Brain correlates of memory dysfunction in alcoholic Korsakoff’s syndrome


Abstract

Objectives—to investigate the relation between anterograde amnesia andatrophy of brain structures involved in memory processing in alcoholic Korsakoff’s syndrome.

Methods—The volume of brain structures involved in memory processing was measured with MRI from 13 subjects with Korsakoff’s syndrome, 13 subjects with chronic alcoholism without Korsakoff’s syndrome, and 13 control subjects. The brain structures analysed were the hippocampus, the parahippocampal gyrus, the mamillary bodies, the third ventricle, and the thalamus. Brain volumes were correlated with the delayed recall of a verbal learning test.

Results—Compared with subjects with chronic alcoholism and control subjects, subjects with Korsakoff’s syndrome had a reduced volume of the hippocampus, the mamillary bodies, and the thalamus, and enlargement of the third ventricle. The impairment of delayed recall correlated with the volume of the third ventricle (r=−0.55, p=0.05) in the Korsakoff group.

Conclusions—Anterograde amnesia in alcoholic Korsakoff’s syndrome is associated with atrophy of the nuclei in the midline of the thalamus, but not with atrophy of the mamillary bodies, the hippocampus, or the parahippocampal gyrus.

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Keywords: Korsakoff’s syndrome; alcoholism; memory; magnetic resonance imaging

Anterograde amnesia is one of the most prominent features of Korsakoff’s syndrome.1 The brain correlate of the anterograde amnesia in Korsakoff’s syndrome is still controversial. Neuroimaging and neuropathological studies have indicated that several structures may be the brain substrate for anterograde amnesia including the mediodorsal nucleus of the thalamus,2–3 the paratenial nucleus of the thalamus,4–5 the mamillary bodies,5–7 the frontal cortex,8 the cingulate gyrus,9 the nucleus basalis of Meynert,10 the nucleus coeruleus,11 the hippocampus,10,11 and the amygdala.10,11 It is surprising that none of the neuroimaging studies so far made use of volumetry on MRI. The advantage of volumetry is that it can demonstrate correlations between the volume of brain structures and memory impairment.12 Another advantage of this technique is that the volume of brain structures and cognitive function can be measured more or less at the same time, by contrast with postmortem studies.

The aim of the present study was to investigate in subjects with alcoholic Korsakoff’s syndrome the relation between anterograde amnesia and the volume of brain structures that are known to be involved in memory processing, focusing on structures of the limbic system. We measured the volume of the hippocampus, the parahippocampal gyrus, the mamillary bodies, and the thalamus on high resolution MRI. We also measured the volume of the third ventricle because dilatation of this structure may reflect atrophy of nuclei in the midline of the thalamus, including the mediodorsal nucleus of the thalamus.13 All the subjects with Korsakoff’s syndrome were alcoholics. Because prolonged alcohol intake is neurotoxic, we included a control group of alcoholics without Korsakoff’s syndrome to identify brain abnormalities that are due to thiamine deficiency and not to prolonged alcohol intake. A second control group consisted of matched healthy volunteers. Care was taken to match the three groups on an individual basis for age, sex, and education. We first determined which brain structures were significantly different between alcoholics with Korsakoff’s syndrome and alcoholics without the syndrome. We then correlated the volume of the structures that were significantly different in subjects with Korsakoff’s syndrome with the severity of anterograde amnesia in these patients.

Methods

SUBJECTS

Thirteen patients with alcohol induced persistent amnestic disorder (Korsakoff’s syndrome; DSM-IV 291.1), 13 patients with alcohol dependence (DSM-IV 303.90), and 13 healthy control subjects participated in the study. These groups are referred to as the Korsakoff group, alcoholic group, and control group, respectively. Patients were diagnosed by a multidisciplinary team consisting of a neuropsychiatrist, a neuropsychologist, and a neurologist. The patients were recruited from specialized departments for patients with Korsakoff’s syndrome or chronic alcoholism from the Vincent van Gogh Institute for Mental Health in Venray, the Netherlands. All patients were abstinent for at least 1 month. The control subjects were recruited via newspaper advertisements. Exclusion criteria for all subjects were: age older than 56 years (because of the interaction between age and alcohol related brain damage13), an intelligence...
p<0.001 compared with alcoholic group and control group.

Values are means (SD).

Table 1  Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Korsakoff</th>
<th>Alcoholic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45.7 (6.3)</td>
<td>45.9 (6.1)</td>
<td>45.9 (5.6)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>11M:2F</td>
<td>11M:2F</td>
<td>11M:2F</td>
</tr>
<tr>
<td>Education (y)</td>
<td>10.8 (3.2)</td>
<td>10.9 (3.1)</td>
<td>11.4 (2.7)</td>
</tr>
<tr>
<td>Alcohol misuse (y)</td>
<td>17.1 (7.5)</td>
<td>17.7 (8.0)</td>
<td>0</td>
</tr>
<tr>
<td>IQ score</td>
<td>104 (14.9)</td>
<td>112 (10.6)</td>
<td>111 (7.4)</td>
</tr>
<tr>
<td>Delayed recall (z score)</td>
<td>−2.82 (0.61)*</td>
<td>−0.09 (1.2)</td>
<td>−0.01 (1.1)</td>
</tr>
</tbody>
</table>

*P<0.001 compared with alcoholic group and control group.

quotient below 80 (to exclude subjects with generalised cognitive impairment), the use of psychotropic medication, the presence of depression, psychotic disorders, anxiety disorders, dementia, diabetes mellitus, liver disease, other CNS diseases, and cardiac, pulmonary, or endocrine diseases that could affect cognitive functioning. Exclusion criteria for control subjects also included a history of alcohol dependence or a current intake or a history (longer than 1 month) of alcohol intake of 28 or more units a week. Subjects with Korsakoff’s syndrome who were not amnestic on neuropsychological testing were also excluded. Written informed consent was obtained from all subjects.

The three groups were matched for age, sex, and education. Subject characteristics are shown in table 1. The duration of alcohol misuse was estimated from the history of the patient and an informed other person, and by examining medical charts. No differences existed in the duration of alcohol misuse between the subjects with Korsakoff’s syndrome and the subjects with chronic alcoholism (table 1).

NEUROPSYCHOLOGICAL METHODOLOGY
The neuropsychological assessment has been described in detail elsewhere. Anterograde amnesia was assessed with the delayed recall of the auditory verbal learning test. Fifteen words were presented five times and after each presentation the subject was asked to reproduce as many words as possible. After 20 minutes, during which non-verbal tests were performed, the delayed recall was tested. The data are expressed as z scores. The z score is the number of SDs that the score deviates from the expected score in a normal population of a given age, sex, and education. The z scores were based on a reference population of 1870 normal and healthy subjects randomly selected from a registry of general practitioners. As expected, the Korsakoff group performed significantly worse than the alcoholic group and the control group on the delayed recall task (table 1). No differences were found between the alcoholic group and the control group.

The shortened form of the Wechsler adult intelligence scale was administered to the patient groups to obtain a measure of general intelligence, and the shortened form of an equivalent Dutch intelligence test, the Groningen intelligence test, was administered to the control group for the same purpose. No significant differences existed between the three groups (table 1).

MRI METHODOLOGY
A 3D volumetric scan (T1 weighted, fast field echo, TR 24 ms, TE 7 ms, flip angle 30°, number of averages=2, FOV 230 mm, resolution 256x154), and an inversion recovery (IR) scan (TR 2107 ms, TE 18 ms, turbofactor=3, flip angle 90°, number of averages=2, FOV 230 mm, resolution 256x177) were made on a 1.5 Tesla scanner (Gyrosan ACS-II, Philips). The slice thickness of the 3D volumetric scan was 1.5 mm and the scan axis was coronal, perpendicular to the intercommissural line. The slice thickness of the IR scan was 3 mm and the scan axis was coronal, perpendicular to the long axis of the hippocampus. The thalamus was measured on the IR scan and all other structures on the 3D volume scan.

Data were transferred to a SUN workstation and the regions of interest were measured with ShowImage (developed at the Department of Clinical Physics and Informatics, Vrije Universiteit, Amsterdam, The Netherlands). A seed function was used to measure the third ventricle. The cut off level between CSF and brain was visually adjusted by the rater on each slice. The other structures were manually traced with a mouse driven cursor. All measurements were taken in a rostrocaudal direction. The volumes of the left side and right side were added in all analyses as the pathological changes in Korsakoff syndrome and alcoholism are bilateral. The volume of the brain structures was calculated by multiplying the surface area of each region of interest by the slice thickness and summing the volumes of all slices on which the structure was measured. Measurements were done with reference to several anatomical atlases. Each structure was measured by one rater who was blinded to all clinical information.

METHODOLOGY OF BRAIN MEASUREMENTS
Hippocampus
Measurements started with the slice on which both the semianular sulcus and a notch between the amygdala and the hippocampus in the medial wall of the lateral ventricle were visible. Then every second slice was measured. The last slice was the slice before the slice on which the crura of the fornices were visible. On average 10 (range 8–13) slices on each side were measured. The measurements included the hippocampus proper, the dentate gyrus, the alveus, and the portion of the subiculum which lies directly underneath the hippocampus.

Parahippocampal gyrus
The same slices on which the hippocampus was measured were used, except for the last slice in order not to include the isthmus of the cingulate gyrus. The upper boundary was the hippocampus or the transverse fissure and the lateral boundary was the collateral sulcus. If this sulcus was not visible, a straight line was drawn perpendicular to the temporal stem through the centre of the first gyrus at the medial site of the temporal stem. The brain tissue medial to this line was considered as the parahippocampal gyrus. The lower and medial
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Intracranial area
The cranial area was measured on three slices: on the first slice on which the third ventricle was measured, on the second slice on which the mamillary bodies were measured, and on the last slice on which the third ventricle was measured. The volume of each section was derived by tracing the outline of the supratentorial compartment, following the dural and tentorial margins.

Intraobserver variability
The structures on 10 scans were remeasured. Pearson’s correlation coefficient between the first and second measurements was 0.91 for the hippocampus, 0.91 for the parahippocampal gyrus, 0.98 for the third ventricle, 0.90 for the whole thalamus, 0.86 for the mamillary bodies, and 0.99 for the intracranial area. These correlations indicate a high level of intrarater agreement for all measurements.

Statistical analysis
The data were analysed using SPSS for the Macintosh 4.0 (SPSS Inc, Chigaco, IL, USA). Categorical data were analysed by χ² test. Group comparisons of continuous data were analysed with a t test. Linear regression analysis was used to analyse the relation between memory score and brain volume. All tests were two tailed, and the significance level was set at 0.05.
Table 2 Brain volumes

<table>
<thead>
<tr>
<th></th>
<th>Korsakoff (Kors)</th>
<th>Alcoholic (Alc)</th>
<th>Control (Con)</th>
<th>p Value</th>
<th>Kors v Alc</th>
<th>Kors v Con</th>
<th>Alc v Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>4.27 (0.28)</td>
<td>4.55 (0.35)</td>
<td>4.52 (0.23)</td>
<td>0.03</td>
<td>0.02</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>6.15 (0.44)</td>
<td>6.15 (0.45)</td>
<td>6.46 (0.40)</td>
<td>1.0</td>
<td>0.07</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Mamillary bodies</td>
<td>0.049 (0.011)</td>
<td>0.068 (0.015)</td>
<td>0.069 (0.013)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Third ventricle</td>
<td>1.79 (0.33)</td>
<td>1.30 (0.44)</td>
<td>1.04 (0.28)</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>12.0 (1.2)</td>
<td>13.5 (1.1)</td>
<td>13.3 (1.4)</td>
<td>0.005</td>
<td>0.02</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Intracranial area</td>
<td>33.0 (2.5)</td>
<td>33.1 (2.1)</td>
<td>33.9 (1.5)</td>
<td>0.91</td>
<td>0.24</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SD) in cm³.

Discussion

Volumetry on high resolution MRI showed that the volume of several brain structures that are involved in memory processing was decreased in subjects with Korsakoff’s syndrome. The anterograde amnesia of the subjects with Korsakoff’s syndrome correlated significantly with the volume of the third ventricle, suggesting that lesions in nuclei in the midline of the thalamus are responsible for the anterograde amnesia of these patients. The involvement of the nuclei in the midline of the thalamus in the anterograde amnesia has also been reported in other studies of patients with Korsakoff syndrome.2,3 Of these midline nuclei, the mediodorsal nucleus has often been related to anterograde amnesia,2,26 but there are also studies that contradict the role of this structure in anterograde amnesia.3,4,5 Other nuclei in the midline of the thalamus that may be involved in the anterograde amnesia of Korsakoff’s syndrome are the parataenial nucleus, the paraventricular nucleus, the intermediodorsal nucleus, the reuniens nucleus, and the rhomboid nucleus.4,5 The severity of the anterograde amnesia may also depend on the number of nuclei that are affected.10

Although the volume of the mamillary bodies was reduced in most subjects in the Korsakoff group, it did not correlate with the severity of anterograde amnesia. This is by contrast with earlier studies that showed a positive relation between mamillary body size and memory.11 The discrepancy might be due to methodological shortcomings in these earlier studies because either the number of subjects was small (n=4),7 or the correlation was performed in a sample of alcoholics that included both subjects without cognitive impairment and subjects with severe cognitive impairment.6 Other studies have questioned the role of the mamillary bodies in anterograde amnesia.2,11 Victor et al reported that some subjects with severe atrophy of the mamillary bodies were not amnesic.2 Shear et al showed that several patients with Korsakoff’s syndrome and severe amnesia had no atrophy of the mamillary bodies.11 Thus atrophy of the mamillary bodies seems not to be sufficient or necessary to cause severe anterograde amnesia.

The medial temporal lobe seemed not to be involved in the anterograde amnesia. The volume of the hippocampus was modestly reduced in the subjects with Korsakoff’s syndrome but it did not correlate with the score on the delayed recall task. A reduced volume of the hippocampus in Korsakoff’s syndrome has been found in one neuropathological study.11 We found that the parahippocampal gyrus tended to be smaller in the alcoholics with or without Korsakoff’s syndrome, which suggests that alcohol may have a neurotoxic effect on this structure.

We could not replicate the finding that atrophy of the mamillary body is common in alcoholics without amnesia.11,12 However, these studies used qualitative rating scales which are less accurate than volumetry. The alcoholics in our study did not have atrophy of the hippocampus, by contrast with other studies.22

One of the strong points of the study was that the brain structures were assessed with volumetry. Earlier neuroimaging studies used linear or qualitative measures, or did not follow anatomical boundaries. The exclusion criteria minimalised the potentially confounding effects of age and concomittant disorders that are often found in subjects with chronic alcoholism. A limitation of the study is that we did not assess all brain structures involved in memory processing such as the frontal lobe, the amygdala, and the cingulate gyrus. These structures may also be associated with the anterograde amnesia. Although our sample was large in comparison with that of other studies,
the group size was still small and this has limited the power of the study. Correlational studies in general have the disadvantage that they show correlations and not causal relations. Studies using functional imaging techniques during neuropsychological testing may therefore further increase insight into the brain substrate of anterograde amnesia in alcoholic Korsakoff's syndrome.

In conclusion, this correlational study indicated that anterograde amnesia in alcoholic Korsakoff's syndrome is associated with atrophy of nuclei in the midline of the thalamus, but not with atrophy of the mamillary bodies, the hippocampus, or the parahippocampal gyrus.

We thank Dr T Wijgdeveld for help in recruiting the subjects with alcoholism, and D Tisserand and S Kumar Rao for assisting in the measurement of the brain structures.

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