

## MAGNETIC RESONANCE IMAGING IN ALCOHOLIC KORSAKOFF'S SYNDROME: EVIDENCE FOR AN ASSOCIATION WITH ALCOHOLIC DEMENTIA

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**Abstract** — A magnetic resonance imaging study of 19 alcoholic Korsakoff patients, 17 non-amnesic alcoholics and 23 non-alcoholic controls was undertaken. Several measures of ventricular size and interhemispheric area were significantly greater in the Korsakoff patients. Interhemispheric fissure size was greater in the non-amnesic alcoholics than the non-alcoholic controls. Cortical grey matter T<sub>1</sub> values were essentially the same for the three groups, whereas the deep grey and the white matter T<sub>1</sub> values for the Korsakoff patients were significantly greater than the non-alcoholic controls. These results indicate widespread cerebral atrophy in alcoholic Korsakoff patients, which is largely subcortical and does not develop independently of the diencephalic pathology. Alcoholic dementia may be a more severe form of alcoholic Korsakoff syndrome, aetiologically related to the nutritionally-induced diencephalic pathology, rather than the neurotoxic effects of alcohol on the cortex.

### INTRODUCTION

The alcoholic Korsakoff syndrome (AKS) manifests clinically as profound amnesia, with varying degrees of other cognitive deficits (Jacobson *et al.*, 1990; Kopelman, 1995). Pathological changes comprising bilateral symmetrical vascular lesions in diencephalic structures are a constant autopsy finding. However, more widespread lesions, including generalized cerebral atrophy have also been reported (Victor *et al.*, 1989) and are now recognized as an important part of the disorder. A dual aetiology has been proposed (Butters, 1985; Lishman *et al.*, 1987). Memory impairment is thought to be a consequence of diencephalic pathology caused by severe thiamine deficiency, whereas the other cognitive deficits result from widespread cerebral shrinkage due to a direct neurotoxic effect of alcohol. The latter mechanism may not be specific to Korsakoff patients, as similar changes have been reported in non-amnesic alcoholics (Shimamura *et al.*, 1988;

Jacobson and Lishman, 1990).

Various studies have investigated the relationship between cognitive deficits and structural cerebral changes in AKS patients, by means of combined neuropsychological and neuroradiological assessment. Carlen *et al.* (1981) reported significantly larger ventricles and wider sulci in AKS and non-amnesic alcoholics compared to non-alcoholic controls. Significant correlations between sulcal widening and cognitive impairment were found in the AKS patients. Jacobson and Lishman (1987) found variable degrees of memory impairment and cognitive decline in 38 AKS patients, with significant correlations between memory impairment and third ventricular size, and between global intellectual impairment and interhemispheric fissure size. Shimamura *et al.* (1988) studied seven AKS patients, seven non-amnesic alcoholics and seven non-alcoholic controls. They found lower computed tomography (CT) scan density values bilaterally in the region of the thalamus, and greater estimated fluid bilaterally in the region of the third ventricle in AKS patients. In both alcoholic groups, cortical atrophy in frontal sulcal and peri-Sylvian areas was found. For the AKS patients, cognitive

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impairment, particularly memory impairment, was significantly correlated with low-density values in the thalamus and with high fluid values in the region of the frontal sulci. In a magnetic resonance imaging (MRI) study, Christie *et al.* (1988) reported elevated  $T_1$  values in grey and white matter in the frontal and parietal cortex of AKS patients, compared to controls. However, no relationship was found between these values and neuropsychological test results. Besson *et al.*, (1989), in an MRI study similar to that of Christie *et al.* (1988), found that only the left parietal white matter  $T_1$  was significantly greater in AKS patients, than in controls. However, significant relationships were found between psychometric estimates of intellectual and mnemonic deterioration and  $T_1$  values in temporal and parietal white matter. Jernigan *et al.* (1991) compared eight AKS patients to 12 non-amnesic alcoholics and 13 non-alcoholic controls using MRI quantitative image-analytic techniques to estimate volumes of ventricular and cortical cerebrospinal fluid (CSF), as well as cortical and subcortical grey matter structures. The non-amnesic alcoholics showed large CSF increases with some circumscribed decreases in grey-matter volumes, and the AKS patients showed widespread reductions in grey matter volumes as well as CSF increases, with greatest reductions in diencephalic structures.

Although these findings are not always clear-cut, they confirm that AKS is a heterogeneous condition regarding the degree of memory and cognitive impairment as well as the extent of structural brain damage. Further, diencephalic damage appears to be associated with memory impairment, whereas widespread cerebral shrinkage is more often associated with other cognitive impairment. Finally, the cerebral shrinkage is more pronounced in the frontal lobes, and may affect subcortical more than cortical structures (Jernigan *et al.*, 1991).

We now report the results of an MRI study of AKS patients, non-amnesic alcoholics and non-alcoholic controls, with larger sample sizes than in the previously reported MRI studies.  $T_1$  values for grey and white matter from various regions were estimated, as were several anatomic measures of ventricular size and interhemispheric area. Correlations were sought between MRI findings and neuropsychological test scores.

## METHODS

### *Subjects*

Informed, written consent was obtained for all subjects. The following three groups were studied.

*The alcoholic Korsakoff's syndrome patients (group A).* Inpatients with a clinical diagnosis of Korsakoff's syndrome from two state psychiatric hospitals in the Cape Town area were considered. Assessment included psychiatric and medical history, mental state examination, physical examination and review of clinical files. The inclusion criteria were: DSM-III-R (American Psychiatric Association, 1987) diagnosis of alcohol amnesic disorder, abstinent for at least 12 weeks, and medication-free for at least 2 weeks. The exclusion criteria were: age > 60 years, <8 years of schooling, history of other substance abuse, previous severe head injury or episode of anoxia, other significant physical illness or psychiatric disorder, or signs on physical or radiological examination of neurological disorder not attributable to alcohol abuse.

*The non-amnesic alcoholic controls (group B).* These subjects were recruited from inpatients of an alcohol rehabilitation unit, as well as abstinent members of Alcoholics Anonymous, who were judged not to have significant memory or other cognitive impairment. The inclusion criteria were: DSM-III-R (American Psychiatric Association, 1987) diagnosis of alcohol dependence, abstinent for at least 12 weeks, and medication-free for at least 2 weeks. Exclusion criteria were as for the Korsakoff patients.

*The non-alcoholic controls (group C).* Healthy volunteers were recruited from hospital and university staff and their relatives, and church organisations. Only total abstainers or occasional drinkers who were medication-free for at least two weeks were considered. Exclusion criteria were as for the other two groups.

The three groups were balanced for age and sex, and the two alcoholic groups for duration of drinking, duration of abstinence and educational status. The duration of drinking was taken from the approximate onset of excessive drinking. For the AKS patients, information was obtained from the clinical files, and, where possible, from family members. The duration of abstinence was calculated from the date of admission, unless the date when the subject last drank was documented in the

clinical file.

### *Magnetic resonance imaging*

MR images were acquired with the South African Medical Research Council's Elscint 0.5 T Gyrex V Imager. All measurements were performed by a single rater without knowledge of subject identity. Routine spin-echo technique protocols were used to demonstrate the brain parenchyma ( $T_1$  weighted) and cerebrospinal fluid spaces ( $T_2$  weighted). The following multislice spin echo study sequences were performed: a  $T_1$  weighted coronal study; a  $T_2$  weighted coronal study; a  $T_2$  weighted axial study; and a midline  $T_1$  weighted sagittal study. The slice width was 6 mm, the interslice gap 3 mm, the field of view 24 cm and the matrix  $220 \times 256$ . The free induction decay values of the  $T_1$  coronal and  $T_2$  coronal sequences were utilized to generate  $T_1$  and  $T_2$  maps, using the standard application software.  $T_1$  and  $T_2$  values were obtained by placing a cursor or region of interest on the image slice and reading the displayed value. The coronal slices were planned at  $90^\circ$  to the orbito-meatal line. A 6 mm slice width with 3 mm (50%) interslice gap was chosen to maximize the tissue contrast without multislice interference. The following measures of cerebral atrophy were calculated for each patient, using the inbuilt image analysis software.

**Ventricle-to-brain ratio (VBR).** On the two consecutive  $T_2$ -weighted axial images showing the maximal dimensions of the lateral ventricles, the cross-sectional area enclosed by the margins of these ventricles was traced and divided by the area enclosed by the outer margin of the brain. The VBR was taken as the mean of those two ratios.

**Third ventricular index (TVI).** From the coronal plane  $T_1$  weighted image, the slice visually adjudged to display the maximum width of the third ventricle was chosen. The TVI was obtained by dividing the maximum width of the third ventricle by the transverse distance between the inner tables of the skull at the same level.

**Bicaudate index (BCI).** From the coronal slice with the most medially placed caudate heads, the bicaudate distance was measured from the maximum convexity of the caudate nuclei, and this was expressed as a percentage of the internal diameter of the calvarium at the same level.

**Bifrontal index (BFI).** In the same coronal slice as the BCI, the greatest transverse distance

between the frontal horns of the lateral ventricles was measured and expressed as a percentage of the diameter of the inner skull table at the same level.

**Interhemispheric fissure (IHF) area.** On the same slice as was chosen to measure the BCI, the cortex of the interhemispheric fissure was traced using the inbuilt software, and the area derived in  $\text{mm}^2$ .

The BCI, BFI and TVI measures were adapted from Geremia and Huckman (1992). For the various measures, the test-retest reliability was: VBR 0.97; IHF 0.90; BCI 0.98; BFI 0.98 and TVI 0.97.

$T_1$  values were measured in the following areas: left and right frontal grey and white matter (LFG, RFG, LFW, RFW), left and right temporal grey and white matter (LTG, RTG, LTW, RTW), left and right parietal grey and white matter (LPG, RPG, LPW, RPW), left and right cerebellar grey and white matter (LCG, RCG, LCW, RCW), and left and right thalamus and caudate nuclei. The following slices were used: for the frontal areas, the most anterior slice (showing the most anterior part of the corpus callosum); for the parietal and temporal areas, at the level of the mamillary bodies; for the cerebellum, the slice showing the largest white matter area in the coronal plane; for the thalamus, the most posterior slice anterior to the cerebellar peduncles; and for the caudate nucleus, at the level of the optic chiasm.

In view of partial voluming problems and inhomogeneity of the contrasted intensity of the cortical grey matter, a multipoint sampling technique using a standard cursor size was carried out. Five points were sampled for each cortical grey matter area. The deep grey required only a single region of interest, which was chosen to be as large as could be manipulated. Similarly, as large a region of interest as possible was chosen for each white matter area, in order to include as many pixels as possible. For the  $T_1$  values, test-retest reliability was as follows: LFG 0.89; RFG 0.80; LFW 0.93; RFW 0.93; LTG 0.94; RTG 0.91; LTW 0.55; RTW 0.70; LPG 0.59; RPG 0.66; LPW 0.87; RPW 0.86; LCG 0.93; RCG 0.95; LCW 0.92; RCW 0.94; left thalamus 0.78; right thalamus 0.81; left caudate 0.81 and right caudate 0.85. Because of the possibility of fluctuation in values over time,  $T_1$  measurements were performed daily on a phantom, and when necessary recalibration was performed.

Table 1. Group median (and interquartile range) values for the measures of atrophy for the alcoholic Korsakoff patients (group A), the non-amnesic alcoholics (group B) and the non-alcoholic controls (group C)

Measure	Group A (n = 19)	Group B (n = 16)	Group C (n = 20)	P values		
				A vs B	A vs C	B vs C
VBR	10.1 (4.4)	7.9 (4.8)	7.5 (2.9)	0.04	0.0008	NS
TVI	5.5 (2.5)	2.9 (2.3)	2.7 (1.8)	0.0005	0.000004	NS
IHF	419 (189)	260 (114)	200 (78)	0.0005	0.000001	0.005
BR	14.9 (6.0)	11.3 (4.5)	12.1 (3.3)	0.005	0.0004	NS
FHR	28.1 (5.9)	25.0 (5.5)	24.3 (3.4)	0.02	0.0004	NS

VBR = ventricle to brain ratio; TVI = third ventricular index; IHF = interhemispheric fissure; BR = bicaudate ratio; FHR = frontal horn ratio; NS = not significant.

Values are expressed as percentages, except for IHF, which is in mm<sup>2</sup>.

Table 2. Group median (and interquartile range) regional T<sub>1</sub> values in ms for alcoholic Korsakoff patients (group A), non-amnesic alcoholics (group B) and non-alcoholic controls (group C)

Region	Group A (n = 18)	Group B (n = 15)	Group C (n = 20)	P values		
				A vs B	A vs C	B vs C
LFW	565 (66)	524 (74)	508 (54)	NS	0.003	NS
RFW	564 (56)	509 (66)	508 (41)	0.02	0.005	NS
LPW	554 (93)	508 (164)	520 (51)	0.02	0.02	NS
RPW	566 (80)	508 (187)	522 (63)	0.03	0.02	NS
LTW	522 (91)	489 (97)	459 (588)	NS	0.007	NS
RTW	498 (76)	461 (70)	445 (67)	NS	0.02	NS
LCW	576 (69)	551 (143)	546 (66)	NS	NS	NS
RCW	553 (74)	575 (182)	550 (78)	NS	NS	NS
LFG	1024 (155)	1018 (125)	949 (150)	NS	NS	NS
RFG	963 (125)	1018 (140)	970 (141)	NS	NS	NS
LPG	963 (170)	969 (128)	951 (146)	NS	NS	NS
RPG	934 (94)	965 (105)	936 (126)	NS	NS	NS
LTG	1058 (236)	962 (348)	921 (198)	NS	NS	NS
RTG	977 (247)	923 (380)	874 (272)	NS	NS	NS
LCG	1020 (38)	929 (166)	938 (144)	NS	0.03	NS
RCG	1016 (126)	969 (161)	952 (191)	NS	NS	NS
L THAL	788 (102)	780 (285)	703 (159)	NS	0.006	NS
R THAL	756 (146)	776 (265)	736 (124)	NS	0.03	NS
L CAUD	888 (153)	865 (129)	808 (117)	NS	0.004	0.02
R CAUD	903 (183)	869 (188)	788 (149)	NS	0.002	NS

Left and right frontal grey and white matter = LFG, RFG, LFW, RFW; left and right temporal grey and white matter = LTG, RTG, LTW, RTW; left and right parietal grey and white matter = LPG, RPG, LPW, RPW; left and right cerebellar grey and white matter = LCG, RCW, LCW, RCW; and left and right thalamus and caudate nuclei = L THAL, R THAL, L CAUD, R CAUD.

NS = not significant.

### Neuropsychological evaluation

The following tests were applied to each subject from groups A and B: Wechsler Adult Intelligence Scale (South African version); Wechsler Memory Scale Form 1 (logical memory, visual reproduc-

tion and associate learning subtests); Rey Complex Figure Test (copy trial and retesting after 30 min); Trail Making Test; Williams Delayed Recall Test; Word Fluency Test; and the Rey Auditory Verbal Learning Test. Tests were administered according to published instructions

and in standard order. Tests were administered individually, over two sessions on consecutive days. Testing and scoring were done in a blind fashion by two clinical psychologists (S.S. and H.P.). Subjects were tested within three weeks of the MRI scan (Emsley *et al.*, 1995).

### Statistical methods

The Kruskal–Wallis test was used to compare groups. When a significant difference was found (at a significance level of 0.05), pairwise comparisons using the Kruskal–Wallis test were performed to ascertain which of the groups differed. To minimize the possibility of a type-I error,  $P$  values were multiplied by 3, the number of pairwise comparisons. The  $\chi^2$ -test or Fisher's exact test was used to compare categorical variables. The Spearman rank order correlation coefficient was used to test the significance of correlations between numeric variables.

## RESULTS

Group A comprised 13 men and 6 women aged 41–60 years (median 54 years). The median duration of drinking was 20 (14) years and duration of abstinence was 40 (93) months. Group B consisted of 15 men and two women aged 30–58 years (median 49 years). The median duration of drinking was 22 (10) years, and the duration of abstinence was 6 (33) months. Group C comprised 15 men and eight women aged 39–57 years (median 51 years). Age and sex distributions did not differ significantly among the three groups, and the two alcoholic groups did not differ significantly regarding the duration of drinking and proportion of subjects who had been abstinent for <1 year.

### Neuropsychological test results

All results of the AKS patients were significantly poorer than the non-amnesic alcoholics (Emsley *et al.*, 1995). Median values for groups A and B respectively, were: Wechsler Adult Intelligence Scale total IQ 88 vs 103 ( $P = 0.007$ ), Wechsler Memory Scale Associate Learning 9 vs 66 ( $P < 0.0001$ ), Visual Reproduction 9 vs 68 ( $P < 0.0001$ ), Logical Memory 14 vs 75 ( $P = 0.0005$ ), Rey Complex Figure Test Memory Percentile 1 vs 10 ( $P = 0.01$ ), Trail Making Test

part A 16 vs 66 ( $P = 0.003$ ), part B 8 vs 48 ( $P = 0.0006$ ), Williams Delayed Recall 10 vs 45 ( $P = 0.001$ ), Word Fluency Test 19 vs 31 ( $P = 0.001$ ) and Auditory Verbal Learning Test average of five presentations 1.8 vs 25 ( $P = 0.0005$ ).

### Atrophy measure

Values for the three groups are given in Table 1. The degree of atrophy was significantly greater in the Korsakoff patients for all measures compared to the non-amnesic alcoholics and the non-alcoholic controls. Except for the IHF, there were no differences between non-amnesic alcoholics and non-alcoholic controls.

### $T_1$ values

The regional  $T_1$  values for the three groups are shown in Table 2. None of the cortical grey matter measures differed significantly among the three groups, except for the left cerebellar grey between Korsakoff patients and non-alcoholic controls. The deep grey  $T_1$  values for the Korsakoff patients were all significantly greater than the non-alcoholic controls. The  $T_1$  values for the white matter in the Korsakoff patients were consistently greater than the non-alcoholic controls, except in the cerebellum, and greater than the non-amnesic alcoholics for the left and right parietal, and right frontal, areas.

### Correlations between neuropsychological test scores and MRI measures

Multiple within-group correlations were performed between all MRI measures and all neuropsychological test scores. To control for type I error, the significance level was set at 0.01. The following significant correlations were found: in the Korsakoff group the Trail Making Test part B percentile showed a significant negative correlation only with  $T_1$  in the LCW and RCW regions ( $r = -0.82$  and  $-0.81$  respectively,  $P < 0.005$ ). In the non-amnesic alcoholics,  $T_1$  in LPW ( $r = 0.69$ ,  $P < 0.01$ ) and RPW ( $r = 0.82$ ,  $P < 0.001$ ) correlated significantly with the visual reproduction subtest of the Wechsler Memory Scale. There were no significant correlations between neuropsychological test scores and atrophy measures at the 0.01 level.

## DISCUSSION

These results provide further evidence of widespread cerebral shrinkage in alcoholic Korsakoff patients. While some previous studies found the atrophy to be more pronounced in the diencephalon and frontal lobes (Shimamura *et al.*, 1988; Jacobson and Lishman, 1990; Jernigan *et al.*, 1991), our patients showed pronounced atrophy on all measures. This may be because we did not exclude those patients showing psychometric evidence of more widespread cognitive impairment (in order to examine the relationship between AKS and alcoholic dementia we decided not to exclude these patients). In fact, some of our patients may be more aptly described as having alcoholic dementia—a condition with an uncertain relationship to AKS (Jacobson and Lishman, 1987). Heterogeneity within AKS patients has been reported, suggesting a continuum rather than sharply defined differences between patients with pure AKS and those with features of alcoholic dementia (Jacobson and Lishman, 1987). Further evidence suggesting that alcoholic dementia and AKS are not separate entities includes post-mortem findings of ventricular dilatation and cortical atrophy in a third of AKS cases reported by Harper (1983) and diffuse cerebral changes in a quarter of AKS cases by Victor *et al.* (1989).

The MRI measures that we employed can only be considered a rough measure of atrophy in specific areas. However, if the IHF is considered a measure of cortical atrophy, the TVI a measure of diencephalic atrophy and the indices of ventricular size (VBR, BCI and BFI) a measure of subcortical atrophy (Jacobson and Lishman, 1990), our results indicate that Korsakoff patients show atrophy in all of these areas. The greater degree of cerebral shrinkage found in the AKS patients compared to the non-amnesic alcoholics could be explained on the basis that the former had consumed more alcohol, and thus suffered more neurotoxic sequelae. We did not estimate the actual quantities of alcohol consumed because the AKS subjects were found to be unreliable in this regard and family members could not often be traced for interview. However, since the alcoholic groups had similar durations of excessive drinking, and most of the non-amnesic alcoholics had been committed to a state institution (an indication of a marked degree of

intractable alcohol abuse), we consider this explanation unlikely. Our results cannot therefore be explained on the basis of the dual aetiology hypothesis for AKS alone (Butters, 1985; Lishman *et al.*, 1987). If the diffuse cerebral shrinkage was due solely to the neurotoxic effects of alcohol, one would have expected it to be similar in both alcoholic groups. This was not the case—in fact, the Korsakoff patients showed significantly more atrophy than the non-amnesic alcoholics for *all* of the anatomical measures.

Elevated  $T_1$  values in abstinent Korsakoff patients most likely reflect neuronal degeneration (Christie *et al.*, 1988).  $T_1$  measurements in white matter and deep grey matter were significantly elevated in the AKS group, compared to the non-alcoholic controls, and those in parietal and right frontal white matter significantly greater than in non-amnesic alcoholics. These findings are consistent with previous reports (Harper *et al.*, 1985; de la Monte, 1988; Jernigan *et al.*, 1991), suggesting that a disproportionate amount of subcortical white matter may be lost in alcoholics. More specifically, our results indicate that this is particularly so for AKS patients.

The non-amnesic alcoholics in our study did not display radiological evidence of cerebral shrinkage to the same extent as those in the study of Ron (1983), probably because of the longer duration of abstinence in our subjects (the above author reported partial reversal of atrophy with continued abstinence). Our findings are more in line with those of Jacobson and Lishman (1990), who found that the ventricular size of non-amnesic alcoholics was similar to the non-alcoholic controls. These authors did, however, find that the non-amnesic alcoholics had wider sulci, suggesting cortical rather than subcortical atrophy in these patients. Similarly, in our study, the IHF was the only anatomical measure to show significantly greater atrophy in the non-amnesic alcoholics compared to the non-alcoholic controls. Again, this is the only measure in our study considered to assess cortical rather than subcortical atrophy. Thus, the findings of Jacobson and Lishman (1990) and those of the present study suggest that in abstinent non-amnesic alcoholics, cerebral atrophy occurs predominantly in the cortex.

The neuropsychological test results indicate more widespread cognitive impairment than just

the memory deficit in AKS, corroborating the work of Jacobson *et al.* (1990) and providing further evidence for an association between AKS and alcoholic dementia. There were generally few significant correlations between neuropsychological test results and the MRI measures. In contrast to the findings of Acker *et al.* (1987), we were unable to demonstrate significant correlations between TVI measures and memory impairment. This could be due to the fact that the severity of memory impairment in Korsakoff patients resulted in a lack of 'spread' of scores—often the scores fell below the 10th percentile. Another consideration is that by being less stringent in excluding patients with other cognitive impairment the relationship between memory impairment and diencephalic damage could not be demonstrated.

A potential limitation of this study concerns the inclusion of female subjects—female alcoholics show an increased sensitivity to brain damage to the extent that they develop cerebral atrophy after a shorter history of alcohol abuse (Jacobson, 1986) and female AKS patients show more widespread cognitive impairment (Jacobson and Lishman, 1987). Further limitations include the relatively small samples, and the unreliable drinking histories of the alcoholic patients.

In conclusion, our results indicate that AKS patients display varying degrees of cognitive impairment and cerebral shrinkage, often in the range seen in patients with dementia. There are indications that the cerebral shrinkage is largely subcortical, and does not develop independently of the diencephalic pathology. Taken together with the previously reported studies, a possible explanation for our findings is that, whereas the neurotoxic effects of alcohol lead to cortical atrophy in alcoholics with and without AKS, in AKS diencephalic atrophy occurs together with further generalized subcortical atrophy—the latter perhaps due to deafferentation, secondary to destruction of subcortical projection nuclei (Hunter *et al.*, 1989). Alcoholic dementia may be a more severe form of AKS, aetiologically related to the nutritionally induced diencephalic pathology, rather than the neurotoxic effects of alcohol on the cortex.

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## REFERENCES

- Acker, C., Jacobson, R. R. and Lishman, W. A. (1987) Memory and ventricular size in alcoholics. *Psychological Medicine* **17**, 343–348.
- American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. American Psychiatric Association, Washington, DC.
- Besson, J. A. O., Crawford, J. R., Parker, D. M. and Smith, F. W. (1989) Magnetic resonance imaging in Alzheimer's disease, multi-infarct dementia, alcoholic dementia and Korsakoff's psychosis. *Acta Psychiatrica Scandinavica* **80**, 451–458.
- Butters, N. (1985) Alcoholic Korsakoff's syndrome: some unresolved issues concerning etiology, neuropathology, and cognitive deficits. *Journal of Clinical and Experimental Neuropsychology*, **7**, 181–210.
- Carlen, P. L., Wilkenson, D. A., Wortzman, G. *et al.* (1981) Cerebral atrophy and functional deficits in alcoholics without apparent liver disease. *Neurology* **31**, 377–385.
- Christie, J. E., Kean, D. M., Douglas, R. H. B., Engleman, H. M., St. Clair, D. and Blackburn, I. M. (1988) Magnetic resonance imaging in pre-senile dementia of the Alzheimer type, multi-infarct dementia and Korsakoff's syndrome. *Psychological Medicine* **18**, 319–329.
- de la Monte, S. M., (1988) Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Archives of Neurology*, **45**, 990–992.
- Emsley, R. A., Roberts, M. C., Aalbers, C., Taljaard, F. J. J., Kapnias, S., Pieters, H. C. and Kotze, T. J. (1995) Vasopressin secretion and memory impairment in alcoholic Korsakoff's syndrome. *Alcohol and Alcoholism* **30**, 223–229.
- Geremia, G. K. and Huckman, M. S. (1992) Degenerative diseases of the cerebral hemispheres, brainstem and cerebellum. In *Radiology: Diagnosis – Imaging – Intervention*, Vol. 3, Taveras, J. M. and Ferucci, J. T. eds. Philadelphia, Lippincott.
- Harper, C. (1983) The incidence of Wernicke's encephalopathy in Australia—a neuropathological study of 131 cases. *Journal of Neurology, Neurosurgery and Psychiatry* **46**, 593–597.
- Harper, C. G., Kril, J. J. and Holloway, R. L. (1985) Brain shrinkage in chronic alcoholics: a pathological study. *British Medical Journal* **290**, 501–504.
- Hunter, R., McLuskie, R., Wyper, D., Patterson, J., Christie, J. E., Brooks, D. N., McCulloch, J., Fink, G. and Goodwin, G. M. (1989) The pattern of function-related regional cerebral blood flow investigated by single photon emission tomography with <sup>99m</sup>Tc-HMPAO in patients with presenile Alzheimer's disease and Korsakoff's psychosis. *Psychological Medicine* **19**, 847–855.
- Jacobson, R. (1986) The contributions of sex and drinking history to the CT brain scan changes in alcoholics. *Psychological Medicine* **16**, 547–559.
- Jacobson, R. R. and Lishman, W. A. (1987) Selective memory loss and global intellectual deficits in alcoholic Korsakoff's syndrome. *Psychological*

- Medicine* 17, 649–655.
- Jacobson, R. R. and Lishman, W. A. (1990) Cortical and diencephalic lesions in Korsakoff's syndrome: a clinical and CT scan study. *Psychological Medicine* 1990 20, 63–75.
- Jacobson, R. R., Acker, C. F. and Lishman, W. A. (1990) Patterns of neuropsychological deficit in alcoholic Korsakoff's syndrome. *Psychological Medicine* 29, 321–334.
- Jernigan, T. L., Schafer, K., Butters, N. and Cermak, L. S. (1991) Magnetic resonance imaging of alcoholic Korsakoff patients. *Neuropsychopharmacology* 4, 175–186.
- Kopelman, M. D. (1995) The Korsakoff syndrome. *British Journal of Psychiatry* 166, 154–173.
- Lishman, W. A., Jacobson, R. R. and Acker, C. (1987) Brain damage in alcoholism: current concepts. *Acta Medica Scandinavica* 717, 5–17.
- Ron, M. A. (1983) The alcoholic brain: CT scan and psychological findings. *Psychological Medicine Monograph Supplement* 3.
- Shimamura, A. P., Jernigan, T. L. and Squire, L. R. (1988) Korsakoff's syndrome: radiological (CT) findings and neuropsychological correlates. *Journal of Neuroscience* 8, 4400–4410.
- Victor, M., Adams, R. D. and Collins, G. H. (1989) In *Wernicke–Korsakoff Syndrome and Related Neurologic Disorders due to Alcoholism and Malnutrition*, 2nd edn, pp. 61–110. F. A. Davis Co., Philadelphia.