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Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings

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ABSTRACT

Background. Neuropsychological and imaging studies suggest that frontal dysfunction may occur in apparently normal chronic alcoholic subjects.

Methods. To investigate this issue further, we performed neuropsychological and fluorodeoxyglucose-PET studies in 17 chronic alcoholics without patent neurological and psychiatric complications.

Results. Metabolic abnormalities were found in the mediofrontal and in the left dorsolateral prefrontal cortex, but not in the orbitofrontal cortex. Neuropsychological testing revealed significantly reduced verbal fluency and impaired performance on the Stroop test. The mediofrontal hypometabolism correlated with the reduction in verbal fluency and the time necessary to perform the interference condition of the Stroop test. The left dorsolateral prefrontal hypometabolism correlated with the number of errors on the Stroop test.

Conclusion. These data indicate that circumscribed frontal dysfunctions may occur in chronic alcoholic subjects before clinically obvious neurological complications, and may account for some of the alcohol-related neuropsychological and behavioural impairments.

INTRODUCTION

Chronic alcoholism has been associated with global changes in brain morphology, such as cortico-subcortical atrophy, reported by pneumo-encephalographic, CT scan and MRI studies (Brewer & Perrett, 1971; Ishii 1983; Jernigan *et al.* 1991) or decreased brain weight (Harper & Blumberg, 1982). In contrast, it is often believed that in the absence of well-defined neurological complications, chronic alcoholism does not alter specific brain systems. This view largely rests on the fact that classical neuropathological studies fail to find specific alcohol-related brain lesions (Adams & Victor, 1993). However, recent data suggest that frontal lobe structures may be specifically altered. Neuropsychological studies have reported selective alterations of frontal executive functions, such as planning or problem-solving ability, in neurologically normal alcoholic patients (Pishkin *et al.* 1985). Moderate neuronal loss has been reported in the frontal cortex and in the cingulate gyrus of alcoholic subjects (Kril & Harper, 1989). In addition, chronic alcoholic patients often suffer from severe behavioural abnormalities, typically characterized by aggressivity, poor adaptation to socio-professional life and frequent breakdowns of family life. Interestingly, very similar abnormalities have been described

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in several patients with frontobasal lesions (Eslinger & Damasio, 1985).

An alcoholic-selective frontal dysfunction is supported by several functional imaging studies. In a previous PET study, we reported a decrease in glucose consumption that selectively affected the medial part of both frontal lobes, including the anterior cingulate gyrus, and suggested that this 'fronto-limbic' hypometabolism may contribute to the behavioural consequences of alcoholism (Samson *et al.* 1986). More recent PET studies have confirmed a glucose hypometabolism in the same part of frontal cortex (Gilman *et al.* 1990; Adams *et al.* 1993) and single photon emission computerized tomography studies showed a decrease of regional cerebral blood flow in the right anterior cingulate (O'Carroll *et al.* 1991) and in the anterior frontal lobes (Nicolas *et al.* 1993). Others found hypometabolism in much larger frontal areas, often combined with a global cortical hypometabolism (Sachs *et al.* 1987; Volkow *et al.* 1992, 1994; Wang *et al.* 1993). These frontal metabolic abnormalities could be linked to some cognitive impairments as values of frontal metabolism were reported to correlate with mental control and category subtest scores, in alcoholics (Gilman *et al.* 1990; Wang *et al.* 1993). Also cingulate metabolism correlated with Wisconsin Card Sorting Test scores in such patients (Adams *et al.* 1993).

To investigate further the involvement of frontal cortical regions and the associated cognitive defects, we studied the frontal metabolic changes in relation with neuropsychological deficits in a population of neurologically normal, but behaviourally impaired chronic alcoholic patients. In the present study, we report data in 17 chronic alcoholics without patent neurological and psychiatric complications, using verbal fluency and Stroop test evaluation, and FDG-PET examination.

METHOD

Patients

Selection criteria and evaluation

We selected patients hospitalized for detoxification in a dedicated unit. The inclusion criteria were: DSM-III-R (APA, 1987) criteria of alcohol dependence; normal clinical, psychiatric and neurological examination; prothrombin time $> 80\%$ of control values; age ranging from 25 to 65 years; hospitalization duration ranging from 1 week to 1 month; and, abstinence since hospitalization. The exclusion criteria were: persistent withdrawal signs; severe hepatic insufficiency; patent neurological, psychiatric or somatic disorders; history of metabolic or Wernicke encephalopathy; epilepsy; severe head injury; drug abuse; contra-indication of intra-arterial catheterization or MRI. The only medications allowed during hospitalization were meprobamate and vitamins. Informed written consent was obtained in all cases and the procedures used here were approved by the local Ethical Committee.

The evaluation of the patients was performed within 48 h of the PET study, and included a general physical and neurological examination, standard laboratory blood tests, a semi-structured psychiatric interview, and neuropsychological testing. The psychiatric interview included a systematic history of the alcoholism and its behavioural consequences, using a standardized questionnaire covering family and professional history, and number of previous detoxifications.

The neuropsychological evaluation was performed the day of the PET scan and included the WAIS global IQ test and the Wechsler memory scale; frontal executive functions were evaluated with verbal fluency tasks and the Stroop test (Stroop, 1935). These tasks were selected because both activate the anterior cingulate gyrus in normal controls (Pardo *et al.* 1990; Friston *et al.* 1991). Both semantic (number of animals per minute) and formal (number of words beginning with m, p, d per minute) verbal fluencies were measured, but since the results were highly intercorrelated ($r_s = +0{\cdot}79$; $P < 0{\cdot}001$), we calculated a total fluency score, as the sum of the semantic and the formal fluency scores. In the Stroop test, we assessed the number of errors and the time needed to perform the condition of the task of interference. Neuropsychological evaluation was available in all but one subject. All results are given as mean $\pm$ S.D.

Nine normal, non-alcoholic subjects (six men, three women, 36 ± 5-years-old) were recruited as controls for imaging studies. Neuropsychological evaluation was performed in eight subjects. These healthy paid volunteers had normal

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Table 1. *Clinical data in* 17 *alcoholic patients*

	Sex	Age	Recent daily consumption (g)	Duration (years)	gammaGT (IU)	RCB volume (μ^3)
A1	M	26	500	4	994	97
A2	F	38	150	3	364	114
A3	M	41	200	10	223	96
A4	M	43	ND	20	1228	111
A5	M	47	200	28	579	101
A6	M	51	200	30	323	101
A7	F	32	150	10	673	109
A8	M	31	50	5	47	107
A9	F	52	300	2	32	102
A10	F	32	150	5	235	109
A11	M	36	200	18	449	116
A12	M	39	400	13	133	95
A13	M	25	360	8	68	93
A14	M	47	350	25	62	92
A15	F	63	100	6	227	110
A16	F	52	180	22	46	93
A17	M	31	400	7	18	98
Mean		40	243	13	335	103
S.D.		11	126	9	353	8

RCB, red blood cells; gammaGT, gamma glutamyl-transferase; ND, not determined.
The duration of alcoholism and the recent daily consumption are based on the report of each patient.
Gamma GT and RCB volume were measured within 2 days of the PET study.

clinical, neurological, psychiatric examination, and normal MRI images.

Description of the alcoholic population

We examined 11 men and six women (14 right-handed and three left-handed). Their mean age was 40 ± 10 years (range 26–63), not significantly different from that of controls ($P = 0{\cdot}27$). Drinking habits and biological markers of alcoholism are shown in Table 1. Prothrombin time was 100% of control values in all subjects. Clinical neurological examination was normal. PET studies were performed 13 ± 5 days after admission. Detoxification was conservatively assessed as the number of days since hospitalization (13 ± 5 days). None of the subjects reached DSM-III-R criteria for depression.

IQ, Wechsler memory scores and educational levels were lower in alcoholic patients than in controls, indicating the lack of amnesia in the alcoholic group (95 ± 11 *v.* 107 ± 10; $P = 0{\cdot}02$/98 ± 10 *v.* 109 ± 7; $P = 0{\cdot}009$/$4{\cdot}24 \pm 1{\cdot}82$ *v.* $7{\cdot}0 \pm 0{\cdot}0$; $P = 0{\cdot}001$).

Most of the patients had impaired adaptation to socioprofessional life. Nine subjects were currently single, and 12 of the 17 had previously divorced. Six had lost their job and were currently unemployed and 12 acknowledged severe work problems related to their alcoholism. Two reported alcohol-related loss of driving privilege. Seven of the subjects had been previously hospitalized for earlier unsuccessful attempts of detoxification.

Brain imaging

For each subject, anatomical (MRI) and functional (PET) studies were performed on the same day and in the same institution. The patient's head was positioned identically for both examinations in order to allow accurate PET-MRI image registration during subsequent analysis. The PET and MRI slices were parallel to the orbitomeatal (OM) plane, so skin marks were made on the head of the subjects. Each subject was positioned in a head-holder with a laser beam aligned on the skin marks, to ensure accurate positioning during the PET and MRI study.

Magnetic resonance imaging

MRI was performed on a 0·5 Tesla MRI imager (MRMAX, General Electric), which has an in-plane spatial resolution of 1 mm. T1 and T2 weighted axial images parallel to the OM plane were obtained. The slice thickness (7 mm) and interslice-space (0·5 mm) of the T1 weighted images were chosen to allow accurate superimposition with the PET slices.

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Positron emission tomography

PET was performed on a four-ring, seven-slice LETI-TTV01 time-of-flight tomograph, which has a resolution of $13 \times 13 \times 12$ mm (full width at half maximum) and which provides seven simultaneous cerebral axial slices (slice thickness 12 mm, interslice-space 3·5 mm). Before the study, a Teflon cannula was placed in a radial artery under local anaesthesia to determine FDG and glucose plasma concentrations. All studies were conducted in a quiet, dimly lit environment with minimal background noise. Subjects were studied at rest, in the morning, with their eyes closed and their ears unplugged. They did not sleep during the examination. Regional cerebral glucose utilization (rCMRglu, in mg/100 ml/min) was measured with the ^{18}[F]-fluorodeoxyglucose (FDG) technique. A transmission scan using ^{68}[Ga]–^{68}[Ge] was obtained, afterwards 3 to 7 mCi ^{18}[F]-fluorodeoxyglucose was injected as an intravenous bolus. Twenty-four blood samples (1 ml each) were collected from the radial artery according to a protocol described elsewhere (Fiorelli *et al*. 1992). Image acquisition started 30 min after the injection and ended at 56 min after the injection. Reconstructed images were corrected for attenuation using the ^{68}[Ga]–^{68}[Ge] transmission scan. Images were quantified with the Sokoloff autoradiographic method adapted to PET by Phelps (Sokoloff *et al*. 1977; Phelps *et al*. 1979).

MRI-PET superimposition

PET and MRI data were transferred to a VAX computer (Digital Equipment Corporation, Maynard, MA) and the MR-PET images put in register using isodensity contours and a custom software allowing in-plane translation and rotation. The accuracy of this registration was assessed by verifying that a successful superimposition was simultaneously obtained at all brain levels. Previously, we showed that simultaneous superimposition cannot be achieved if registration error exceeds 5 mm on the surface of the cortex in *x*, *y* or *z* axes (Rémy *et al*. 1994).

Regions of interest (ROIs) and metabolic parameters

Image analysis was performed blind to diagnosis. All regions of interest were drawn on MRI images, and subsequently copied onto the corresponding set of PET images. First, 14 mm thick hemispheric cortical ribbons were drawn on the images localized at OM + 40, + 55, + 70 mm. Each hemispheric ribbon was then divided according to individual MR sulcal anatomy into four large regions, corresponding to frontal, temporal, parietal and occipital lobes. In addition, smaller regions were drawn in three frontal regions, which were localized on MR using Damasio's templates and individual sulci (Damasio & Damasio, 1989). The mediofrontal region was localized in the internal face of the frontal lobes, including the anterior cingulate gyrus (Brodmann's areas 24 and 32), and the adjacent medial part of the prefrontal cortex (medial parts of Brodmann's areas 9 and 10). The dorsolateral prefrontal region included the lateral part of Brodmann's areas 9, 10 and the anterior part of 46. The orbitofrontal region was localized in the interior face of the frontal lobe (Brodmann's areas 11, 25 and part of 47). We did not distinguish left and right mediofrontal regions, because a preliminary analysis showed that regional metabolic values were very highly correlated ($r_s = +0{\cdot}86$; $P < 0{\cdot}001$) in left and right mediofrontal regions, as a probable result of the limited spatial resolution of the camera and the resulting partial volume effect. Finally, because of the importance of inner temporal structures in memory, we also defined a mesiotemporal region, encompassing the hippocampus, and the adjacent perihippocampal cortex.

The global cortical metabolic rate was determined by averaging absolute CMRglu values obtained in the left and right hemispheric cortical ribbons, after verifying the lack of significant right–left asymmetry in both patients and controls. To minimize the effect of global changes in cerebral metabolism, all regional metabolic values were normalized by dividing each regional metabolic value by the global cortical metabolic rate value.

Quantification of MR cortical atrophy

The degree of cortical atrophy was assessed in the whole cortical mantle and within the mediofrontal and the dorsolateral prefrontal regions studied with PET.

An index of global atrophy was assessed on the T2-weighted horizontal image at the level of

the corona radiata, immediately above the roof of the lateral ventricles. On this image, we calculated the ratio between CSF area in the subarachnoid space and brain surface, and we used this ratio as a quantitative index of global cortical atrophy. To determine CSF and brain surfaces, we used a semi-automatic segmentation method, in which CSF–brain interface was determined using a threshold value, corresponding to the mean of the density values of brain and ventricular CSF, as measured in each patient.

Mediofrontal and dorsolateral prefrontal atrophies were measured in frontal areas centred on the PET ROIs, by calculating CSF to brain ratios within standardized circular 6·5 cm^2 regions placed tangentially to the inner table of the cranial vault.

Statistical analysis

Statistical analyses were performed with Student's *t* tests and appropriate Bonferroni's correction for multiple comparisons, and with Spearman's non-parametric correlations. All correlations between neuropsychological, MR atrophy index and metabolic values were performed within the group of alcoholic subjects. In order to reduce the total number of correlations, and the risk of false positive findings, it was *a priori* decided that the correlations would only be carried out for the regions with a significant hypometabolism, and for the global cortical metabolic rate values.

RESULTS

Positron emission tomography

Global cortical metabolism was decreased in patients ($4{\cdot}51 \pm 1{\cdot}04$ *v.* $5{\cdot}67 \pm 0{\cdot}97$ ml/min/100 mg; $P = 0{\cdot}01$). We found a significant decrease of metabolic values in all cortical lobar regions (frontal lobe: $4{\cdot}45 \pm 1{\cdot}07$ *v.* $5{\cdot}78 \pm 1{\cdot}03$ ml/min/100 mg; $P = 0{\cdot}005$ – temporal lobe: $4{\cdot}37 \pm 1{\cdot}01$ *v.* $5{\cdot}59 \pm 1{\cdot}02$ ml/min/100 mg; $P = 0{\cdot}01$ – parietal lobe: $4{\cdot}63 \pm 1{\cdot}14$ *v.* $5{\cdot}58 \pm 0{\cdot}87$ ml/min/100 mg; $P = 0{\cdot}04$), except for the occipital lobe ($5{\cdot}02 \pm 1{\cdot}11$ *v.* $5{\cdot}95 \pm 1{\cdot}13$ ml/min/100 mg; NS).

The analysis of normalized metabolic values revealed a significant decrease in the right and left frontal lobes, in the mediofrontal region, and in the left prefrontal region (Table 2). The apparent increase in the left parietal lobe was likely due to the effect of the frontal hypometabolism on the global cortical metabolism, as previously found in other studies (D'Antona *et al.* 1985). After Bonferroni's correction, the hypometabolism remained statistically significant in the left frontal lobe ($P = 0{\cdot}048$), in the mediofrontal region ($P = 0{\cdot}002$) and close to significance in the left prefrontal region ($P = 0{\cdot}084$). Using global IQ as a covariate, the hypometabolism remained statistically significant in the left frontal lobe ($P = 0{\cdot}027$), the mediofrontal region ($P = 0{\cdot}005$), and failed to reach significance in the left prefrontal region ($P = 0{\cdot}11$). The mediofrontal hypometabolism is clearly visible on the PET images of a chronic alcoholic subject, and contrasts with the very mild degree of cortical atrophy in the same area (Fig. 1).

Verbal fluency and Stroop tasks

Verbal fluency was significantly decreased in alcoholic patients (56 ± 15 *v.* 74 ± 16 words; $P = 0{\cdot}014$). In the Stroop test, alcoholics performed slower (131 ± 29 s *v.* 93 ± 18 s; $P = 0{\cdot}003$), and made more errors ($4{\cdot}1 \pm 3{\cdot}8$ *v.* $0{\cdot}7 \pm 1$; $P = 0{\cdot}026$) during the interference condition than normal subjects. The difference in Stroop test time remained significant using number of errors as a covariate ($P = 0{\cdot}05$).

MR measurements of cortical atrophy

The analysis of CSF to brain surface ratios showed a significant global cortical atrophy in alcoholic patients ($0{\cdot}28 \pm 0{\cdot}06$ *v.* $0{\cdot}15 \pm 0{\cdot}07$; $P < 0{\cdot}001$). The atrophy was also detected in the mediofrontal ($0{\cdot}27 \pm 0{\cdot}07$ *v.* $0{\cdot}16 \pm 0{\cdot}05$; $P = 0{\cdot}001$), the right dorsolateral prefrontal ($0{\cdot}12 \pm 0{\cdot}04$ *v.* $0{\cdot}07 \pm 0{\cdot}04$; $P = 0{\cdot}005$) and the left dorsolateral prefrontal ($0{\cdot}13 \pm 0{\cdot}04$ *v.* $0{\cdot}06 \pm 0{\cdot}03$; $P < 0{\cdot}001$) regions. However, the frontal atrophy had the same magnitude as the global cortical atrophy, since frontal to global atrophy index ratios were similar in patients and controls.

Cortical atrophy appeared not directly linked to the metabolic abnormalities, since global metabolism did not significantly correlate with global cortical atrophy ($r_s = -0{\cdot}293$; $P = 0{\cdot}25$), and the regional metabolic values were not significantly correlated with focal cortical atro-

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Table 2. *Normalized metabolic data in alcoholic patients and healthy controls*

	Alcoholic patients ($N = 17$)		Healthy controls ($N = 9$)		
	Mean	S.D.	Mean	S.D.	*P*
Lobar regions					
Right frontal	0·990	0·035	1·018	0·021	*
Left frontal	0·980	0·034	1·020	0·026	**
Right temporal	0·966	0·049	0·963	0·021	NS
Left temporal	0·971	0·036	0·973	0·038	NS
Right parietal	1·005	0·043	0·983	0·046	NS
Left parietal	1·043	0·049	0·992	0·044	*
Right occipital	1·108	0·080	1·039	0·120	NS
Left occipital	1·127	0·087	1·064	0·117	NS
Frontal regions					
Mediofrontal	0·961	0·044	1·030	0·030	***
Right dorsolateral prefrontal	0·990	0·054	1·017	0·042	NS
Left dorsolateral prefrontal	0·976	0·044	1·028	0·052	*
Right orbitofrontal	1·059	0·098	1·005	0·129	NS
Left orbitofrontal	1·041	0·119	0·986	0·115	
Temporal regions					
Right mesiotemporal	0·789	0·084	0·761	0·066	NS
Left mesiotemporal	0·799	0·099	0·770	0·057	NS

* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$; NS, not significant.

phy, neither in the mediofrontal region ($r_s = -0·459$; $P = 0·064$), nor in the left prefrontal region ($r_s = -0·165$; $P = 0·54$).

Correlations between metabolic abnormalities and clinical characteristics of the patients

Global cortical metabolism correlated negatively with the biological markers of the current degree of alcoholism, i.e. gammaGT ($r_s = -0·72$; $P = 0·001$) and red blood cells (RBC) volume ($r_s = -0·48$; $P = 0·05$) values, but not with the explicit (estimation of drinking severity and duration), or implicit (age) indices of cumulative severity of alcoholism. By contrast, mediofrontal metabolism was correlated with age ($r_s = -0·49$; $P = 0·04$), but not with gammaGT, or with RBC volume values. Left prefrontal metabolism did not correlate with any of these parameters. None of the frontal metabolic abnormalities correlated to the patients' IQ and educational level, two general parameters that were different in the patients and in the control group.

Correlations between neuropsychological, metabolic and structural abnormalities in patients.

The verbal fluency correlated significantly with the metabolism of the mediofrontal region ($r_s = +0·55$; $P = 0·026$). To investigate the effect of frontal atrophy on this result, we performed a multiple regression model using verbal fluency as dependent variable and mediofrontal metabolism and mediofrontal atrophy as independent variables. The partial regression coefficient was highly significant for the metabolism ($r_p = 0·65$; $P = 0·008$), but not for atrophy ($r_p = 0·42$; $P = 0·12$). The verbal fluency did not correlate with the other metabolic parameters. Significant correlations were also found on the Stroop test. They occurred in different regions for the interference time and the number of errors. The interference time correlated with the metabolism of the mediofrontal region ($r_s = -0·515$; $P = 0·041$). With multiple regression, a similar, although not significant trend was found for the metabolism ($r_p = -0·45$; $P = 0·09$), but not for atrophy ($r_p = 0·008$; $P = 0·98$). The number of errors correlated with the metabolism of the left prefrontal region ($r_s = -0·694$; $P = 0·003$). This correlation remained significant if the patient with 13 errors was excluded as a possible outlier. With multiple regression, the number of errors remained highly significant with the left prefrontal region ($r_p = -0·64$; $P = 0·009$) and not with the left prefrontal atrophy ($r_p = -0·25$; $P = 0·38$).

The simple correlations between the neuropsychological performances and the indices of MR cortical atrophy obtained in these frontal regions were not significant. In addition, the

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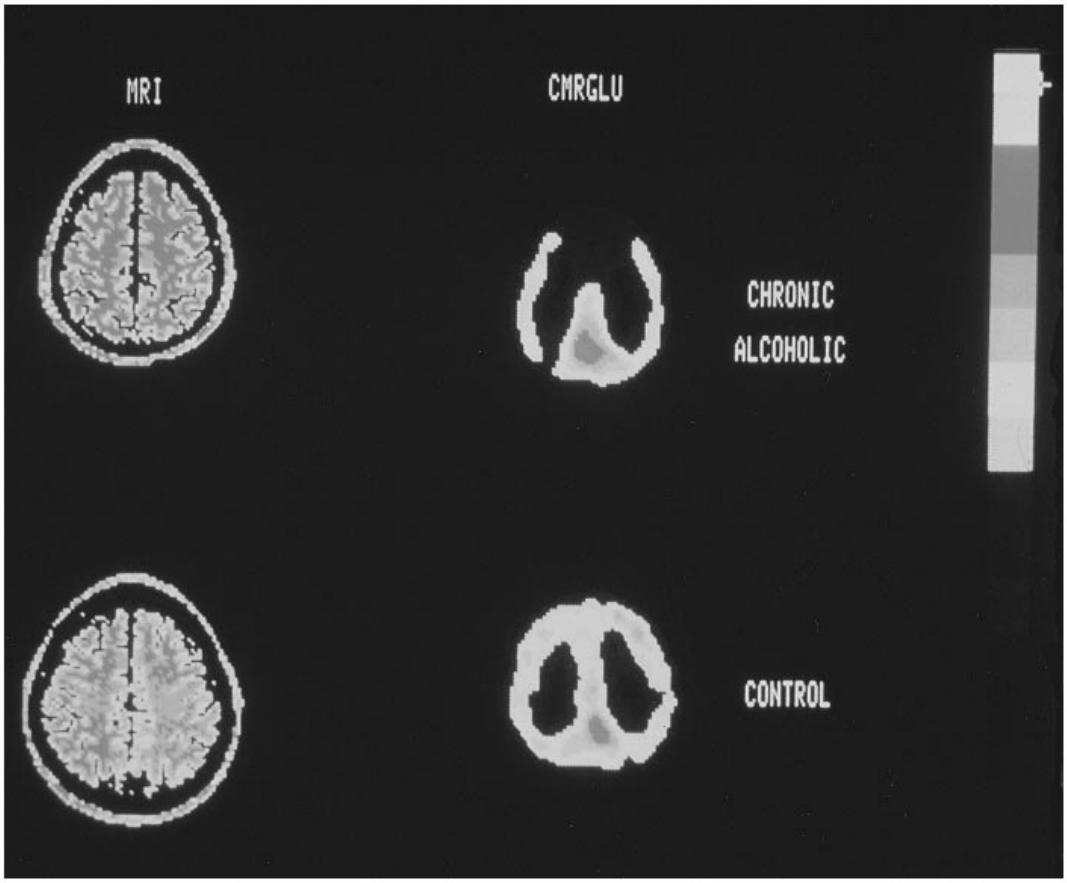

FIG. 1. MRI and PET images in an alcoholic subject and a healthy volunteer. The mediofrontal hypometabolism is clearly visible on the PET image of the alcoholic patient, despite the very slight degree of cortical atrophy at MRI.

index of global cortical atrophy was not correlated with any of the neuropsychological measurements.

The global IQ, the educational level and the Wechsler memory score did not correlate with any of the metabolic abnormalities.

DISCUSSION

We report global metabolic changes and an alteration in the regional metabolic pattern in alcoholic patients. The regional metabolic pattern was characterized by frontal abnormalities, mainly affecting the limbic or limbic-related mediofrontal areas, and to a lesser degree, the left dorsolateral prefrontal cortex.

Global cortical metabolic changes

We found a 20% global reduction of the glucose metabolism in the cerebral cortex, which is consistent with the results of previous PET studies of neurologically intact chronic alcoholics (Sachs *et al*. 1987; Volkow *et al*. 1992; Wang *et al*. 1993). Accumulating data suggest that these global metabolic changes may be reversible after alcohol discontinuation. For example, Volkow *et al*. found that the whole brain metabolic rate returned to almost normal values within 60 days of detoxification (Volkow *et al*. 1994), and correlated with the amount of time since alcohol discontinuation (Volkow *et al*. 1992). This is consistent with the negative

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correlation between global metabolism rate and gammaGT values, an index of the recent severity of alcohol consumption. The reversibility indicates that the global hypometabolism is not caused by permanent brain damage; rather, it may be related to reversible structural or biochemical changes, such as those accounting for the partially reversible alcoholic cortical atrophy or 'shrinkage' (Ron *et al.* 1982). Whatever the mechanism of the global hypometabolism, it should be emphasized that it was of little clinical significance in these patients, since the global hypometabolism did not correlate with any of the neuropsychological or attentional abnormalities.

Regional metabolic changes

Unlike global metabolic changes, regional abnormalities of resting brain glucose metabolism usually reflect functional and/or structural changes in specific brain systems that can often be linked to specific behavioural dysfunctions (see for example Metter, 1991). Here, the only focal metabolic abnormalities were found within the frontal lobes. Frontal hypometabolism has been previously reported in many of the FDG PET studies of chronic alcoholic patients (Samson *et al.* 1986; Gilman *et al.* 1990; Adams *et al.* 1993; Wang *et al.* 1992, 1993; Volkow *et al.* 1992, 1994), and in three of these studies, the hypometabolism occurred selectively in the medial part of the frontal lobes, including the anterior cingulate gyrus (Samson *et al.* 1986; Gilman *et al.* 1990; Adams *et al.* 1993). The frontal lobe is of special interest in chronic alcoholism because alcoholic subjects are often impaired on tasks involving executive functions and attention, indicative of frontal dysfunction. Furthermore, the aggressivity and impulsiveness of alcoholic subjects shares some similarity with the neurobehavioural abnormalities recently described in patients with frontal lesions (Eslinger & Damasio, 1985).

In the present study, we showed that metabolic dysfunction predominated in the mediofrontal cortex, which was the most significantly affected. Since this area is considered as a bridge between the prefrontal cortex and the limbic system (Baleydier & Mauguiere, 1980), one may speculate that its dysfunction explains some of the behavioural abnormalities of alcoholic subjects. We also found a significant hypometabolism in the left dorsolateral prefrontal cortex, which plays an important role in cognitive and working memory functions (Wilson *et al.* 1993). These findings may be an artefact of failure to match for pre-morbid IQ, and therefore it would be useful to replicate these findings in samples matched for pre-morbid intelligence. Yet, using global IQ as covariate did not modify our metabolic findings. Furthermore, IQ values did not correlate with metabolic abnormalities, or with verbal fluency and Stroop test in these subjects.

The neurobehavioural significance of the metabolic dysfunctions in these frontal structures is highlighted by their correlations with specific neuropsychological abnormalities. The degree of mediofrontal hypometabolism correlated with the reduction in verbal fluency and with slower realization on the Stroop interference condition. These findings are consistent with PET activations studies in normal subjects, since the mediofrontal region includes the anterior cingulate gyrus, which is activated in both verbal fluency and Stroop tasks (Pardo *et al.* 1990; Friston *et al.* 1991). The left dorsolateral prefrontal metabolism correlated negatively with the number of errors at the Stroop test. A similar correlation has been previously reported in patients with obsessive–compulsive disorder (Martinot *et al.* 1990). It could reflect the involvement of working memory for decision making during the processing of simultaneous interfering information.

An unresolved issue concerns the mechanism of these frontal metabolic abnormalities. They may reflect functional changes in synaptic activity. Such changes should be reversible during detoxification (Volkow *et al.* 1994). However, in the present study, the mediofrontal hypometabolism did not correlate with gammaGT values, which decrease during detoxication. Thus, structural changes may also be considered. Interestingly, neuronal loss from the frontal superior cortex of the brains of alcoholics has been recently documented (Krill & Harper 1989). Alternatively, silent lesions of anterior diencephalic structures may induce a deafferentation hypometabolism of the mediofrontal cortex. Indeed, patients with Korsakoff's disease, who have prominent diencephalic lesions, have a severe mediofrontal hypometabolism (Joyce *et al.* 1991). Interestingly, anterior diencephalic

lesions have been found with an unexpected high frequency in systematic neuropathological examination of alcoholic brains in patients without history of Wernicke–Korsakoff encephalopathy (Torvik *et al*. 1982). This suggests that clinically silent diencephalic lesions may develop in chronic alcoholic patients, as also supported by CT scan studies (Gebhardt *et al*. 1984; Acker *et al*. 1987). This hypothesis is supported in the patients of the present study, whose measures of the diameter of the mamillary bodies on the MRI were found significantly lower than that of the controls ($5{\cdot}2 \pm 0{\cdot}7$ mm *v*. $6{\cdot}6 \pm 0{\cdot}8$ mm; $P < 0{\cdot}001$). Therefore, we hypothesize that slowly developing and clinically silent Wernicke-like diencephalic lesions should be considered as a possible explanation of mediofrontal hypometabolism.

In summary, neurologically normal but behaviourally impaired chronic alcoholic patients suffer not only from global and rather unspecific brain alterations, but also from a specific mediofrontal/anterior cingulate dysfunction, as evidenced here by the finding of converging neuropsychological and metabolic abnormalities. Further studies are indicated to determine to what extent this anterior limbic dysfunction accounts for the development of this addictive behaviour, and of its behavioural consequences.

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