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Voxel-based statistical analysis of thalamic glucose metabolism in traumatic brain injury: Relationship with consciousness and cognition

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Abstract

Objective: To study the relationship between thalamic glucose metabolism and neurological outcome after severe traumatic brain injury (TBI).

Methods: Forty-nine patients with severe and closed TBI and 10 healthy control subjects with ^{18}F-FDG PET were studied. Patients were divided into three groups: MCS&VS group ($n = 17$), patients in a vegetative or a minimally conscious state; In-PTA group ($n = 12$), patients in a state of post-traumatic amnesia (PTA); and Out-PTA group ($n = 20$), patients who had emerged from PTA. SPM5 software implemented in MATLAB 7 was used to determine the quantitative differences between patients and controls. FDG-PET images were spatially normalized and an automated thalamic ROI mask was generated. Group differences were analysed with two sample voxel-wise *t*-tests.

Results: Thalamic hypometabolism was the most prominent in patients with low consciousness (MCS&VS group) and the thalamic hypometabolism in the In-PTA group was more prominent than that in the Out-PTA group. Healthy control subjects showed the greatest thalamic metabolism. These differences in metabolism were more pronounced in the internal regions of the thalamus.

Conclusions: The results confirm the vulnerability of the thalamus to suffer the effect of the dynamic forces generated during a TBI. Patients with thalamic hypometabolism could represent a sub-set of subjects that are highly vulnerable to neurological disability after TBI.

Keywords: *Voxel-based analysis, positron emission tomography, consciousness, PET-FDG, prognosis, thalamus, traumatic brain injury*

Introduction

Most traumatic brain injuries (TBI) result in widespread damage to the brain from the shearing forces exerted during rapid accelerations and decelerations during impact. This mechanism may produce both focal and diffuse axonal injury (DAI). Focal cerebral contusions result from mechanical distortion of tissue preferentially in the ventral and polar frontal and anterior temporal areas, where the brain is confined by the bony ridges of the inner skull.

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This focal damage is usually easily detected with conventional neuroimaging techniques [1]. On the other hand, diffuse axonal disruptions are caused by both linear and rotational acceleration-deceleration forces and exhibit a centripetal gradient such that the more severe the injury, the deeper are the lesions in the brain [2, 3]. The presence of DAI makes TBI particularly challenging for anatomic-clinical correlations because, although DAI is considered to be the major determinant of outcome after TBI, it is usually under-diagnosed by conventional neuroimaging techniques [4, 5].

The unique combination of diffuse and focal damage as well as the transient visibility of DAI have been proposed to explain why standard neuroimaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), which are traditionally useful in other neurological diseases, have failed to reveal a consistent relationship between function and the site of structural lesions in most cases of TBI [4, 6–8]. The advent of new functional neuroimaging techniques has revealed areas of cerebral dysfunction in regions that appear structurally intact on CT or MRI [1, 9–13]. This differential sensitivity of neuroimaging techniques has special clinical relevance when functional changes in the deep brain nuclei affected by DAI are to be detected. In this sense, the thalamus is a particularly interesting structure to study since it plays a crucial role in neurocognitive processes as a centrally located relay station for information through the brain [14]. Thalamic functions include the integration of sensorimotor functions through its connections with the associative cortex, the regulation of consciousness and arousal mechanisms through the reticulothalamic system, the control of emotions as a component of the limbic system, and it is also involved in language and cognitive functions through specific thalamo-cortico-thalamic connections [14–16].

Most previous investigations on thalamic metabolism in patients with TBI have focused on its relationship with the level of consciousness through its connections with the ascending reticular activating system [17–19]. The clinical relevance of thalamic metabolism in non-comatose patients, as well as the participation of this structure in neuronal networks responsible of more complex cognitive functions, has been limited by difficulties in neuroimaging data analysis that can make one understand brain function in terms of a dynamic flow of information across large-scale brain pathways [20, 21].

In recent years, the development of different voxel-based image analysis methods has improved the accuracy and objectivity in the detection of metabolic abnormalities between groups of patients with injuries in the central nervous system [13]. Specifically, studies of the functional connectivity in patients with a low level of arousal have identified a specific metabolic impairment in a wide cortico-subcortical network as an expression of a disconnection syndrome encompassing cortico-thalamo-cortical connections affected by DAI lesions [18]. The clinical relevance of thalamic metabolisms in TBI patients without disorders of consciousness, such as those in a post-traumatic amnesia (PTA) period or those who have emerged from PTA has been poorly investigated.

Previous studies have focused on quantifying neuronal volume loss in TBI and studying the physiopathological mechanisms that cause this loss (diffuse vs traumatic axonal injury, stretching vs shearing, etc.). This neuronal damage, which is more pronounced in thalamic nuclei, has been associated to traumatism severity and to patients' outcome [22–24]. This paper studied the relationship between neurological outcome and thalamic function, measured through glucose metabolism, in a sample of patients who had sustained a severe TBI. This study has compared functional and structural neuroimaging data in an effort to explain those mechanisms affecting thalamic metabolism after a TBI. For these purposes, a slightly modified version of the voxel-based morphometry technique (VBM) is introduced that was originally planned for the analysis of anatomical MRIs [25, 26] to analyse ^{18}FDG-positron emission tomography (PET) images. The aim of this study is to observe the differences in thalamic metabolisms by comparing one-volume-per-subject PET scans. In that way, the method is more similar in concept to the original VBM [25, 26], contrasting one scan per subject, than the previously referenced studies, in which the tests were conducted on images obtained at various time points in the same session for each patient. It is hypothesized that patients with lower thalamic metabolism represent a sub-set of subjects that are highly vulnerable to neurological and functional disability after TBI.

Material and methods

Patients

From February 2000 through May 2009, 158 of 317 consecutive head-injury patients attending an Acquired Brain Injury Rehabilitation Service of a large metropolitan hospital underwent an ^{18}F-FDG PET. PET imaging data of 99 patients from the total pool were available or had sufficient quality for quantitative statistical analysis.

Seventy-nine of the 99 TBI patients with a Glasgow Coma Scale score (GCS) $\leq$8, aged between

16–65 years, were initially eligible for this study. All patients underwent a structural neuroimaging examination (MRI: $n = 32$ and CT: $n = 17$) a mean of 47.6 (SD 46.8) days after FDG-PET. All patients with large focal thalamic lesions or penetrating brain injury were excluded from the study and the presence of DAI on both sides of the thalamus was registered. All remaining patients were classified at inclusion in three clinical groups according either to their level of awareness (vegetative state and minimally consciousness state) or their cognitive status (PTA and out-of-PTA). The clinical criteria for a vegetative state and a minimally conscious state were adapted from the American Academy of Neurology recommendations [27]. Post-traumatic amnesia was prospectively evaluated with the Galveston Orientation and Amnesia Test (GOAT) [28] in all patients admitted during the PTA period or was retrospectively calculated on the basis of information given by family members in those patients who had already recovered from PTA at the time of admission to the facility.

According to this classification, a patient's neurological status at admission was defined as: vegetative state or minimally conscious state (MCS&VS group: $n = 17$), PTA (In-PTA group: $n = 12$) and Out of PTA patients (Out-PTA group: $n = 20$) matched in age and chronicity with the two other groups. Ten healthy adult volunteers (mean age 40.8 (SD 15.4) years, range 21–49 years; six men and four women) were recruited as normal controls. None had a history of head injury or a major neurological, physical or psychiatric disorder. All study participants gave written informed consent. In patients with a low level of consciousness, consent was obtained from a close relative. Table I summarizes the demographic data of the three groups.

Acquisition of PET images

All patients underwent a PET/CT brain study after an intravenous injection of a dose of 1–10 MBq kg^{-1} of 2-fluorine-2-deoxy-18F-D-glucose (FDG), with a maximum dose of 370 MBq. All patients remained without any food ingestion for at least 4–6 hours prior to the injection of the radiotracer. Furthermore, all of them presented blood glucose levels below 150 mg dl^{-1}. Patients remained at rest and in a supine position in a quiet, dark room from several minutes prior to the administration of the radiopharmaceutical until 30 minutes afterwards.

Images were obtained using a tomograph PET/CT (GE Discovery LS4 PET/CT Scanner System) with the acquisition of a CT transmission scan, followed by a 3D PET emission study that lasted for 10 minutes obtaining 4–5 mm slices. The reconstruction of the PET images was performed using an iterative algorithm with attenuation correction from the CT. The images were reoriented in a XELERIS console following the orbitomeatal axis, allowing the presentation of the study in transverse, coronal and sagittal views.

Voxel-based PET analysis

Images were processed and analysed on a Microsoft workstation with MATLAB 7.4 software (The MathWorks, Natick, MA) and SPM software (Statistical Parametric Mapping 5, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The SPM standard functional method analysis could not be applied in this study, since the image acquisition consisted of a single image volume by subject. Besides, the PET standard template that is available in SPM5 was originally built using (15)O-H(2)O PET images.

Table I. Comparison of characteristics between patients. Data are mean (SD).

	MCS&VS ($n = 17$)	In-PTA ($n = 12$)	Out-PTA ($n = 20$)	p
Age (years)	30.3 (7.7)	35.2 (15.8)	30.9 (9)	NS
Chronicity (days)	293.9 (234.3)	255 (143.9)	217 (126)	NS
Sex (male/female)	14/3	7/5	17/3	NS
Education (years)	10 (3.4)	10 (4)	9.7 (3.3)	NS
Coma (days)	–	42.9 (58.6)	19.9 (18.9)	NS
PTA (days)	–	–	78.5 (72.5)	–
TCDB (n)				
Diffuse I/II/III/IV	0/1/8/0	0/6/2/0	0/12/2/1	0.03
Focal evacuated yes/no	6/2	2/2	3/2	
CT/MRI thalamic lesion (n)				
Diffuse unilateral	1	1	2	NS
Diffuse bilateral	1	0	0	
Aetiology (n)				NS
Traffic Motor/Pedestrian	12/1	6/1	13/2	
Falls	1	2	3	
Violent injuries	3	3	2	

These two possible confounds and the use of a template not originated from the study subjects' data, could lead to inconsistent interpretations of the statistical analysis [29]. To avoid these confounders, a custom template was generated for each pair of groups to be compared. That was a reliable and near to reality source of information and avoided specific bias that would result from the use of a standard template. In the process of creating the custom template, the SPM5 PET standard template was used.

The image intensity between participants was normalized before the creation of the template. This normalization consisted of detecting the voxel with maximum intensity in the image and dividing the intensity in each voxel by the maximum value. These intensity values, indicators of metabolism, became comparable values between subjects, removing variations such as metabolic differences because of weight, age, etc. Spatial location was manually checked for each volume image. Two volumes were manually reoriented, as their centres were not aligned with the anterior-posterior commissure line.

Afterwards, an initial spatial normalization to the SPM PET standard template was achieved by using an affine transformation of the normalized intensity images of the study. The aim of such normalization, i.e. placing all the brain regions in the same space, was to obtain a custom PET template. The process began by transferring each one of the normalized-in-intensity images of the study to the same space by means of a 12° of freedom affine transformation. The output images were averaged to get a volumetric reference image that summed up information from all the original images. Subsequently, the average image was smoothed by a three-dimensional filter, a Gaussian kernel with full-width-at-half-maximum of $6\,\text{mm} \times 6\,\text{mm} \times 6\,\text{mm}$. This smoothed image was the custom PET template for this study. The use of the Gaussian kernel made the voxel values follow a normal distribution, while individual anatomical differences that did not come from each subject's clinical status were eliminated, thus increasing the validity of the subsequent statistical analysis [30].

After the PET template creation step, the original volumes were warped by means of a non-linear spatial normalization procedure to take them to the custom PET template space. A selection of a Region of Interest (ROI) that included the thalamus was then made. The thalamus was traced automatically by generating a mask of the region of interest using the atlas proposed by Tzourio-Mazoyer et al. [31], Automated Area Labeling (AAL) with the software MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/), by creating a volume of interest (VOI 3D) around the region classified by AAL as the thalamus, with a morphometrical dilation of three voxels. By checking the generated mask on the images to be analysed, it could be observed that the obtained mask also took regions that could hinder the study (pallidum and putamen). The mask was therefore manually diminished, taking out these two regions.

Statistical analyses

Statistical analysis of the images was carried out under the framework of the General Linear Model (GLM) using the SPM software. A design matrix and a model of statistical test for comparison were defined for each pair of groups (Controls > MCS&VS, Controls > In-PTA, Controls > Out-PTA, Out-PTA > MCS&VS, Out-PTA > In-PTA and In-PTA > MCS&VS and their opposites).

The model fitting consisted of estimating the parameters to obtain the best approximation of the data to the model. A resolution of the model was made by means of a two-sample Student's *t*-test that was independently applied to each voxel using contrasts, with the aim of measuring the interactions and, therefore, the possible differences between each pair of groups.

The levels of statistical significance were established by applying, in each case, a correction for multiple comparisons using the technique of ratio of false positives (False Discovery Rate, FDR) [32], which controls the proportion of false positives in the study and corrects potential problems of repeating a linear statistical test on hundreds of thousands of voxels. Thus, differences in the thalamic metabolism between the three groups of patients and the healthy control group were tested using $p < 0.05$ as a level of statistical significance for an FDR-corrected value.

Results

There were significant differences in the thalamic metabolism comparisons between the four groups, compared two by two. Those differences are specified below. The control group showed the largest difference in thalamic metabolism compared against the other groups, achieving the greatest difference between the healthy controls and MCS&VS group (patients in Minimally Conscious State or Vegetative State) (Figure 1, upper part). The second greatest difference was observed between the healthy controls and In-PTA group (patients in post-traumatic amnesia) (Figure 1, middle part) and finally the controls and Out-PTA group (patients who have emerged from PTA) (Figure 1, lower part). Otherwise, no differences were detected in the opposite direction

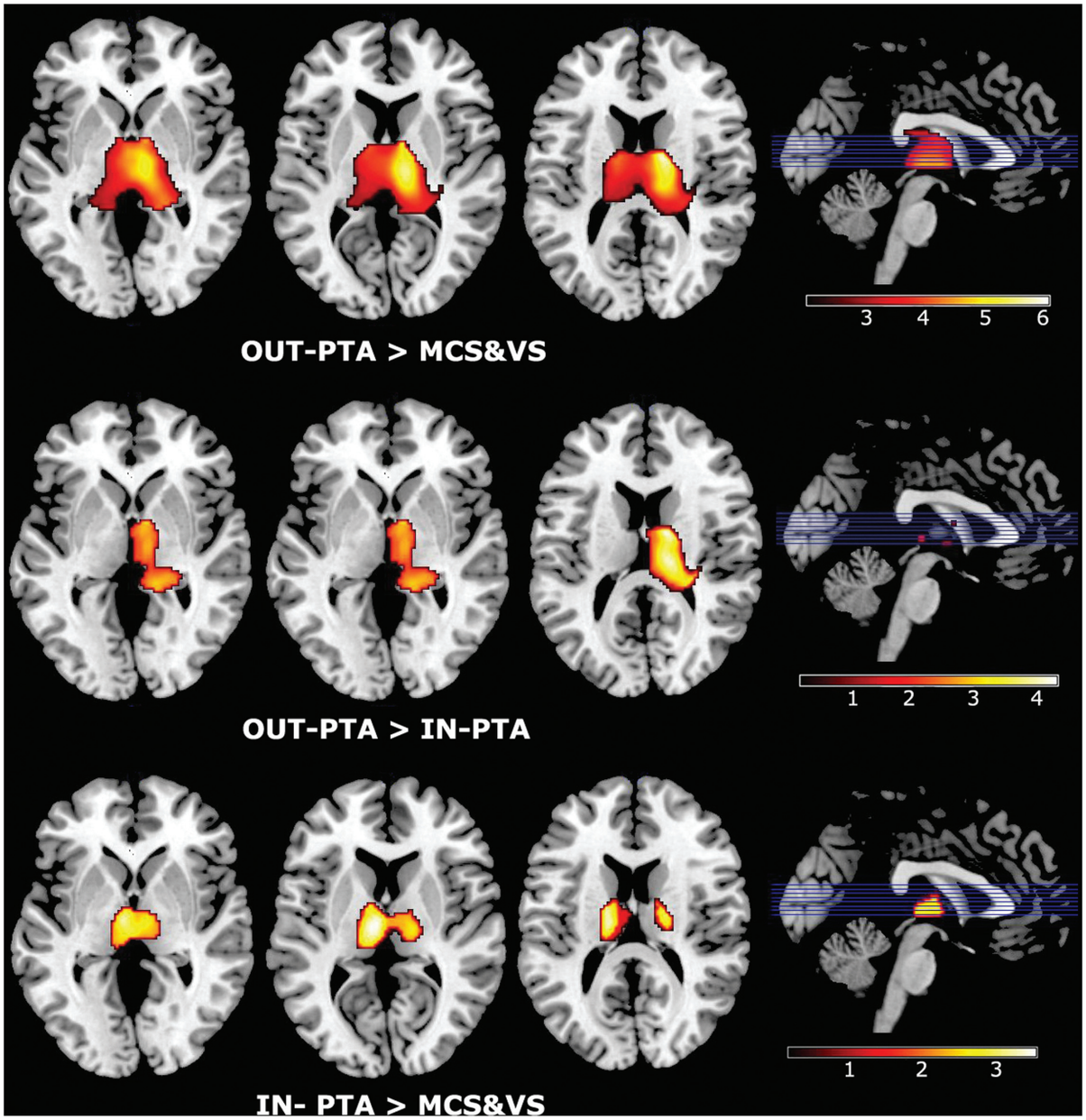

Figure 1. Metabolic differences between controls and patients. Upper part: metabolic differences between controls and patients in minimally conscious state or vegetative state (Control > MCS&VS). Middle part: metabolic differences between controls and patients in a post-traumatic amnesia state (Controls > In-PTA). Lower part: metabolic differences between controls and patients who have emerged from a post-traumatic amnesia state (Control > Out-PTA). Right part: Sagital view of thalamus with metabolism-differences-intensity-bar with *Z*-values below.

(i.e. no voxel survived the comparisons: MCS&VS > Control, In-APT > Control and Out-APT > Control).

An increased thalamic metabolism was found in the Out-PTA group compared to the MCS&VS group (Figure 2, upper part). This comparison showed the higher metabolism difference between patients. Increased metabolism was also detected in the Out-PTA group compared to the In-PTA group (Figure 2, middle part), but in this case, as is observed in Figure 2, only unilateral thalamic metabolic differences had been detected. Between-groups differences in the number and location of thalamic lesions or the existence of focal lateralized lesions in cortical areas which are connected to the thalamus, in combination

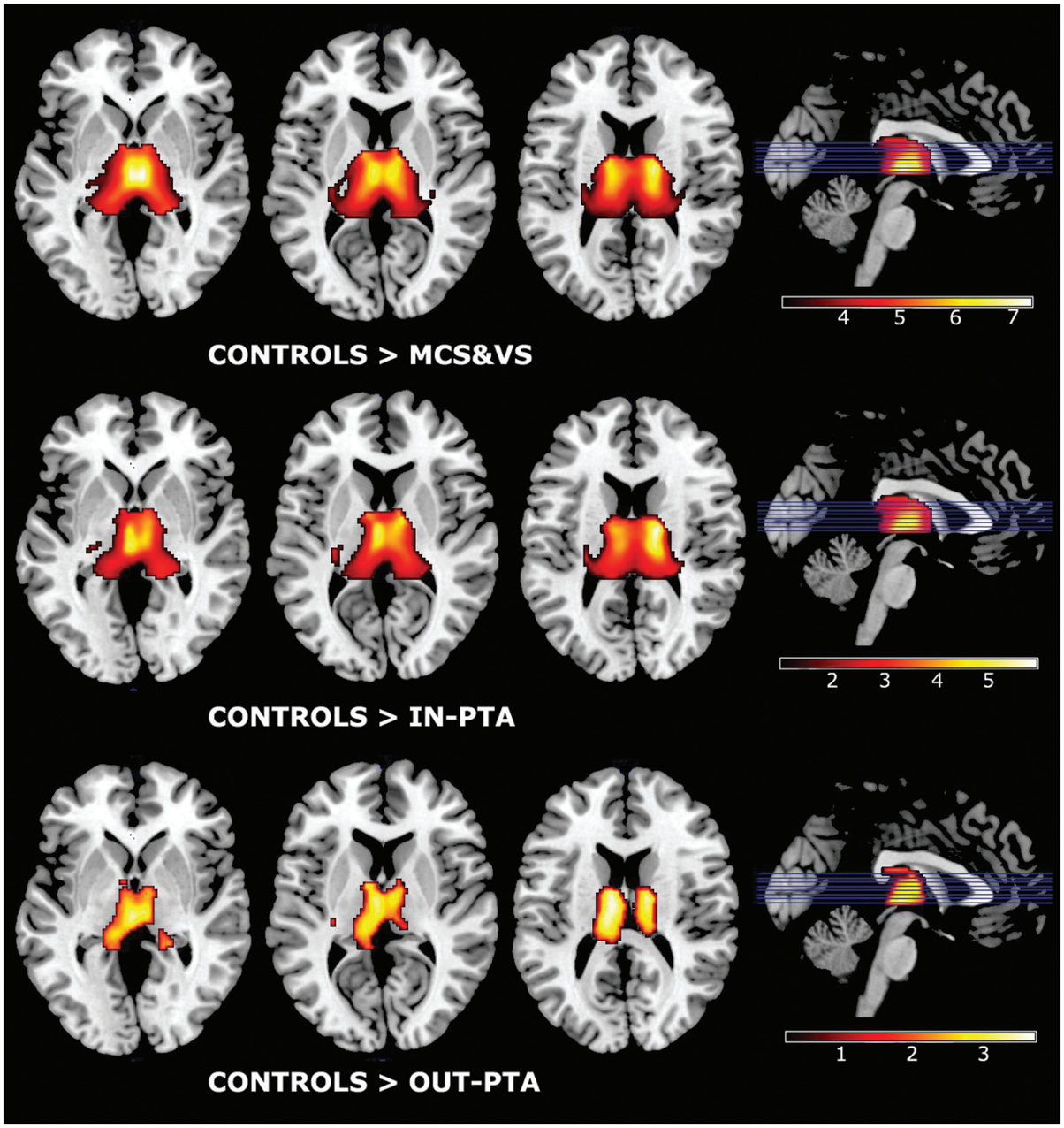

Figure 2. Metabolic differences between patients. Upper part: metabolic differences between patients who have emerged from a PTA state and patients in minimally conscious state or vegetative state (Out-PTA > MCS&VS). Middle part: metabolic differences between patients who have emerged from a PTA state and patients in a PTA state (Out-PTA > In-PTA). Lower part: metabolic differences between patients in a PTA state and patients in a minimally conscious state or vegetative state (In-PTA > MCS&VS). Right part: Sagital view of thalamus with metabolism-differences-intensity-bar with *Z*-values below.

with sample length limitations, could possibly explain the results. Specifically, six (30%) of the Out-PTA patients had unilateral focal lesions in the frontal cortex compared to three (25%) of the In-PTA patients, but between-groups hemispheric differences in the location of those lesions reached 80%.

There was no increased activation in any area of the thalamus when testing in the opposite direction (In-PTA > Out-PTA or MCS&VS > Out-PTA). Finally, significant metabolism differences were found in the comparison In-PTA > MCS&VS (Figure 1, lower part). No voxel survived the reverse test (MCS&VS > In-PTA).

The results are presented in the form of parametric probability maps where the intensity or brightness of each voxel was determined by its corresponding *z* statistic (Table II).

Table II. Representation of studies and significant values: corrected *p*-values, Ke (number of voxels), maximum *Z*-values, MNI coordinates (mm) and region.

Groups	*p* corrected	Ke	*Z*-values	Coordinates (mm)	Region
Controls > MCS&VS	0.008	4260	7,07	4–18 0	Right Thalamus
			6,78	16–10 16	Right Thalamus
			6,28	−12–14 18	Left Thalamus
Controls > In-PTA	0.002	3758	5,88	14–12 16	Right Thalamus
			5,75	16–20 18	Right Thalamus
			5,48	−2–12 6	Left Thalamus
Controls > Out-PTA	0.010	1942	3,87	−10–16 18	Left Thalamus
			3,75	14–12 18	Right Thalamus
			3,55	−2–20 0	Left Thalamus
Out-PTA > MCS&VS	0.032	3533	6,07	14–2 14	Right Thalamus
			5,61	12–16 8	Right Thalamus
			4,04	18–34 0	Right Thalamus
Out-PTA > In-PTA	0.025	1664	4,15	12–4 14	Right Thalamus
			3,96	14–22 16	Right Thalamus
			3,93	12–2 6	Right Thalamus
In-PTA > MCS&VS	0.022	1140	3,6	−16–14 18	Left Thalamus
			3,59	−6–12 6	Left Thalamus
			3,43	−16–6 16	Left Thalamus

Discussion

Knowledge about structural and functional brain connectivity has recently improved thanks to the development of new neuroimaging techniques and new mathematical models precise enough to detect the location and quantify the function of specific brain structures and neuronal pathways [20]. Recent functional connectivity studies based on these advances have shed some light on some of the neural structures and activity patterns that underlie specific human behaviours in normal and pathological conditions [14, 15, 17, 18]. Fragmentations by regions of interest (ROI) and especially VBM techniques have been used recently in these studies to understand some of the symptoms that occur in patients who have suffered a TBI [13, 33]. These techniques have been able to characterize quantitatively the distribution of anatomical structures [24], such as the thalamus, that appear more functionally involved in maintaining consciousness [12, 17, 18, 34, 35].

Using a VBM technique, the results agree with previous studies that have documented a selective vulnerability of the thalamus and a direct relationship between greater thalamic injury and poorer clinical outcome after a TBI, suggesting that thalamic metabolism may provide valuable information regarding long-term morbidity [3, 12, 36–38]. The greatest thalamic hypometabolism in the group of patients with the worst functional status, as well as the severity of this hypometabolism in the deepest thalamic nuclei, agree with the TBI depth of lesion model postulated by Ommaya and Gennarelli [39]. According to this theory, the distribution of lesions after a TBI follows a centripetally directed cortical–subcortical–brainstem sequence of progression, which correlates precisely with the increasing severity of head injury. Conventional imaging studies supporting this theory have shown a clear relationship between the depth of brain lesions and the severity of impaired consciousness [3, 36, 40]. Anatomical studies confirm this assumption since it is well known that the reticular activating system, including mid-line structures in the upper pons, midbrain and thalamus, is crucial to the maintenance of wakefulness [41]. Unfortunately, limitations in the sample size did not allow one to differentiate between patients who were in a vegetative state or in a minimally conscious state. In this sense, Nakayama et al. [12] have previously shown that the gradient of thalamic hypometabolism described here can also distinguish between these two clinical situations.

Many neuropathological studies have shown that lesions in the thalamic mid-line and intralaminar nuclei that act as the apex of this 'activating system', even in the presence of a relatively intact cortex, are enough to justify a low state of awareness as described in cases of vegetative state [42]. The decreased thalamic metabolism, occurring not only in the patients in a vegetative or minimally conscious state, but also in the patients with an adequate level of awareness, might be related to many of the cognitive problems presented by these patients, especially those studied during the PTA period [43]. Data on functional neuroimaging studies including patients during the PTA period are still not available to the authors' knowledge. Furthermore, the few structural neuroimaging

studies previously published during this period have shown a preferential involvement of the medial temporal cortex, the central brain structures or the connections between both [44, 45].

Three main possibilities have been suggested in the literature to explain the diminished thalamic metabolism found in this study [12, 17, 18, 34, 36]. First, it could be more reflective of the diminished activity in thalamic regions due to focal thalamic injuries; second, it could also be a disconnection process caused by DAI in the white matter; or, third, it could represent a downstream deafferentation phenomenon caused by focal cortical contusions in structures that are connected with the thalamus. Prior studies show that the thalamus is protected from the direct traumatic insult which is caused after a TBI, so the appearing of neuropathological changes in the thalamus are most probably due to secondary degeneration, when other structures, especially cortical, are damaged [46]. The vast majority of the patients showed an absence of structural lesions in the thalamus, which may suggest that the thalamic hypometabolism described here supports the disconnection/deafferentation theory. However, it is also possible that the low sensitivity of the structural neuroimaging technique used or the chronicity of this sample precluded the detection of focal structural damage. Future studies, including data analysis of the cortical metabolism in those areas anatomically connected with the thalamus, are currently being carried out in the institution to resolve this question.

Given the physiological relevance of thalamic connections, not only with cortical, but also with subcortical structures, thalamic hypometabolism in severe TBI should be interpreted as an alarm sign since it clearly represent a decrease in connectivity and therefore in functionality of such networks. The data are consistent with the findings of Little et al. [47] using Diffusion Tensor Image, suggesting that cognitive dysfunction after TBI is correlated with the integrity of thalamocortical projection fibres. Other clinical responses, ranging from coma through better stages of recovery, could be the expression of the level of functionality of these neuronal connections.

These results suggest that functional neuroimaging techniques offer the clinician a more accurate picture of the cerebral dysfunction resulting after TBI than conventional techniques. This information may help to understand the pathophysiological mechanisms that underlie many of the symptoms that these patients present along the evolution of the disease. Functional neuroimaging will never replace clinical assessment, but both combined can help clinical decision-making, rehabilitation planning and communication with patients and their families by showing a vision of residual brain function after the injury. Bearing in mind the cross-sectional design of this study and considering that PET imaging was performed at rest, the challenge now is to discover the conditions and mechanisms by which some of these patients regain consciousness and improve cognition.

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