Research Article

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Cerebral magnetic resonance imaging reveals marked abnormalities of brain tissue density in patients with cirrhosis without overt hepatic encephalopathy

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Background & Aims: We applied advanced magnetic resonance imaging and Voxed based Morphometry analysis to assess brain tissue density in patients with cirrhosis.

Methods: Forty eight patients with cirrhosis without overt hepatic encephalopathy (17 Child A, 13 Child B, and 18 Child C) and 51 healthy subjects were matched for age and sex. Seventeen patients had history of overt hepatic encephalopathy, eight of them had minimal hepatic encephalopathy at inclusion, 10 other patients had minimal hepatic encephalopathy at inclusion but without history of previous overt hepatic encephalopathy, and 21 patients had none of these features.

Results: Patients with cirrhosis presented decreased brain density in many areas of the grey and white matter. The extension and size of the affected areas were greater in patients with alcoholic cirrhosis than in those with post-hepatitic cirrhosis and correlated directly with the degree of liver failure and cerebral dysfunction (as estimated by neuropsychological tests and the antecedent of overt hepatic encephalopathy). Twelve additional patients with cirrhosis who underwent liver transplantation were explored after a median time of 11 months (7–50 months) after liver transplant. At the time of liver transplantation, three patients belonged to class A of the Child-Pugh classification, five to class B and four to class C. Compared to healthy subjects, liver transplant patients showed areas of reduced brain density in both grey and white matter.

Conclusions: These results indicate that loss of brain tissue density is common in cirrhosis, progresses during the course of the disease, is greater in patients with history of hepatic encephalopathy, and persists after liver transplantation. The significance, physiopathology, and clinical relevance of this abnormality cannot be ascertained from the current study.

Keywords: Cirrhosis; Hepatic encephalopathy; Magnetic resonance images; Voxel-based Morphometry.

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Introduction

Hepatic encephalopathy is a cerebral disorder of patients with liver failure and/or porto-systemic shunting caused by ammonia and other endogenous substances that escape from hepatic metabolism [1]. The spectrum of the syndrome ranges from minimal hepatic encephalopathy to deep coma. Since hepatic encephalopathy reverses in most patients after appropriate treatment, it is considered a functional disorder [2]. The methodology used to explore cerebral function in cirrhosis includes: the EEG and the mean dominant frequency, neuropsychological tests exploring attention and cognitive functions, and the critical flicker frequency and other recently introduced computerized tests that estimate the reactive ability of the patients to a visual stimulus [3–6]. Most of these tests have been developed to diagnose minimal hepatic encephalopathy.

Magnetic resonance imaging is widely used for research and diagnosis of cerebral diseases. Voxel-based Morphometry, which measures brain tissue density (concentration), has been proved of great interest in the assessment of regional areas of atrophy in neurodegenerative cerebral diseases such as Alzheimer's Disease, Huntington's Chorea, and Multiple Sclerosis [7–11]. Regional areas of density loss diagnosed by Voxel-Based Morphometry in Alzheimer Disease correlate with areas of atrophy on histopathology [12].

The current article reports the first study using Voxel-based Morphometry in a large series of patients with cirrhosis of different aetiologies, with and without previous history of hepatic encephalopathy but without overt hepatic encephalopathy at the time of the investigation. The aim of the study was to assess brain tissue density in patients with cirrhosis and its relationship with the severity of the disease and history of hepatic encephalopathy.

Patients and methods

Forty-eight patients with compensated and decompensated cirrhosis and 51 healthy subjects of similar age and educational level were investigated. No subject with active alcoholism (three months prior to the study), gastrointestinal haemorrhage or bacterial infection (1 month prior to the study), age lower than 18 or greater than 75 years, neurological or psychiatric diseases, overt hepatic encephalopathy, transjugular intrahepatic portosystemic shunt or surgical portocaval shunt, treatment with drugs that could alter cerebral function or contraindication to magnetic resonance imaging (MRI) were studied. The study was approved by the Ethical Committee of the Hospital Clinic of Barcelona. Written informed consent was obtained from each subject.

Twelve additional cirrhotic patients submitted to liver transplantation were studied after a median period of 11 months (range 7–50 months) after liver transplant and compared to 12 healthy subjects matched by sex and age. Patients with liver transplant had minimal or no fibrosis in liver biopsy at the time of the study.

Physical examination, standard laboratory parameters, and a battery of neuropsychological tests were performed in all subjects. Patients with ascites were studied after at least 1 week without diuretics. Neuropsychological tests were administered by a trained neuropsychologist and included NCT-A, NCT-B, block-design test, and digit-symbol test. Minimal hepatic encephalopathy was defined as the presence of at least two neuropsychological tests with abnormal values (± 2SD of values obtained in normal subjects) [13]. History of overt hepatic encephalopathy was retrospectively taken from the clinical records. In our Unit, we use the West Haven criteria to classify hepatic encephalopathy.

Magnetic resonance imaging

3D-Inversion Recovery Prep images of the entire brain (TR = 12 ms, TE = 52 ms, FOV = 24, acquisition matrix 256 × 192 mm, slice thickness 1.5 mm) were obtained using a 1.5T GE Nvi/Cvi Magnetic Resonance Apparatus and the head coil. Regular quality assurance was performed during each study by an experienced observer, and only good quality images were accepted.

Voxel Based-Morphometry (VBM) allows comparing local concentrations of grey and white matter between two groups of subjects. This is performed at a voxel level, which in this study had a dimension of 1 mm^3, and involves spatial normalization of all MR images to the same stereotactic space, followed by segmenting the tissue from the normalized images, smoothing, and performing a statistical analysis. At the end, a statistical parametric map is obtained showing regions where a concentration of a certain tissue type differs between groups. In our study, MR images were post processed using methods implemented in the statistical parametric mapping software (SPM2, Welcome Department of Cognitive Neurology, London, UK). Smoothed grey and white matters were analysed with an ANCOVA model to detect regions of decreased density and two-side *t*-test were used to assess differences in grey or white matter density between groups. Age and sex were included as nuisance covariates. False Discovery Rate (FDR) was set at $p < 0.05$ for corrected VBM. When patients and normal subjects are compared, a one way statistical analysis is performed, subtracting from the voxel-density detected in controls the density detected in patients in a voxel by voxel manner. However, when two groups of patients are compared, the analysis has to be performed in two ways to assess areas with low density in one group with respect to the other and vice versa. The *Z* scores are a way that SPM uses to display and analyze the *p* values from the *t* statistics. They are the numbers from the unit normal distribution that would give the same *p* values as the *t* statistics. The areas (clusters) with the higher *Z* scores indicate the most robust changes in brain density. Clusters with a size lower than 100 k were not considered for statistical comparisons. For further details on post processing analysis and other aspects of the methodology used see references [7,14,15].

Statistical analysis of clinical and biochemical data

The non-parametric Mann–Whitney test for continuous data and the Chi-square and Fischer tests for categorical data were applied for comparisons between clinical and laboratory data. The SPSS 12 statistical software (SPSS Inc. and Microsoft Corp., Chicago, IL) was used and results are given as mean ± SD. $p < 0.05$ was considered statistically significant.

Results

Clinical and laboratory parameters of the group of patients with cirrhosis are shown in Table 1. Seventeen patients had previous episodes of overt hepatic encephalopathy and 18 had minimal

Table 1. Demographic, clinical, and biochemical data of the patients with cirrhosis and healthy subjects included in the study.

Variable	Cirrhotic patients (n = 48)	Healthy subjects (n = 51)	*p* value
Age (years)*	61 ± 9 (44-75)	60 ± 11 (33-85)	NS
Sex: male/female (n)	30/18	23/28	NS
Years of education*	9 ± 5 (0-20)	10 ± 4 (3-20)	NS
Post-hepatitic cirrhosis (n)	27	-	
Alcoholic cirrhosis (n)	21	-	
Previous hepatic encephalopathy (n)	17	-	
Ascites at inclusion (n)	30	-	
Child-Pugh's class: A/B/C (n)	17/13/18	-	
Child-Pugh's score*	8 ± 2.5 (5-13)	-	
MELD score	13 ± 5 (7-27)	-	
Serum bilirubin (mg/dl)*	3.1 ± 4.6 (0.4-30.5)	0.6 ± 0.3 (0.3-1.7)	<0.001
Prothrombin time (%)*	62 ± 17 (20-100)	95 ± 6 (82-100)	<0.001
Serum albumin (g/L)*	32 ± 7 (21-47)	42 ± 3 (35-48)	<0.001
Serum creatinine (mg/dl)*	1.05 ± 0.4 (0.7-2.8)	0.95 ± 0.15 (0.7-1.3)	NS
BUN (mg/dl)*	23 ± 14 (7-68)	19 ± 4.6 (9-26)	NS
Serum sodium (mEq/L)*	134 ± 7 (118-147)	140 ± 2 (136-144)	<0.001
Serum ammonia (μMol/L)*	47 ± 28 (7-129)	18 ± 11 (0-47)	<0.001
Hematocrit (%)*	35 ± 7 (20-49)	40 ± 4 (34-50)	<0.001
Minimal hepatic encephalopathy (n)	18	-	

*Values are mean ± SD or number of patients. Values in brackets are ranges.

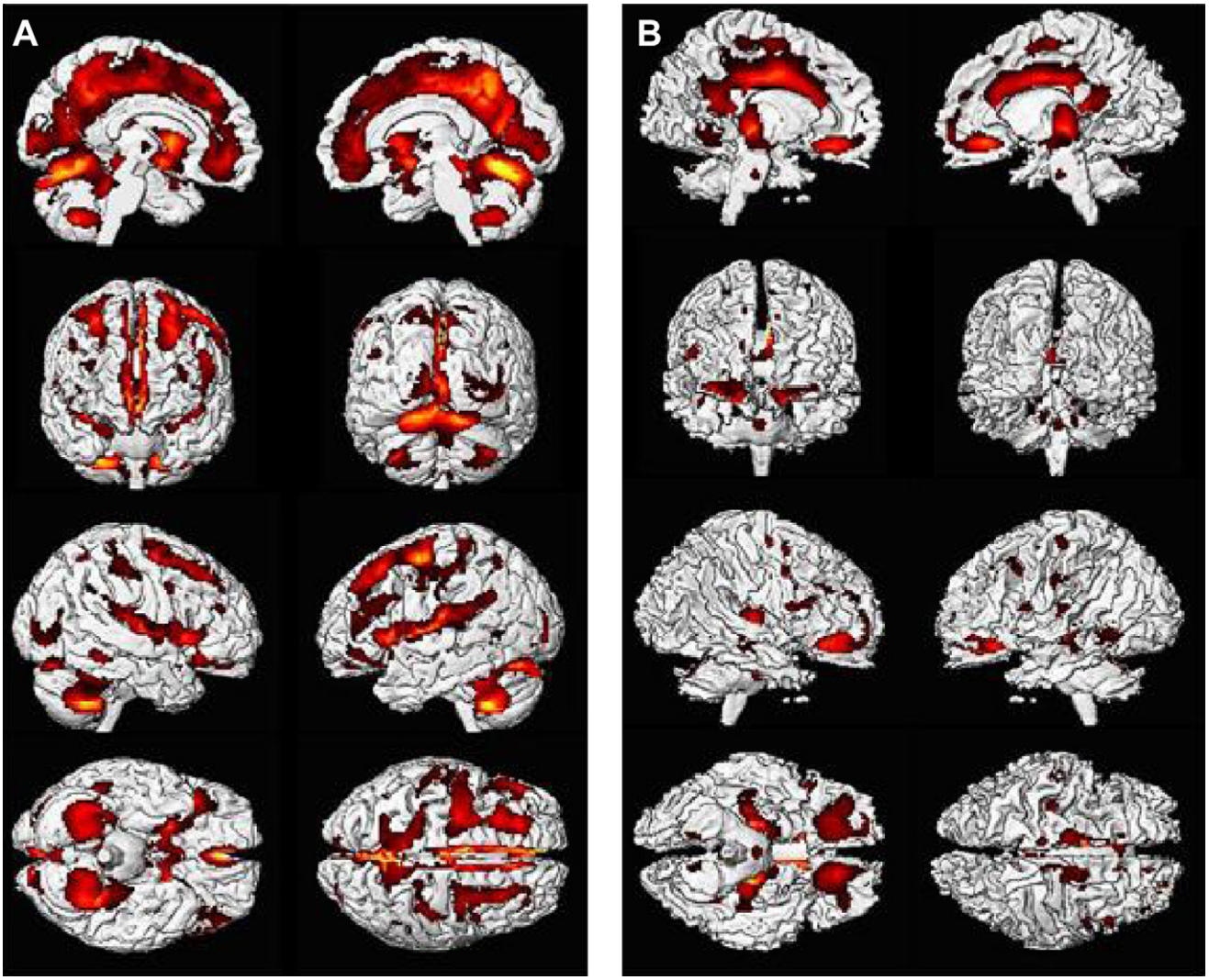

Fig. 1. Voxel Based-Morphometry comparing a group of 48 patients with cirrhosis with 51 healthy subjects. (A) Zones of red colour represent areas of decreased grey matter density in patients with cirrhosis compared to healthy subjects. (B) Zones of red colour represent areas of decreased white matter density in patients with cirrhosis compared to healthy subjects. (Corrected; FDR at p <0.05.)

hepatic encephalopathy at inclusion (eight of them had previous episodes of overt hepatic encephalopathy). Twenty-one patients had neither previous history of hepatic encephalopathy or minimal hepatic encephalopathy at inclusion. No significant differences in age, sex, and clinical and laboratory parameters were observed between patients with post-hepatitic cirrhosis and patients with alcoholic cirrhosis (data not shown).

Of the 12 patients explored after liver transplantation, the aetiology was alcoholic in five patients and post-hepatitic B or C virus in seven patients. At the time of transplantation, three patients were Child–Pugh class A, five class B, and four child C.

Comparison of Voxel based Morphometry between cirrhotics patients and healthy subjects

Fig. 1 shows VBM analysis comparing cirrhotic patients and control subjects included in the study. There was a significant decrease in brain density in many areas in patients with cirrhosis. The clusters (areas) with the higher Z scores were the frontal and parietal regions and putamen for grey matter, and the cingulate gyrus and temporal (parahippocampal and fusiform gyrus) and frontal regions (middle, superior and medial frontal gyrus) for white matter. Cluster size, stereotactic coordinates and Z scores of all cerebral regions, showing significant differences between cirrhotics and controls, are shown in Table 2.

Comparison between patients with alcoholic cirrhosis or patients with post-hepatitic cirrhosis and healthy subjects showed a decreased brain density in the frontal and parietal regions and putamen in the grey matter and the cingulated gyrus and temporal and frontal regions in the white matter in both groups (data not shown). Comparison between patients with alcoholic cirrhosis and patients with post-hepatitic cirrhosis had to be analysed in two ways. The first analysis assessed the presence of areas with decreased brain density in patients with alcoholic cirrhosis with respect to patients with post-hepatitic cirrhosis. This analysis showed significantly decreased grey

Table 2. Decreased grey and white matter density in 48 patients with cirrhosis compared to 51 healthy subjects (setting FDR* at 0.05). Age and sex were included as nuisance covariates.

Grey Matter

Cluster size k**	Region	Stereotactic coordinates (mm)			
		x	y	z	*Z score*
17570	R Precuneus	2	-50	40	6.53
	R Paracentral Lobule	2	-22	48	6.36
	L Paracentral Lobule	0	-22	48	6.12
7228	L Putamen	-26	2	6	6.40
	L Putamen	-30	-10	-2	6.33
	R Putamen	32	-12	-2	6.07
106	R Fusiform Gyrus	50	-44	14	4.81
1905	L Precentral Gyrus	-44	-2	60	4.66
	L Superior Frontal Gyrus	-30	-4	66	4.20
	L Middle Frontal Gyrus	-26	38	44	3.83
774	R Middle Frontal Gyrus	30	16	52	4.48
	R Superior Frontal Gyrus	28	-2	66	3.79
	R Middle Frontal Gyrus	34	-2	58	3.33
194	R Middle Occipital Gyrus	24	-94	8	3.78
	R Inferior Occipital Gyrus	32	-88	-4	3.54
	R Inferior Occipital Gyrus	40	-82	-2	3.44
376	L Middle Frontal Gyrus	-56	28	24	3.46
	L Middle Frontal Gyrus	-46	36	38	3.25
	L Middle Frontal Gyrus	-52	38	18	3.12
204	R Postcentral Gyrus	38	-28	52	3.07
	R Precentral Gyrus	44	-16	44	2.84
	R Postcentral Gyrus	22	-34	68	2.71

White Matter

Cluster size k	Region	Stereotactic coordinates (mm)			
		x	y	z	*Z score*
3797	L Cingulate Gyrus	-6	-16	34	7.61
	R Cingulate Gyrus	8	-16	36	7.60
	R Cingulate Gyrus	8	10	30	7.56
773	R Extra Nuclear	20	-26	4	6.24
	R Sub-Gyral	22	-28	-4	6.08
	R Parahippocampal Gyrus	16	-8	-16	3.76
705	L Extra Nuclear	-20	-28	0	5.99
	L Parahippocampal Gyrus	-22	-26	-10	5.57
	L Fusiform Gyrus	-40	-30	-18	3.91
575	L Sub-Gyral	-12	40	-18	5.90
	L Middle Frontal Gyrus	-22	28	-16	5.39
	L Superior Frontal Gyrus	-12	52	-12	3.87
741	R Middle Frontal Gyrus	24	30	-16	5.20
	R Medial Frontal Gyrus	10	34	-16	4.72
	R Sub-Gyral	12	42	-18	4.72
106	L Sub-Gyral	-30	-58	-6	4.96
	L Temporal Lobe	-34	-54	-12	4.26
232	R Medial Frontal Gyrus	10	-10	62	3.85
	R Sub-Gyral	16	-2	56	3.34
	R Paracentral Lobule	10	-30	62	2.80
127	R Precentral Gyrus	50	6	12	3.84
	R Inferior Frontal Gyrus	52	16	16	3.41

* FDR False discovery rate. **Cluster size is indicated by the *K* value, which represents the number of significant voxels in the particular cluster.

matter density in the medial frontal and occipital lobes, insula, and cerebellum (Fig. 2). The second analysis assessed the areas of low brain density that were observed in the group of patients with post-hepatitic cirrhosis with respect to patients with alcoholic cirrhosis. This comparison showed a decreased grey density in only two small areas in the right cerebellum and in the left anterior frontal lobe in the group of patients with post-hepatitic cirrhosis (see Patients and methods) (Fig. 2). No differences were found between these groups in white matter changes.

Relationship of changes in Voxel based Morphometry and liver failure and hepatic encephalopathy

Comparison between patients with cirrhosis grade A, B, and C of the Child–Pugh classification with healthy subjects showed a progression in the extension and size of the affected area in grey and white matter in parallel with the degree of liver failure (Fig. 3).

Twenty-one patients had no history of overt hepatic encephalopathy or minimal hepatic encephalopathy at inclusion, 10 had no history of overt hepatic encephalopathy but they had minimal hepatic encephalopathy at inclusion and, finally 17 patients had history of previous episodes of overt hepatic encephalopathy (eight of these cases had minimal hepatic encephalopathy at inclusion). Comparison of these three subgroups of cirrhotic patients with healthy subjects showed a clear relationship between the extension and size of decreased brain density areas and the severity of cerebral dysfunction (Fig. 4).

Voxel based Morphometry after liver transplantation

Fig. 5 shows the comparison between patients after liver transplantation and their corresponding healthy subjects. Transplant patients showed reduced grey and white matter density in the frontal region, cingulated gyrus, and temporal and parietal lobes.

Discussion

Very few detailed neuro-anatomical and histological investigations in patients with cirrhosis exist and most of them are focussed on the morphology of the cells in the central nervous system. Most data on cerebral neuro-anatomical changes associated with cirrhosis, therefore, rely on morphological studies using computed tomography or magnetic resonance of the brain. The current opinion is that the main pathological abnormality in these patients is diffuse increase in the size of astrocytes due to the entry of water from the extracellular to the

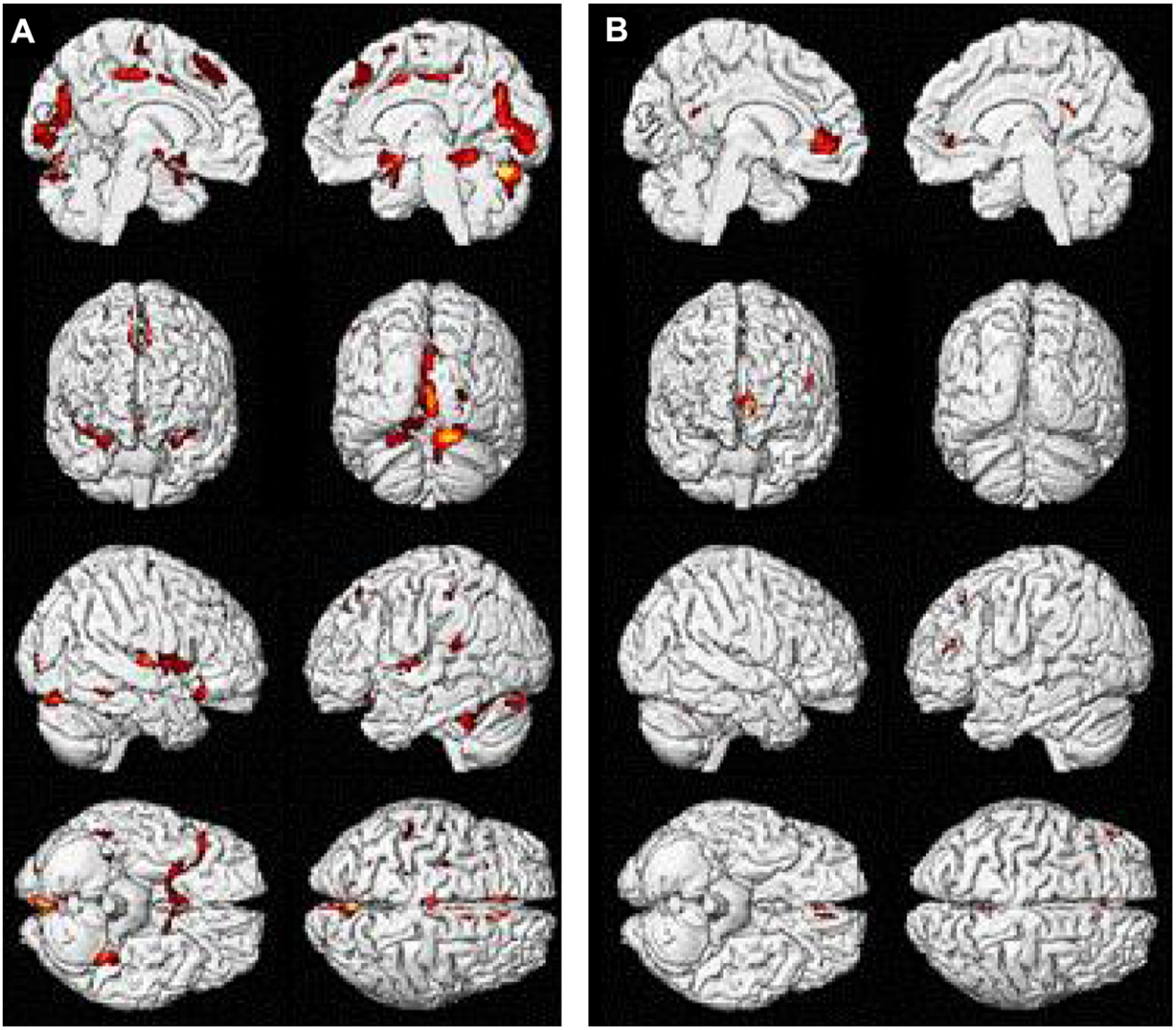

Fig. 2. Voxel based Morphometry comparing patients with alcoholic cirrhosis *vs.* post-hepatitic cirrhosis. (A) Grey matter density loss in patients with alcoholic cirrhosis compared with patients with post-hepatitic cirrhosis (areas in red represent zones of decreased brain density in patients with alcoholic cirrhosis compared to patients with post-hepatitic cirrhosis). (B) Grey matter density loss in patients with post-hepatitic cirrhosis compared to patients with alcoholic cirrhosis. (Areas in red represent zones of decreased brain density in patients with post-hepatitic cirrhosis compared to patients with alcoholic cirrhosis.) (Corrected; FDR p <0.05.) This figure, therefore, compares patients with alcoholic *vs.* patients with post-hepatitic cirrhosis and viceversa, but it does not reflect differences between each group of patients in comparison to healthy subjects.

intracellular space in relation to the increase in intracellular glutamine concentration [1]. This causes a low grade cerebral edema which may be involved in the pathogenesis of hepatic encephalopathy [16,17]. Studies using standard magnetic resonance imaging have demonstrated symmetrical hyper intense globus pallidus in cirrhosis and autopsy investigations demonstrated that it is due to accumulation of manganese [18,19]. It is found in most patients with cirrhosis, independently on the presence of hepatic encephalopathy. Chronic hepatic encephalopathy, a condition frequently seen in the past as a consequence of surgical porto-caval shunt operations, is associated with a patchy but diffuse spongy degeneration of the cortex in which histological neuronal degeneration microcavitation in the striatum, and in rare cases spinal demyelination can be observed [20,21]. Finally, diffuse brain atrophy has been reported in histological and computed tomography studies. It is observed mainly in patients with severe liver failure or chronic hepatic encephalopathy [22,23].

The current article describes what it could be a new cerebral lesion in cirrhosis. We observed that in comparison to healthy subjects, patients with cirrhosis present a significant loss in brain density in many areas of grey matter. The similarity between these images and those observed in patients with Alzheimer Disease [8,9] suggests areas of brain atrophy. This is also suggested by the coincident loss of white matter density, which could represent a loss of axons secondary to the loss of neurones.

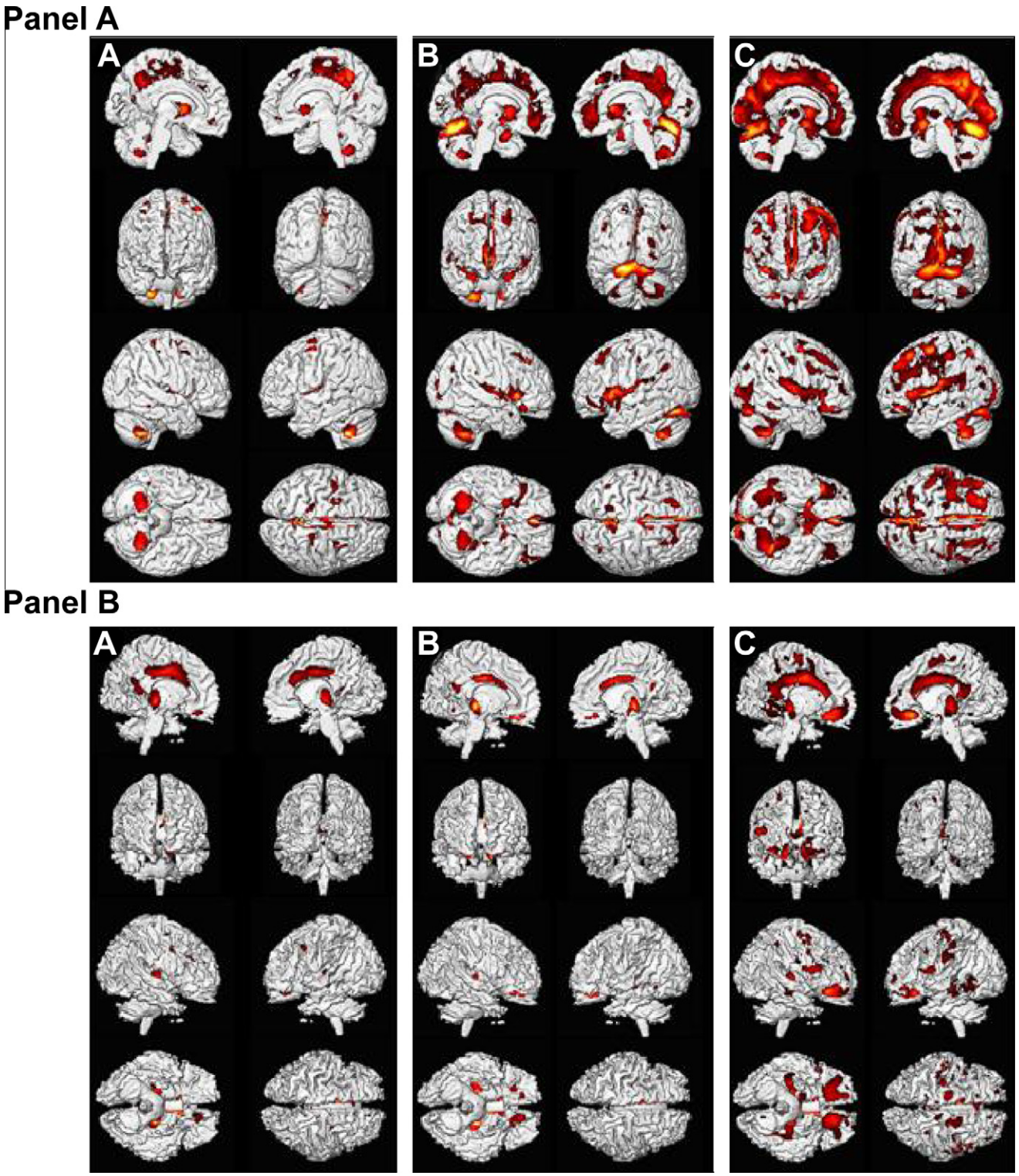

Fig. 3. Voxel based Morphometry comparing patients with cirrhosis divided in groups according to the Child–Pugh classification *vs.* healthy subjects. (A) Red colour areas of reduced grey matter density in cirrhotic patients divided according to the Child–Pugh classification (Child–Pugh Class A–C) with respect to 51 healthy subjects. (B) In red, areas with reduced white matter density in cirrhotic patients divided according to the Child–Pugh classification compared to 51 healthy subjects. (Corrected, FDR at 0.05.)

When patients with alcoholic and post-hepatitic cirrhosis were compared to healthy subjects, the areas with decreased brain density, both in grey and white matter, were similar in the two aetiologic group. However, when each of the group of

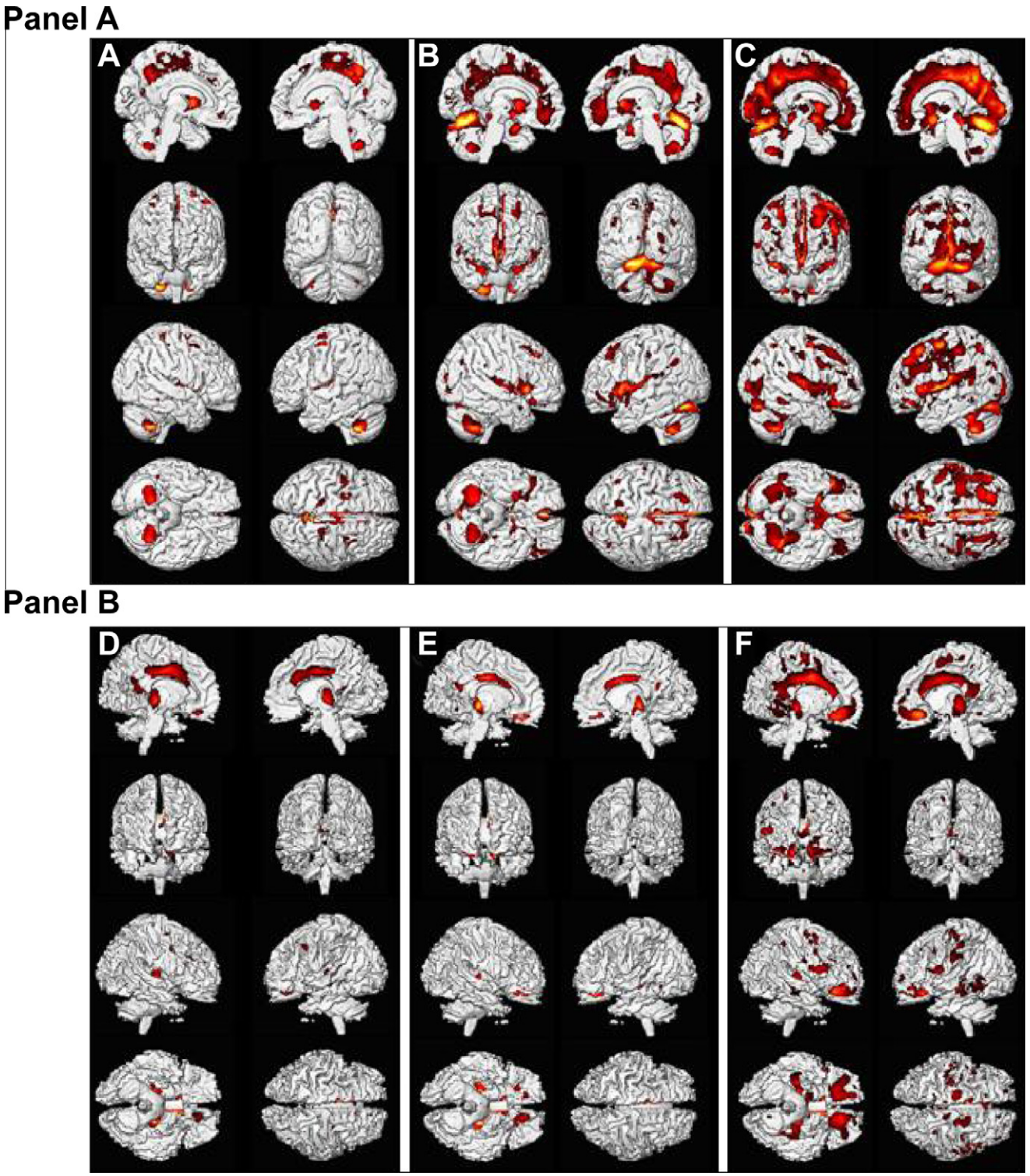

Fig. 4. Voxel based Morphometry comparing patients with cirrhosis divided in groups according to the presence or absence of hepatic encephalopathy *vs.* healthy subjects. (A) Grey matter density loss in cirrhotic patients without history of overt hepatic encephalopathy or minimal hepatic encephalopathy at inclusion (sub-panel A), without history of overt hepatic encephalopathy but with minimal hepatic encephalopathy at inclusion (sub-panel B) and with history of overt hepatic encephalopathy (sub-panel C) compared with 51 healthy subjects (setting FDR at 0.05). (B) White matter density loss in cirrhotic patients without history of overt hepatic encephalopathy or minimal hepatic encephalopathy at inclusion (sub-panel D), without history of overt hepatic encephalopathy but with minimal hepatic encephalopathy at inclusion (sub-panel E), and with history of overt hepatic encephalopathy (sub-panel F) compared to 51 healthy subjects. (Corrected, FDR at 0.05.)

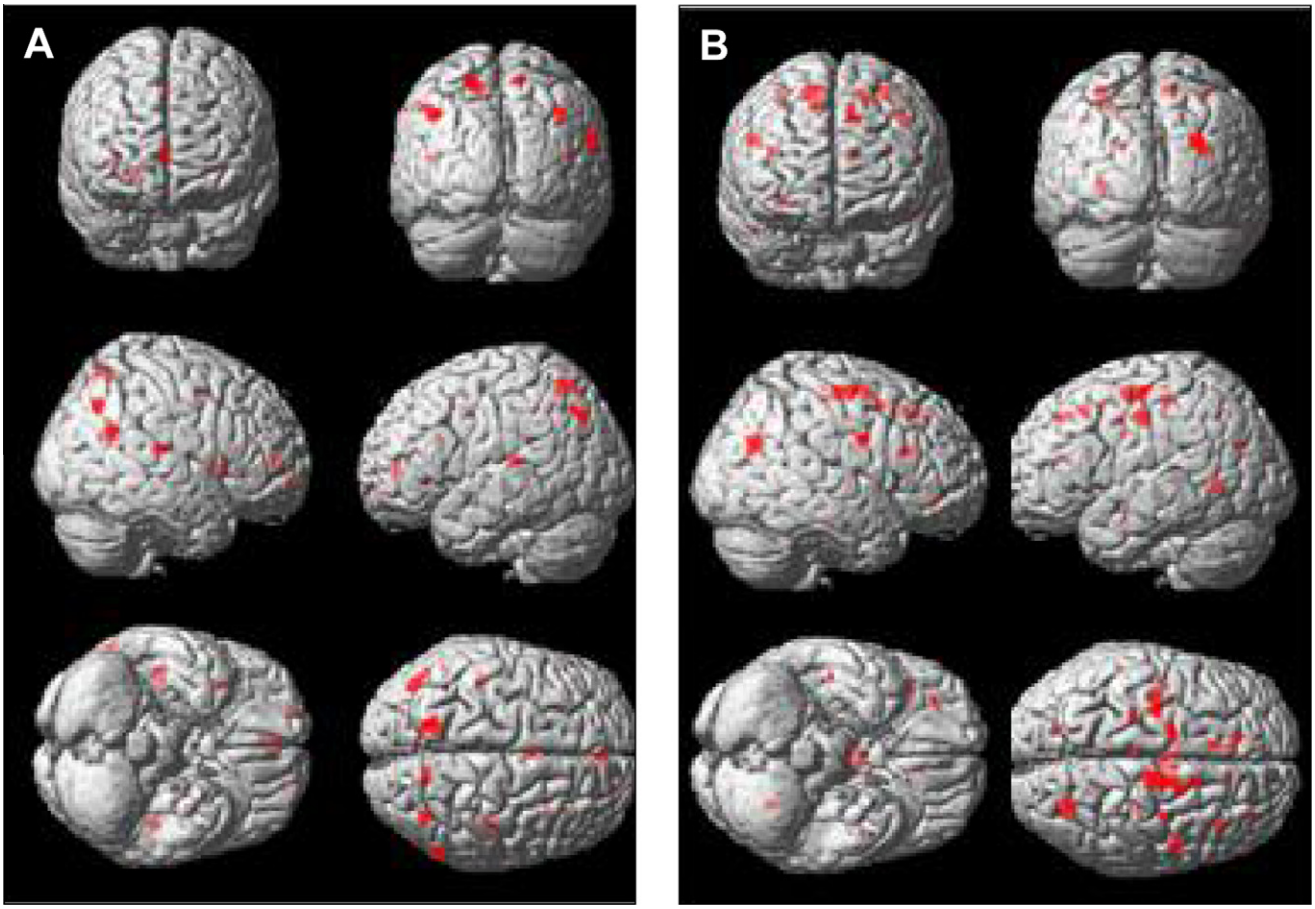

Fig. 5. Voxel based Morphometry comparing patients with liver transplantation *vs.* healthy subjects. (A) Red colour areas of grey matter density loss in the transplant group of patients compared to 12 matched healthy subjects. (B) Red colour areas of white matter density loss in the transplant group of patients compared to 12 matched healthy subjects. (Corrected, FDR at 0.05.)

patients was compared to the other group of patients a significantly greater decrease of density was observed in alcoholic cirrhosis in many areas in the grey matter but not in the white matter. Previous studies have described cortical atrophy mainly in the frontal lobes and loss of brain tissue associated to chronic alcoholism [24,25]. Therefore, an additional effect of chronic alcohol consumption on the brain may account for the more extensive hypo-density abnormalities in patients with alcoholic cirrhosis in relation to post-hepatitic cirrhosis. In this sense, a study, evaluating HMR spectroscopy, magnetization transfer, and Diffusion weighted Imaging in alcoholic and non-alcoholic patients with hepatic encephalopathy, suggested a direct toxic effect of alcohol on the brain [26].

The relationship between the progression of liver failure or the development of hepatic encephalopathy with cerebral magnetic resonance findings was investigated by comparing the different subgroups of patients with the whole group of healthy subjects included in the study and not by comparing one group of cirrhotic patients to the other group. This methodology, widely used in this type of investigations in which there is great individual variability in each of the affected areas, guarantees an appropriated number of cases for morphometric comparison.

There was a clear relationship between the progression of liver failure and the extension and number of the areas of decreased brain density. For example, in the grey matter, the initial areas affected, as indicated by the results obtained by Child–Pugh grade A patients as well as in cases without history of hepatic encephalopathy or minimal hepatic encephalopathy at inclusion, were the frontal lobes, putamen, cerebellum, pre-cuneus, post-central, and fusiform gyrus, and left insula. As liver failure progressed, these areas of reduced brain density increased in size and new areas developed in other zones. In the white matter, a progression in extension and number of the affected areas was also observed with the progression of liver failure. There was also a relationship between the extension of decreased brain density and hepatic encephalopathy, patients with previous history of hepatic encephalopathy being those with the largest and most extensive hypo-density areas. Interpretation of these data is difficult. It is possible that decreased brain density is a consequence of liver failure with no relationship to hepatic encephalopathy. However, an alternative explanation is that neurotoxins involved in hepatic encephalopathy reduce brain density in areas of white and grey matter. In this case, reduced brain density could participate in or predispose to the development of hepatic encephalopathy. The possibility that neurotoxins are capable to produce brain lesions in patients with hepatic encephalopathy has been proposed by other investigators and raises the important potential issue of neuroprotection. Episodes of hepatic encephalopathy

(either minimal or overt) would be associated to the development of organic brain lesions and could be prevented by prophylactic treatment.

An intriguing observation of the current study was the finding of areas of decreased brain density in patients with cirrhosis submitted to liver transplantation studied several months after surgical procedure. As liver biopsy in these patients showed minimal or no fibrosis, these findings cannot be explained by cirrhosis recurrence. A possible explanation is that the decreased brain density observed in cirrhosis does not totally reverse or reverse very slowly after liver transplantation. This is in keeping with old and recent studies in patients with cirrhosis and encephalopathy suggesting that the neurological injury caused by neurotoxins may be persistent or permanent [19,27–29]. Along this line, a recent study observed that even after the first episode of overt hepatic encephalopathy there are residual effects on cognitive function. Moreover, the psychometric dysfunction impaired with continuous episodes of overt hepatic encephalopathy [30]. Finally, in an other study, lack of normalization in neuropsychological tests in transplanted patients was also observed [29].

The effect of factors other than liver failure or hepatic encephalopathy, present in patients with cirrhosis or transplant patients but not in healthy subjects that could affect brain density, was not considered in the current investigation. Anaemia, coagulation disorders, diuretics, beta blockers or immunosuppressors may affect the cerebral circulation and, therefore, brain tissue density. Further studies to clarify the relationship between these factors and changes in brain density in cirrhosis are clearly needed.

In summary, the current study using cerebral magnetic resonance imaging and Voxel based Morphometry shows that patients with cirrhosis present decreased brain density in many areas of the grey and white matter. Although the nature of these changes cannot be ascertained from the present study, the similarities with the lesions observed in Alzheimer Disease suggest that it may represent organic lesions. This is supported by the observation of low brain density areas many months after liver transplantation. Changes in brain density in alcoholic cirrhosis appear to be more intense than in post-hepatitic cirrhosis. On the other hand, there is a clear direct correlation between the size and extension of brain tissue hypodensity areas and the degree of liver failure or cerebral dysfunction. The study has some limitations in its design. To evaluate the effect of liver transplant on brain density losses, patients should be studied prior and after liver transplantation. In our study, measurements before liver transplantation were not performed. We could not study patients with overt hepatic encephalopathy due to the difficulty to apply MRI technique to patients with altered mental function. Further studies are, therefore, needed to expand our findings and to better characterize the clinical significance of decreased brain density in patients with cirrhosis.

Author's contribution

Monica Guevara and P. Ginès have participated in conception and design of the study; generation, collection, assembly, analysis and interpretation of data and drafting the manuscript. M.E. Baccaro, A. Torre and E.U. Sotil have participated in: generation, collection, assembly and analysis of data. Gómez-Ansón and J.L. Molinuevo have participated in: assembly and analysis of data and drafting the manuscript. L. Rami has participated in the evaluation of neuropsychological status and in the analysis of the results. C. Testa, G. Frisoni, and G. Pereira have participated in: generation and assembly of data. V. Arroyo has participated in conception of the study and drafting the manuscript. J. Córdoba has participated in the analysis of data and approval of the final version of the manuscript.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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