PERGAMON

Progress in Neurobiology Vol. 58, pp. 381 to 387, 1999

Printed in Great Britain
0301-0082/99/$ - see front matter

PII: S0301-0082(98)00091-4

BRAIN SHRINKAGE IN ALCOHOLICS: A DECADE ON AND WHAT HAVE WE LEARNED?

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(*Received* 23 *September* 1998)

Abstract—Brain atrophy in alcoholics has been identified using both radiological and pathological techniques. However the magnitude and topography of the atrophy, and the factors which contribute to it, are unclear. This review compares the results of imaging and pathological studies in alcoholics examining variables which may contribute to any discrepancies.

We conclude that significant brain damage does occur as a result of alcohol abuse *per se*, that the damage is regionally specific with the frontal lobes being particularly affected, and that both grey matter and white matter components are damaged.

CONTENTS

ABBREVIATIONS

CT Computerized tomography
MRI Magnetic resonance imaging

1. INTRODUCTION

The short-term consequences of alcohol ingestion on cognition, perception and motor coordination are known to most. These deficits rapidly recover as blood alcohol levels fall, however, doubt remains as to how much alcohol one needs to consume, and for how long, before permanent organ damage is sustained. At the other end of the spectrum prolonged, high level alcohol consumption is a recognized cause of brain damage. Alcohol-related brain damage is seen in many patients consuming greater than 100 g ethanol per day yet which brain areas and in which individuals remains far from clear and apparently contradictory findings still exist after two decades of imaging and pathological studies. The aim of this review is to explore the extent of brain pathology in alcoholics in light of the many of confounding variables which occur in these populations. In particular the brain shrinkage often reported in alcoholics using both neuroimaging and pathological techniques is examined.

In alcoholics, as with most investigations of human populations, a variety of factors both inherent to the population being studied and in study design have the potential to influence the outcome of the study. These factors include variations in alcohol dose and pattern of consumption, interval of abstinence prior to testing, gender differences in response to alcohol abuse, individual genetic variation and presence of concomitant disease. The impact of each of these factors is considered below.

The history of alcohol consumption may vary greatly between individuals. This issue may be addressed in a number of ways. Threshold level of consumption (e.g. $\geqslant 80\ g\ day^{-1}$) for a specified period (e.g. ≥ 10 years) may be used to dichotomize groups, lifetime consumption may be estimated (daily intake $\times$ 365 $\times$ number of years) to produce a continuous variable or behavioural measures of dependence and tolerance (e.g. DSM-IV) used to specify state characteristics. Each of these methods may best serve specific hypotheses but they may also produce fundamental differences in the populations being studied. Further complications resulting from uneven drinking patterns (e.g. binge) have rarely been addressed but may result in different pathology due to the higher blood alcohol levels attained during these periods.

Radiological studies have not identified robust correlations between brain volume changes and lifetime alcohol consumption in the majority of alco-

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holics studied (Ron, 1983; Pfefferbaum *et al*., 1992; Sullivan *et al*., 1995; Pfefferbaum *et al*., 1996). However in those alcoholics with withdrawal seizures the relationship between lifetime consumption and temporal lobe grey matter and white matter volumes neared significance (Sullivan *et al*., 1996). A similar relationship was not identified in alcoholics without seizures, nor was there a difference in alcohol history between the seizure and non-seizure groups of alcoholics suggesting a more complex relationship than a direct dose effect. This absence of correlation between magnetic resonance imaging (MRI) structural measures and alcohol consumption does not eliminate the possibility of a relationship. MRI T_1 relaxation times have been found to positively correlate with lifetime alcohol consumption in recently detoxified alcoholics (Chick *et al*., 1989). T_1 relaxation times are related to the state of water in the tissue and a correlation with alcohol consumption in alcoholics who have recently ceased drinking may be part of the recovery processes, although dehydration is not believed to be the substrate for the atrophy in the brains of alcoholics (Harper *et al*., 1985a; 1998b).

In contrast to radiological studies a pathological study of brain volume changes in alcoholics has demonstrated a significant negative correlation between cerebral white matter volume and maximum daily alcohol consumption in all alcoholics (Kril *et al*., 1997). This relationship represents a marked loss of white matter as there is over a 20% decrease in volume in those who consume 300 g ethanol per day. No correlation with cortical grey matter volume was found, however, the volume of the thalamus showed a significant negative correlation with alcohol consumption (Kril *et al*., 1997). In the hypothalamus, a significant negative correlation with alcohol consumption $>100\ \mathrm{g\ day^{-1}}$ was found in the number of vasopressin-containing neurons (Harding *et al*., 1996). Interestingly there was also a correlation between loss of neurons from the paraventricular nucleus and the duration of alcohol consumption. As these neurons are vital for osmoregulation, these findings indicate a potential substrate for fluid inbalances in alcoholics (Harding *et al*., 1996).

The interval between cessation of drinking and investigation is also of paramount importance. Reversibility of brain shrinkage with abstinence from alcohol has been recognized since the earliest studies which documented atrophy (Carlen *et al*., 1978; Artmann, 1981) and has subsequently been confirmed by a number of investigators using MRI (e.g. Schroth *et al*., 1988; Zipursky *et al*., 1989; Shear *et al*., 1994; Pfefferbaum *et al*., 1995). Correction of brain shrinkage appears to begin soon after cessation of alcohol consumption, within 2–4 weeks, and continues for up to 1 year (Zipursky *et al*., 1989; Pfefferbaum *et al*., 1995). Most studies have demonstrated a decrease in the volume of CSF which appears to be due to expansion of the white matter component of the brain with little or no contribution from the cerebral cortex (Shear *et al*., 1994). Nevertheless improvement in cognitive function is noted with abstinence (di Scalafani *et al*., 1995). The substrate for this reversibility of atrophy is unknown. Initial suggestions that it is due to rehydration are not supported by either MRI (Schroth *et al*., 1988) or pathological (Harper *et al*., 1985a; 1988b) studies.

In addition to improvement in structural elements, improvement in brain glucose metabolism has also been demonstrated with abstinence (Volkow *et al*., 1994; Johnson-Greene *et al*., 1997). Sequential analyses demonstrate that the majority of function is recovered within 30 days of cessation of drinking (Volkow *et al*., 1994). Interestingly Volkow *et al*. (1994) also illustrated that lower metabolic indices at the completion of the abstinence period were most prominent in older alcoholics with longer drinking histories. Consideration of the importance of abstinence interval is often made in neuropsychological and longitudinal volumetric studies. However, in many pathological studies the period of abstinence prior to death is generally not considered.

Individual differences both as a result of gender and genetic variation have also been demonstrated to result in differing response to alcohol abuse. On a population basis, women consume less alcohol and less frequently have alcohol-related problems (Glenn, 1993). However, radiological studies have demonstrated that, for an equivalent degree of brain shrinkage, women have a shorter drinking history and a lower peak alcohol consumption than men (Jacobson, 1986). Neuropsychological performance in female alcoholics has also been found to be impaired to an equivalent degree as males, but with a shorter drinking history (Glenn, 1993). Overall these findings suggests that females are more susceptible to alcohol-induced brain damage than males. However, an important caveat to these studies is that marked differences between males and females in the volume of specific brain regions have been identified (Harasty *et al*., 1997) and these may underlie differences in performance on selected tasks. In addition, both neuroimaging and neuropsychological studies suggest that the pattern of alcohol-related brain damage is different in young versus old alcoholics (see below) and as there are gender differences in the pattern of brain atrophy with age (Coffey *et al*., 1998; Raz *et al*., 1998) careful consideration of the age and gender spread of group data needs to be made.

Genetic variation between individuals may contribute to differences between experimental groups in two ways. Firstly allelic variation may confer differential susceptibility to the damaging effects of alcohol. For example a recent report suggests that allelic variation in the $ADH2^1$ gene may underlie differential brain atrophy in alcoholics (Maezawa *et al*., 1996). Furthermore allelic variations may result in life-long differences in brain architecture or function. Smaller right hippocampi have been noted in non-demented subjects across the age-range who carry the apolipoprotein E $\epsilon 4$ allele (Toghi *et al*., 1997). This allele is known to be associated with a higher incidence and earlier onset of Alzheimer's disease (Roses, 1996), but has also been shown to be more prevalent in alcoholic patients with the Wernicke–Korsakoff syndrome who have a more global intellectual impairment than those with a

more 'pure' amnesia (Muramatsu *et al*., 1997). In the case of alcoholics, another potential contributor is the presence of a family history of alcoholism. Subjects with a first degree relative with alcoholism have been shown to have poor performance on neuropsychological tests, even in the absence of alcohol abuse (Pihl and Bruce, 1995). However, a recent study has shown no significant difference in cerebral glucose metabolism between alcoholics with and without a family history of alcoholism (Adams *et al*., 1998). It is only recently that the contribution of genetic variables to structural and functional studies of the brain has received attention. Further elucidation of the contribution of these variables may provide a number of diagnostic and treatment benefits. However, as more associations are revealed it may mean that much of the data available today will need to be re-examined.

A further confounder in the investigation of brain damage in alcoholics is the presence of diseases secondary to alcohol abuse which may influence the brain. The two most frequently encountered complications are hepatic encephalopathy, which can result from cirrhosis of the liver (Harper and Kril, 1993; Butterworth, 1995), and the Wernicke–Korsakoff syndrome which results from co-existing thiamin deficiency (Charness *et al*., 1989; Harper and Kril, 1993). Recently developed operational criteria for the classification of alcoholics, including identification of those with hepatic encephalopathy and the Wernicke–Korsakoff syndrome (Caine *et al*., 1997), allow patients with these diseases to be excluded and relatively homogeneous groups of alcoholics examined for the role of alcohol toxicity in alcohol-related brain damage. Consequently studies concentrating on patients with either hepatic encephalopathy or the Wernicke–Korsakoff syndrome have not be reviewed although their importance in the resulting pattern of brain damage is acknowledged.

2. BRAIN VOLUME CHANGES IDENTIFIED IN CHRONIC ALCOHOLICS

Brain shrinkage in alcoholics identified by neuroimaging extends back to the time when pneumoencephalography was used to identify ventricular enlargement (Brewer and Perrett, 1971). This was later confirmed using computerized tomography (CT) (Bergman *et al*., 1980; Ron, 1983) and the sensitivity of detection of atrophy has improved with successive improvements in neuroimaging techniques. Current MRI techniques offer high resolution images and allow for the delineation of discrete neuroanatomical structures. Initially MRI studies in alcoholics confirmed ventricular enlargement (Schroth *et al*., 1988; Zipursky *et al*., 1989) and used linear measures of brain atrophy (Chick *et al*., 1989). They also confirmed the reversibility of ventricular enlargement following abstinence which had been demonstrated on CT studies (Schroth *et al*., 1988; Zipursky *et al*., 1989). Quantitative image analysis techniques which estimated brain size in three-dimensions were applied to alcoholics by Jernigan *et al*. (1990, 1991). These allowed the volume of both the whole brain and individual brain structures to be measured and compared. The combination of anatomical specificity and accurate morphometry also enabled specific hypotheses concerning regional susceptibility to alcohol toxicity and correlations with psychometric testing to be made. Overall these studies have resulted in the consensus that brain shrinkage does occur in alcoholics, however, the exact pattern and extent of shrinkage and in which groups of alcoholics remains undecided.

Volumetric analysis of MR images have yielded valuable data on the pattern of neuropathology in alcoholics, however, a number of methodological issues remain unresolved. Considerable variation in brain size exists both between individuals and between males and females (Appel and Appel, 1942; Dekaban, 1978; Harasty *et al*., 1997; Raz *et al*., 1998) making direct comparisons in the volume of brain structures between individuals inappropriate. In addition, there is a well recognized negative correlation between age and brain weight (Dekaban, 1978) resulting from the secular increase in brain size during this century (Miller and Corsellis, 1977) and a small reduction in brain size with advancing age (Double *et al*., 1996). Methods for normalizing MRI volumes have therefore been developed. A number of methods have been employed including proportional volumes ($V_{\text{region}}/V_{\text{intracranial cavity}}$) (Shear *et al*., 1994), linear (Mathalon *et al*., 1993) and non-linear (Jernigan *et al*., 1990) regressions. However, such techniques may introduce biases from a number of sources. For example in those studies which used proportional values variation may occur depending on whether the intracranial cavity volume is measured from an entire series of sections through the vault (Schroth *et al*., 1988) or calculated as a sphere equivalent from linear measures of brain height (Mathalon *et al*., 1993). Similarly in those studies which use corrections based on regression equations the cases from which the standard equation is obtained are critical. In the Jernigan *et al*. (1990) study a group of 58 normal volunteers aged 8–79 years and comprising of 23 females and 35 males were used. Cases were screened to exclude medical, psychiatric and developmental abnormalities, however, as with all clinical studies, the possibility remains for the inclusion subjects with preclinical or prodromal disease, especially in the older groups. As only a small number of cases at any age were studied the inclusion of subjects with early disease would significantly bias the results towards a decrease in brain volume with increasing age. Furthermore, the authors report significant volume reductions in grey and white matter with age yet in a recent pathological study we identified a small decrease in white matter volume with age, but were unable to identify any loss of grey matter, although there was significant grey matter shrinkage in patients with Alzheimer's disease (Double *et al*., 1996). In addition, differences in cortical (Harasty *et al*., 1997) and cerebellar (Raz *et al*., 1998) volumes between males and females have recently been reported and the pooling of volumes from both genders may also result in inaccurate normalization of data. The implementation of such corrections factors also assumes uniform shrinkage within a brain

compartment (i.e. grey matter or white matter) with age and this may not be a valid assumption. Variations in regional susceptibility to brain atrophy have been noted in pathological studies in the prefrontal white matter of alcoholics (Kril *et al*., 1997) and in the cerebral cortex of patients with Alzheimer's disease (Double *et al*., 1996). This regional variation in atrophy may also occur in ageing, where one brain regions shrinks more that others, and the application of generalized correction factors may result in the under- or over-estimation of changes with disease in specific brain regions. Overall the use of correction factors in the determination of volume changes is necessary to allow comparison of brain volumes in subjects with different initial brain sizes, however, one should be aware of the possible sources of error and the limitations of this practice.

The identification of regions of interest in quantitative MRI studies is performed using either of two methods for delineations. Regions may be identified by eye by an operator who then traces around the structure using a cursor (e.g. Sullivan *et al*., 1995; Pfefferbaum *et al*., 1996) or they may be separated using computer algorithms which segment into grey matter, white matter and cerebrospinal fluid (e.g. Pfefferbaum *et al*., 1992) or a combination of both methods may be used to first separate into compartments and then into anatomical regions. The accuracy of drawing around structures with a mouse or cursor is poor resulting in a high measurement error (Weibel, 1979) which must be considered when reporting small differences between groups. Intra-rater and inter-rater errors are rarely reported in quantitative MRI studies.

Shrinkage of the white matter component of the cerebral hemispheres has been identified in a number of neuropathological studies (Harper *et al*., 1985b; de la Monte, 1988; Kril *et al*., 1997). An overall shrinkage of nearly 14% was identified (Harper *et al*., 1985b) and this has been found to be most marked in the prefrontal area (anterior to the amygdala) with no loss from the posterior regions (Kril *et al*., 1997).

Radiological studies have concentrated more on volume changes in the cortex and CSF of alcoholics, however, a number have identified significant white matter shrinkage. Pfefferbaum *et al*. (1992) found an overall 5% loss of cerebral white matter. This was not found to be greater in any lobe, but a later study (Pfefferbaum *et al*., 1997) identified marked frontal white matter loss which was restricted to older alcoholics.

White matter atrophy has been further examined by quantifying the area of the corpus callosum in midsagittal sections. A significant decrease of *ca* 11% was noted in alcoholic men compared to non-alcoholic men (Pfefferbaum *et al*., 1996). Furthermore, this atrophy was found to be more marked in the anterior portions (Genu and body) than the posterior (splenium) portion of the corpus callosum. Hommer *et al*. (1996) also found corpus callosum atrophy in alcoholic women, however, in this latter study no significant difference between alcoholic and non-alcoholic men was observed. Thinning of the corpus callosum in alcoholics was described in postmortem studies by Harper and Kril (1988) a decade ago and this was not found to relate to focal degeneration of the corpus callosum (e.g. Marchiafava–Bignami disease), but rather represents a generalized decrease in white matter.

It has been suggested that significant shrinkage of the white matter in alcoholics is as a result of dehydration and that the reversibility is as a result of rehydration. However, both neuropathological (Harper *et al*., 1988b) and radiological (Schroth *et al*., 1988) studies have presented evidence that this is not the case. Indeed Harper *et al*. (1988b) found that brain water is increased in the white matter of non-abstinent alcoholics rather than decreased as would be expected. Not in agreement with these studies, Chick *et al*. (1989) found that T_1 indices, a measure of brain water, are increased in whole brain and white matter of detoxified alcoholics indicating that there is greater brain water in these patients.

Studies examining the total lipid and protein content of the brain in alcoholics compared to non-alcoholics have not identified a generalized loss of these constituents (Harper *et al*., 1987b; 1988a). Furthermore more specific studies examining individual component lipids of brain myelin have also failed to identify any alterations in alcoholics (Olsson *et al*., 1996). These studies suggest that the white matter loss in alcoholics is a balanced loss of all structural elements, rather than a specific loss of one lipid component.

The functional consequences of a loss of cerebral white matter are not fully understood. No studies specifically examining correlations between white matter atrophy and neuropsychological performance have been reported. However, correlations between the degree of brain atrophy and functional performance have been demonstrated in a number of studies. Ron (1983) identified a significant relationship between measures of verbal memory and ventricular enlargement in alcoholics. Similarly, Acker *et al*. (1987) found a correlation between decreased memory performance and the size of the third ventricle, but not the lateral ventricles, in alcoholic men. In contrast, Wang *et al*. (1993) found no correlation between measures of cognitive performance and MRI measures. The authors did, however, find a correlation between ventricular enlargement and cerebral metabolism measured using positron emission tomography.

3. GREY MATTER CHANGES

Volumetric MRI studies have consistently revealed reduced grey matter volumes in alcoholics. Significantly smaller volumes have been identified in the subcortical grey matter, dorsolateral frontal and parietal cortices and the medial temporal lobe (Jernigan *et al*., 1991). Similarly, Shear *et al*. (1992) also showed atrophy of a number of cortical regions, particularly the lateral cortices. Pfefferbaum *et al*. (1992) found cortical atrophy of *ca* 5% which was not localized to any specific cortical region. Furthermore they found that this atrophy is more marked in older alcoholics despite similar drinking histories (Pfefferbaum *et al*., 1992). More recent

analyses have established that frontal lobe atrophy is selectively greater in older alcoholics (Pfefferbaum *et al*., 1997). The authors found that when the alcoholic group was divided into younger (26–44 years) and older (45–63 years) alcoholics a similar degree of atrophy was noted in all cortical regions except the frontal cortex. The results of these studies may be interpreted in a number of ways. Firstly similar atrophy in most cortical regions in younger and older individuals with similar drinking histories may indicate a threshold effect whereby the amount of damage to the brain is a result of the cumulative effect of the amount of alcohol consumed not the period over which it was consumed. While the greater degree of atrophy in the frontal cortex of older alcoholics may indicate a reduced capacity of the aged brain to cope with the damaging effects of alcohol. It is interesting to note that the dorsolateral prefrontal cortex has been found to demonstrate the most marked age-related atrophy (Raz *et al*., 1997). This, together with the MRI findings may indicate a selective sensitivity of this cortical region to damage. Thus frontal lobe atrophy in older alcoholics may reflect a combination of both alcohol and age effects.

No generalized decrease in cortical grey matter volume has been identified in any of the quantitative pathological studies (Harper *et al*., 1985b; de la Monte, 1988; Kril *et al*., 1997). However, a number of cortical regions, especially the dorsolateral frontal association cortex showed marked variability in alcoholics (Kril *et al*., 1997). This latter study did not compare younger and older alcoholics, so the frontal atrophy reported by Pfefferbaum *et al*. (1997) may have been masked in the combined group.

Medial temporal lobe atrophy affecting both cortex and white matter which is greater in older alcoholics has also been reported (Sullivan *et al*., 1995). Further analysis of these data revealed firstly that the anterior portion of the hippocampus is selective damaged compared to the posterior portion (Sullivan *et al*., 1995), and secondly that the loss of white matter in the temporal lobe of alcoholics is fully accounted for by white matter loss in those alcoholics with seizures (Sullivan *et al*., 1996). Whether this white matter atrophy is causative or as a result of the seizures is at present unknown. No correlation between hippocampal atrophy and tests of memory function was identified (Sullivan *et al*., 1995).

Reduced subcortical grey matter volume in alcoholics has been reported by a number of studies (Pfefferbaum *et al*., 1992; Shear *et al*., 1992). The magnitude of this changes is approximately the same as that for the cerebral cortex and appears to involve the caudate and lenticular nuclei (Shear *et al*., 1992).

Although regionally specific cortical atrophy has been identified in alcoholics, it should be noted that the magnitude of these changes varies from region to region and that, overall, it is much less severe than one sees when conducting similar studies in patients with neurodegenerative diseases. Volumetric analyses of Alzheimer's disease reveal a loss of between 10 and 15% for the total cerebral cortex which is greatest in the temporal lobe which has a 22% loss of cerebral cortex (Double *et al*., 1996). Furthermore, MRI and CT studies have demonstrated atrophy of a similar magnitude (Shear *et al*., 1995; Kidron *et al*., 1997).

Initial studies examining the cerebral cortex in alcoholics used density measures (No. neurons per mm^2 or mm^3) to estimate neuronal loss and found a selective 22% decrease in the density of neurons in the superior frontal association cortex, but no decrease in the primary motor, anterior cingulate or inferior temporal cortices (Harper *et al*., 1987a; Kril and Harper, 1989). However, density measures may not accurately reflect changes in total neuron number if there are alterations in the volume of the tissue quantified (Oorschot, 1994) and a study using unbiased estimates of total neuronal number detected no loss of neurons from any lobe of the cerebral cortex in 11 alcoholic men when compared to non-alcoholic controls (Badsberg Jensen and Pakkenberg, 1993). The quantitative methodology employed in this study compared only lobar estimates of neuronal number and did not take into account regional and laminar variations in neuronal distribution. Consequently it is not possible, using this methodology, to draw conclusions about neuronal loss in functionally-discrete regions of the brain as such site-specific neuronal loss would be masked by the inter-regional variation in neuronal density within any lobe of the brain. What it does tell us, however, is that there is not a marked, global loss of neurons following alcohol abuse.

Recently using both unbiased quantitative techniques and regional measures of cortical volume, we estimated the total neuronal number in the dorsolateral association and primary motor cortices (Kril *et al*., 1997). A 23% loss of cortical neurons was found from the dorsolateral association cortex but not from the primary motor cortex of alcoholics.

Few studies examining other cortical regions have been reported. In a study of the hippocampal formation, Harding *et al*. (1997) found no neuronal loss from any of the subregions of the hippocampal formation in alcoholics. A significant reduction in volume was observed and this was accounted for by reduced white matter in alcoholics who were not abstinent at the time of death (Harding *et al*., 1997). This finding in humans is in direct contrast to those in animal models of alcohol abuse where hippocampal neuronal loss is frequently reported (Riley and Walker, 1978; Paula-Barbosa *et al*., 1993). The absence of neuronal loss from the hippocampus in humans does not necessarily imply that this region is spared in alcoholics. Other alterations such as neurotransmitter perturbations or dendritic remodelling may occur and result in disturbances of hippocampal function. Impaired memory and other functions attributable to hippocampal damage have been reported in alcoholics (Ryan and Butters, 1983) and the finding of reduced white matter volume (Harding *et al*., 1997), which appears to recover at least in part with abstinence, supports the supposition that mechanisms other than neuronal loss underlie this impaired function. Evidence for this suggestion also comes from a study by Ibanez *et*

al. (1995) who have shown reduced nuclear size in neurons of the entorhinal cortex of alcoholics.

Abnormalities in executive functions such as planning, abstraction and working memory have been identified in alcoholics and all may be attributed to deficits in the frontal lobes (Adams *et al*., 1995; Johnson-Greene *et al*., 1997). Correlations between neuropsychological deficits in executive tasks and impaired [^{18}F]fluorodeoxyglucose metabolism in the frontal lobes have been identified (Adams *et al*., 1995).

The functional correlates of the subcortical atrophy noted in alcoholics is not apparent. However, one study has shown a correlation between impaired olfaction and atrophy of the thalamus in alcoholics (Shear *et al*., 1992).

4. CONCLUSION

Taken together the radiological and pathological evidence suggests a regional sensitivity to the deleterious effects of alcohol. The frontal cortex together with its associated white matter appears to be the most sensitive to alcohol-induced damage. Neuropsychological evaluations which find a specific pattern of functional deficits, rather than a global deterioration in all functions, confirm the suggestion that prefrontal association regions are damaged in alcoholics.

The exact mechanism of brain damage in alcoholics remains unknown. By careful exclusion of cases with co-existing pathologies it is now apparent that alcohol *per se* is responsible for many of the functional and structural abnormalities seen in alcoholics. Partial recovery of brain function with abstinence suggests that a proportion of the deficits must be neurochemical in origin while neuronal loss from selected brain regions indicates permanent and irreversible damage. The factors influencing these two components are unknown and elucidation of these may provide insight into effective strategies for combating the widespread and devastating effects of alcohol abuse in our community.

Acknowledgements—This work was supported by grants from the Medical Foundation of The University of Sydney and the National Health and Medical Research Council of Australia. JJK is a Medical Foundation Fellow.

REFERENCES

Acker, C., Jacobson, R. R. and Lishman, W. A. (1987) Memory and ventricular size in alcoholics. *Psychol. Med.* **17,** 343–348.

Adams, K. M., Gilman, S., Koeppe, B., Kluin, K., Junck, L., Lohman, M., Johnson-Green, D., Berent, S., Dede, D. and Kroll, P. (1995) Correlation of neuropsychological function with cerebral metabolic rate in subdivisions of the frontal lobes of older alcoholics patients measures in [18F]fluorodeoxyglucose and positron emission tomography. *Neuropsychology* **9,** 275–280.

Adams, K. M., Gilman, S., Johnson-Greene, D., Koeppe, R. A., Junck, L., Kluin, K. J., Martorello, S., Johnson, M. J., Heumann, M. and Hill, E. (1998) The significance of family history staus in relation to neuropsychological test performance and cerebral glucose metabolism studied with positron emission tomography in older alcoholic patients. *Alcohol: Clin. Exp. Res.* **22,** 105–110.

Appel, F. W. and Appel, E. M. (1942) Intracranial variation in the weight of the human brain. *Human Biol.* **14,** 48–67.

Artmann, H. (1981) Reversible enlargement of cerebral spinal fluid spaces in alcoholics. *Am. J. Nutr. Res.* **2,** 23–27.

Badsberg Jensen, G. and Pakkenberg, B. (1993) Do alcoholics drink their neurons away? *Lancet* **342,** 1201–1203.

Bergman, H., Borg, S., Hindmarsh, T., Idestrom, C. M. and Mutzell, S. (1980) Computered tomography of the brain and neuropsychological assessment of male alcoholic patients and a random sample from the general male population. *Acta Psychol. Scand.* **62**(Suppl. 286), 77–88.

Brewer, C. and Perrett, L. (1971) Brain damage due to alcohol consumption: an air-encephalographic, psychometric and electroencephalographic study. *Br. J. Addict.* **66,** 170–182.

Butterworth, R. F. (1995) Hepatic encephalopathy. *The Neurologist* **1,** 95–104.

Caine, D., Halliday, G. M., Kril, J. J. and Harper, C. G. (1997) Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. *J. Neurol. Neurosurg. Psychiat.* **62,** 51–60.

Carlen, P. L., Wortzman, G., Holgate, R. C., Wilkinson, D. A. and Rankin, J. G. (1978) Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomographic scans. *Science* **200,** 1076–1078.

Charness, M. E., Simon, R. P. and Greenberg, D. A. (1989) Ethanol and the nervous system. *N. Engl. J. Med.* **321,** 442–454.

Chick, J. D., Smith, M. A., Engleman, H. M., Kean, D. M., Mander, A. J., Douglas, R. H. B. and Best, J. J. K. (1989) Magnetic resonance imaging of the brain in alcoholics: cerebral atrophy, lifetime alcohol consumption, and cognitive deficits. *Alcohol: Clin. Exp. Res.* **13,** 512–518.

Coffey, C. E., Lucke, J. F., Saxton, J. A., Ratcliff, G., Unitas, L. J., Billig, B. and Bryan, R. N. (1998) Sex differences in brain aging. A quantitative magnetic resonance imaging study. *Arch. Neurol.* **55,** 169–179.

Dekaban, A. S. (1978) Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann. Neurol.* **4,** 345–356.

di Scalafani, V., Ezekiel, F., Meyerhoff, D. J., MacKay, S., Dillon, W. P., Weiner, M. W. and Fein, G. (1995) Brain atrophy and cognitive function in older abstinent alcoholic men. *Alcohol: Clin. Exp. Res.* **19,** 1121–1126.

Double, K., Halliday, G., Kril, J., Harasty, J., Cullen, K., Brooks, W., Creasey, H. and Broe, G. (1996) Topography of brain atrophy during normal aging and Alzheimer's disease. *Neurobiol. Aging* **17,** 513–521.

Glenn, S. W. (1993) Sex differences in alcohol-induced brain damage. In: *Alcohol-induced brain damage. Vol. Research Mongraphy No. 22*, pp. 195–212, Eds. W. A. Hunt and S. J. Nixon. US Department of Health and Human Services, Rockville, MD.

Harasty, J., Double, K. L., Halliday, G. M., Kril, J. J. and McRitchie, D. A. (1997) Language-associated cortical regions are proportionally larger in the female brain. *Arch. Neurol.* **54,** 171–176.

Harding, A. J., Halliday, G. M., Ng, J. L. F., Harper, C. G. and Kril, J. J. (1996) Loss of vasopressin-immunoreactive neurons in alcoholics is dose-related and time-dependent. *Neuroscience* **72,** 699–708.

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

Harper, C., Kril, J. and Daly, J. (1987a) Are we drinking our neurones away? *Br. Med. J.* **294,** 534–536.

Harper, C., Kril, J. and Daly, J. (1988a) Does a "moderate" alcohol intake damage the brain? *J. Neurol. Neurosurg. Psychiat.* **51,** 909–913.

Harper, C. G. and Kril, J. J. (1988) Corpus callosal thickness in alcoholics. *Br. J. Addict.* **83,** 577–580.

Harper, C. G. and Kril, J. J. (1993) Neuropathological changes in alcoholics. In: *Research Monograph No. 22. Alcohol-induced Brain Damage*, pp. 39–70, Eds. W. A. Hunt and S. J. Nixon. National Institutes of Health, Washington.

Harper, C. G., Daly, J. and Kril, J. (1985a) Brain water in chronic alcoholics: a necropsy study. [Letter]. *Lancet* **2,** 327.

Harper, C. G., Kril, J. J. and Holloway, R. L. (1985b) Brain shrinkage in chronic alcoholics—a pathological study. *Br. Med. J.* **290,** 501–504.

Harper, C. G., Kril, J. J. and Daly, J. M. (1987b) The specific gravity of the brains of alcoholic and control patients: a pathological study. *Br. J. Addict.* **82,** 1349–1354.

Harper, C. G., Kril, J. J. and Daly, J. M. (1988b) Brain shrinkage in alcoholics is not caused by hydration—a pathological study. *J. Neurol. Neurosurg. Psychiat.* **51,** 124–127.

Hommer, D., Momenan, R., Rawlings, R., Ragan, P., Williams, W., Rio, D. and Eckardt, M. (1996) Decreased corpus callosum size among alcoholic women. *Arch. Neurol.* **53,** 359–363.

Ibanez, J., Herrero, M. T., Insausti, R., Belzunegui, T., Tunon, T., Garcia-Bragado, F. and Gonzalo, L. M. (1995) Chronic alcoholism decreases neuronal nuclear size and the human entorhinal cortex. *Neurosci. Lett.* **183,** 71–74.

Jacobson, R. (1986) The contributions of sex and drinking history to the CT brain scan changes in alcoholics. *Psychol. Med.* **16,** 547–559.

Jernigan, T. L., Press, G. A. and Hesselink, J. R. (1990) Methods for measuring brain morphologic features on magnetic resonance images: validation and normal aging. *Arch. Neurol.* **47,** 27–32.

Jernigan, T. L., Butters, N., di Traglia, G., Schafer, K., Smith, T., Irwin, M., Grant, I., Schuckit, M. and Cermak, L. S. (1991) Reduced cerebral gray metter observed in alcoholics using magnetic resonance imaging. *Alcohol: Clin. Exp. Res.* **15,** 418–427.

Johnson-Greene, D., Adams, K. M., Gilman, S., Koeppe, R. A., Junck, L., Kluin, K. J., Martorello, S. and Heumann, M. (1997) Effects of abstinence and repalse upon neuropsychological function and cerebral glucose metabolism in severe chronic alcoholism. *J. Clin. Exp. Neuropsychol.* **19,** 378–385.

Kidron, D., Black, S. E., Stanchev, P., Buck, B., Szalai, J. P., Parker, J., Szekely, C. and Bronskill, M. J. (1997) Quantitative MR volumetry in ALzheimer's disease. Topographic markers and the effects of sex and education. *Neurology* **49,** 1504–1512.

Kril, J. J. and Harper, C. G. (1989) Neuronal counts from four regions of alcoholic brains. *Acta Neuropathol.* **79,** 200–204.

Kril, J. J., Halliday, G. M., Svoboda, M. D. and Cartwright, H. (1997) The cerebral cortex is damaged in chronic alcoholics. *Neuroscience* **79,** 983–998.

Maezawa, Y., Yamauchi, M., Searashi, Y., Takeda, K., Mizuhara, Y., Kimura, T., Toda, G., Suuzuki, H. and Sakurai, S. (1996) Association of restriction fragment-length polymorphisms in the alcohol dehydrogenase 2 gene with alcoholic brain atrophy. *Alcohol: Clin. Exp. Res.* **20,** 29A–32A.

Mathalon, D. H., Sullivan, E. V., Rawles, J. M. and Pfefferbaum, A. (1993) Correction for head size in brain-imaging measurements. *Psychiat. Res. Neuroimaging* **50,** 121–139.

Miller, A. K. H. and Corsellis, J. A. N. (1977) Evidence for a secular increase in human brain weight during the past century. *Ann. Human Biol.* **4,** 253–257.

de la Monte, S. M. (1988) Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Arch. Neurol.* **45,** 990–992.

Muramatsu, T., Kato, M., Matsui, T., Yoshimasu, H., Yoshino, A., Matsushita, S., Higuchi, S. and Kashima, H. (1997) Apolipoprotein E e4 allele distribution in Wernicke–Korsakoff syndrome with and without global intellectual deficits. *J. Neural Trans.* **104,** 913–920.

Olsson, N. U., Harding, A. J., Harper, C. and Salem, N. J. (1996) High-performance liquid chromatography method with light-scattering detection for measurement of lipid class composition: analysis of brains from alcoholics. *J. Chromatography B* **681,** 213–218.

Oorschot, D. E. (1994) Are you using neuronal densities, synaptic densities or neurochemical densities as your definitive data? There is a better way to go. *Prog. Neurobiol.* **44,** 233–247.

Paula-Barbosa, M. M., Brandao, F., Madiera, M. D. and Cadete-Leite, A. (1993) Structural changes in the hippocampal formation after long-term alcohol consumption and withdrawal in the rat. *Addiction* **88,** 237–247.

Pfefferbaum, A., Lim, K. O., Zipursky, R. B., Mathalon, D. H., Rosenbloom, M. J., Lane, B., Ha, C. N. and Sullivan, E. V. (1992) Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcohol: Clin. Exp. Res.* **16,** 1078–1089.

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

Pfefferbaum, A., Lim, K. O., Desmond, J. E. and Sullivan, E. V. (1996) Thinning of the corpus callosum in older alcoholic men: a magnetic resonance imaging study. *Alcohol: Clin. Exp. Res.* **20,** 752–757.

Pfefferbaum, A., Sulliavn, E. V., Mathalon, D. H. and Lim, K. O. (1997) Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol: Clin. Exp. Res.* **21,** 521–529.

Pihl, R. O. and Bruce, K. R. (1995) Cognitive impairment in children of alcoholics. *Alcohol Health Res. World* **19,** 142–147.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., Loken, W. J., Thornton, A. E. and Acker, J. D. (1997) Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cerebral Cortex* **7,** 268–282.

Raz, N., Dupuis, J. H., Briggs, S. D., McGavran, C. and Acker, J. D. (1998) Differential effects of age and sex on the cerebellar hemispheres and the vermis: a prospective MR study. *American Journal of Neuroradiology* **19,** 65–71.

Riley, J. N. and Walker, D. W. (1978) Morphological alterations in the hippocampus after long-term alcohol consumption in mice. *Science* **201,** 646–648.

Ron, M. A. (1983) The alcoholic brain: CT scan and psychological findings. *Psychol. Med.* **3**(Monograph Supplement), 1–33.

Roses, A. D. (1996) Apolipoprotein E in neurology. *Curr. Opin. Neurol.* **9,** 265–270.

Ryan, C. and Butters, N. (1983) Cognitive deficits in alcoholics. In: *The Pathogenesis of Alcoholism*, pp. 485–538. Eds. B. Kissin and H. Begleiter. Plenum, New York.

Schroth, G., Naegele, T., Klose, U., Mann, K. and Petersen, D. (1988) Reversible brain shrinkage in abstinent alcoholics, measured by MRI. *Neuroradiology* **30,** 385–389.

Shear, P. K., Butters, N., Jernigan, T. L., di Traglia, G. M., Irwin, M., Schuckit, M. A. and Cermak, L. S. (1992) Olfactory loss in alcoholics: correlations with cortical and subcortical MRI indices. *Alcohol* **9,** 247–255.

Shear, P. K., Jernigan, T. L. and Butters, N. (1994) Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics. *Alcohol: Clin. Exp. Res.* **18,** 172–176.

Shear, P. K., Sullivan, E. V., Mathalon, D. H., Lim, K. O., Davis, L. F., Yesavage, J. A., Tinklenberg, J. R. and Pfefferbaum, A. (1995) Longitudinal volumetric computed tomographic analysis of regional brain changes in normal aging and Alzheimer's disease. *Arch. Neurol.* **52,** 392–402.

Sullivan, E. V., Marsh, L., Mathalon, D. H., Lim, K. O. and Pfefferbaum, A. (1995) Anterior hippocampal volume defecits in nonamnesic, ageing chronic alcoholics. *Alcohol: Clin. Exp. Res.* **19,** 110–122.

Sullivan, E. V., Marsh, L., Mathalon, D. M., Lim, K. O. and Pfefferbaum, A. (1996) Relationship between alcohol withdrawal seizures and temporal lobe white matter volume deficits. *Alcohol: Clin. Exp. Res.* **20,** 348–354.

Toghi, H., Takahashi, S., Kato, E., Homma, A., Niina, R., Sasaki, K., Yonezawa, H. and Sasaki, M. (1997) Reduced size of right hippocampus in 39- to 80-year-old normal subjects carrying the apolipoprotein E e4 allele. *Neurosci. Lett.* **236,** 21–24.

Volkow, N. D., Wang, G.-J., Hitzemann, R., Fowler, J. S., Overall, J. E., Burr, G. and Wolf, A. P. (1994) Recovery of brain glucose metabolism in detoxified alcoholics. *Am. J. Psychiat.* **151,** 178–183.

Wang, G.-J., Volkow, N. D., Roque, C. T., Cestaro, V. L., Hitzmann, R. J., Cantos, E. L., Lvey, A. V. and Dhawan, A. P. (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.

Weibel, E. R. (1979) *Steological Methods*. Academic Press, London.

Zipursky, R. B., Lim, K. O. and Pfefferbaum, A. (1989) MRI study of brain changes with short-term abstinence from alcohol. *Alcohol: Clin. Exp. Res.* **13,** 664–666.