mammillary bodies and colliculi, indicative of inflammation in the acute phase of WE (taken from Sullivan and Pfefferbaum, 2008). b-c) Sagittal slice of b) an early-echo structural image and c) of a grand average post-pre difference image showing hyperintense areas in the thalamus and mammillary nuclei in pyrithiamine-treated rats (taken from Pfefferbaum, et al., 2007). d-e) T1-weighted SPoiled GRadient echo (SPGR) MR images of 53 year old man with a history of Wernicke's Encephalopathy, which developed into Korsakoff's Syndrome (KS). Note the shrunken mammillary bodies (arrows), indicative of necrosis, in the man with KS compared with the 59 year old healthy, nonalcoholic control man (taken from Sullivan and Pfefferbaum, 2008).