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# Thalamic metabolism and neurological outcome after traumatic brain injury. A voxel-based morphometric FDG-PET study

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Voxel-based analysis;
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**Abstract**
*Objective:* To study the relationship between thalamic metabolism and neurological outcome in patients who had sustained a traumatic brain injury (TBI).
*Methods:* Nineteen patients who had sustained a severe TBI and ten control subjects were included in this study. Six of the 19 patients had a low level of consciousness (vegetative state or minimally conscious state), while thirteen showed normal consciousness. All patients underwent an 18F-FDG PET, 459.4±470.9 days after the TBI. The FDG-PET images were normalised in intensity, with a metabolic template being created from data derived from all subjects. The thalamic trace was generated automatically with a mask of the region of interest to evaluate its metabolism. A comparison between the two groups was carried out by a two sample voxel-based T-test, under the General Linear Model (GLM) framework.
*Results:* Patients with low consciousness had lower thalamic metabolism (MNI-Talairach coordinates: 12, —24, 18; T=4.1) than patients with adequate awareness (14, —28, 6; T=5.5). Control subjects showed the greatest thalamic metabolism compared to both patients groups. These differences in metabolism were more pronounced in the internal regions of the thalamus.
*Conclusions:* The applied method may be a useful ancillary tool to assess neurological outcomes after a TBI, since it permits an objective quantitative assessment of metabolic

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function for groups of subjects. Our results confirm the vulnerability of the thalamus to suffering the effects of the acceleration-deceleration forces generated during a TBI. It is hypothesized that patients with low thalamic metabolism represent a subset of subjects highly vulnerable to neurological and functional disability after TBI.


**PALABRAS CLAVE**
Análisis basado en vóxel;
Conciencia;
PET-FDG;
Pronóstico;
Tálamo;
Traumatismo craneoencefálico;
Tomografía por emisión de positrones

**Metabolismo talámico y situación neurológica tras un traumatismo craneoencefálico. Estudio mediante PET-FDG y morfometría basada en vóxel**

**Resumen**
*Objetivos:* Estudiar la relación entre el metabolismo talámico y la situación neurológica en pacientes que han sufrido un traumatismo craneoencefálico (TCE).
*Material y métodos:* Se incluyó a 19 pacientes que habían sufrido un TCE grave y 10 sujetos control. De los 19 pacientes, 6 presentaban un grado de alerta bajo (estado vegetativo o estado de mínima conciencia), mientras que 13 mostraban un grado de alerta normal. A todos los pacientes se les realizó una tomografía con emisión de positrones (PET) con 18-fluorodesoxiglucosa (18F-FDG) 459,4 ± 470,9 días después del TCE. Las imágenes de PET-FDG se normalizaron en intensidad, creándose posteriormente una plantilla metabólica del grupo entre todos los sujetos. El trazado talámico se generó automáticamente con una máscara de la región de interés. Se comparó el metabolismo talámico de los dos grupos de pacientes respecto al grupo control, para ello se utilizó un método de análisis basado en vóxel, con significación estadística, $p < 0,05$ corregido para múltiples comparaciones.
*Resultados:* Los pacientes con grado de alerta bajo mostraron menor metabolismo talámico (coordenadas MNI-Talairach, 12, —24, 18; T = 4,1), con respecto a los sujetos control, que los pacientes con grado de alerta adecuado (14, —28, 6; T = 5,5). Estas diferencias en el metabolismo fueron más acentuadas en las regiones internas del tálamo.
*Conclusiones:* La PET-FDG puede ser una herramienta útil para valorar la situación neurológica después de un TCE. El método utilizado permite una evaluación objetiva y cuantitativa de imágenes de PET-FDG para grupos de sujetos. Nuestros resultados confirman la vulnerabilidad del tálamo a sufrir los efectos de las fuerzas de aceleración-desaceleración generadas durante un TCE.


## Introduction

Within acquired brain pathologies, traumatic brain injury (TBI) represents the paradigm of heterogeneity in terms of clinical presentation and neuropathology. The variety of dynamic forces generated during each trauma, associated with the different elastic tolerance of intracranial tissues, causes each patient to present a unique, complex combination of clinical changes express a wide variability of tissue lesions[1]. Establishing an early, accurate prognosis is particularly relevant in cases of prolonged alteration of consciousness, such as vegetative states or minimally conscious states, given the high degree of future dependence that these situations involve[2,3].

In the case of TBI, due to the peculiar variety of traumatic injuries, the clinician faces an additional problem: structural imaging tests, which are of clear clinical use in other acquired neurological diseases, may be unhelpful in establishing anatomical-clinical correlations[4]. For practical purposes, it is assumed that the dynamic forces generated after closed head injury often produce contusive focal lesions due to the effect of the impact or impact-backlash, and/or diffuse lesions by phenomena of acceleration-deceleration or rotation of the brain parenchyma within the skull bone structure. Characteristically, while focal lesions are relatively easy to identify with conventional imaging techniques, diffuse axonal damage (DAD) lesions may go unnoticed or be only partially visible and for a limited time with neuroimaging techniques that are not highly sensitive[5-7]. The interesting part of the case is that these DAD-like lesions, even though they are more difficult to visualise, often have a more direct relationship with the ultimate recovery than the presence and volume of focal brain lesions[8].

It is currently assumed that the distribution of these DAD lesions follows a depth gradient that depends on the intensity of the traumatic forces exerted at the level of the encephalon[9,10]. The involvement of deep structures, such as

the thalamus, basal ganglia or brainstem, is particularly relevant, insofar as these areas act as nodes linking different brain areas; at the same time, these structures assume the role of contact between the pathways responsible for maintaining alertness, awareness and atention[11].

That the techniques for structural and functional neuroimaging for the detection of lesions after TBI have different sensitivities is a known fact[12-14]. This difference in favour of functional neuroimaging techniques is especially remarkable in the detection of DAD lesions, particularly in the detection of abnormalities in the function of the deep nuclei responsible for maintaining the degree of alertness[12,13,15]. In this regard, the studies carried out to date with positron emission tomography (PET) in patients with TBI have shown a close link between the level of awareness and thalamic metabolism[16]. In recent years, the development of various voxel methods by voxel image analysis has improved accuracy and objectivity in the detection of metabolic abnormalities between groups of patients with central nervous system injuries. In particular, in patients in post-TBI vegetative states, these methods have identified a specific alteration of the metabolism in a wide cortico-subcortical network as an expression of disconnection syndrome involving the cortico-thalamo-cortical pathways caused by DAD-type lesions[17-19].

The present study introduces an adaptation of the voxel-based morphometry method (VBM)[20,21], originally raised for anatomical images from magnetic resonance imaging (MRI), for the analysis of PET images. Our main objective was to study the differences in thalamic metabolism between a group of patients with different clinical courses after suffering TBI, focusing specifically on the analysis of the thalamus as a structure involved in maintaining the level of awareness and connection with the environment. The method is similar in concept to that of VBM, in the sense that it uses a single volumetric image of each patient, unlike the previously-mentioned works[16-18], where the study was based on images obtained at various points in time for each patient. Our hypothesis is that patients with higher thalamic hypometabolism represent a group of subjects with increased susceptibility to more severe post-TBI neurological disability.

## Material and methods

### Patients

The initial sample consisted of 19 patients who had suffered a severe TBI (Glasgow = 8 at any time during the 48 h after TBI) and were completing a neurorehabilitation programme in a specialised centre, plus 10 control subjects. All study participants gave their written informed consent. In patients with a low level of awareness, consent was obtained from a relative or guardian.

The 19 patients were divided into two groups based on their level of alertness. Group A (low alertness level) included 6 male patients with an average ± standard deviation (SD) age of 33.1 ± 11.6 years, who were in a vegetative state (n = 3) or minimally conscious state (n = 3), according to their score on the Coma Recovery Scale and following the criteria of the American Academy of Neurology adapted to the clinical protocol followed at our service[22]. Group B (adequate alertness level) was composed of 10 men and 3 women aged 27.3 ± 11.1 years, who had passed the period of posttraumatic amnesia (PTA) 112.6 ± 68.3 days after TBI. According to the results of neuroimaging studies conducted in the first week after TBI (computed tomography [CT] in 5 cases and MRI in 14), 12 patients presented diffuse lesions according to the classification of the Traumatic Coma Data Bank (TCDB)[23] (TCDB II, n = 7; TCDB III, n = 5) and 7 presented focal lesions, 3 of which required surgical evacuation. Only 1 patient in group B presented focal lesions involving the thalamus identifiable by conventional neuroimaging tests. The control group consisted of 7 men and 3 women, relatives of the patients, with an average age ± SD of 45.6 ± 17.6 years, who participated in this study voluntarily.

### PET image acquisition

All subjects underwent a PET with 18-fluorodeoxyglucose ($^{18}$F-FDG), an average of 459.4 ± 470.9 days after TBI. Patients were kept fasting for 6 h and remained at rest for 30 min prior to image acquisition. They were injected with 200-300 MBq of $^{18}$F-FDG intravenously; 30-60 min later, a single 3D acquisition was carried out for 10 min in a PET tomograph (Advance®, General Electric Health-Care Technical Systems). The image was reconstructed using a filtered, back projection algorithm (Hanning filter, cutoff 4.8) and attenuation correction by contours, obtaining 4.5-mm cuts that were redirected along the orbitomeatal axis to obtain transverse, coronal and sagittal sequences.

### Voxel-based PET analysis

We performed a voxel by voxel image analysis using Statistical Parametric Mapping software (SPM) (Wellcome Department of Cognitive Neurology; Institute of Neurology, London, UK), which is freely available to the scientific community and which operates under MATLAB software (The MathWorks, Natick, MA, USA). Since image acquisition consisted of a single volumetric image per subject, we did not use the standard SPM voxel-based analysis method, but instead started from the VBM implementation for anatomical image comparison.

The standard PET template of SPM2 was originally constructed using images (15)O-H(2)O PET. Initially, because using that template (being of a different tracer) could lead to inconsistent interpretations of the statistical analysis[24], we generated our own template that was representative of the group we wished to study. In this way, we had a reliable source of information that was close to the reality of the survey data and avoided the specific biases that would result from the use of a standard template. In the process of creating our own template, we used images from all the individuals in the study, both control subjects and patients. Otherwise, the template would present deviations towards a particular group and the normalisation processes would yield biased data. The SPM2 PET template, images of the

controls and also of the patients, all normalised in intensity, intervened in creating our own template. Normalisation in intensity of each brain volume acquired, before the creation of the template, consisted of detecting the maximum-intensity voxel in the volumetric image and dividing the intensity of each voxel in the volume by the intensity of the maximum. Thus, the intensity values, metabolism indicators, were converted into values comparable between subjects. We then performed an initial spatial normalisation using an affine transformation of the SPM PET template and our intensity-normalised images. The process began by transferring, through affine transformations with 12 degrees of freedom, each of the intensity-normalised original images in the study into the same space. Next, the images obtained were averaged, obtaining a reference that brought together the information from all the initial data. The averaged image was then softened with a three-dimensional 8×8×8-mm Gaussian filter. The use of this type of three-dimensional filter enabled the values of each image to follow a distribution allowing estimation in Gaussian fields, which increased the validity of subsequent statistical analysis[25].

Finally, the intensity-normalised original images were subjected to nonlinear normalisation (warping) to transport them into the space of our own template. After this last non-linear spatial normalisation of each image, we selected the region of interest (the thalamus). The thalamic tracing was performed automatically, and a mask of the region of interest was generated using the atlas proposed by Tzourio-Mazoyer et al.[26], which was superimposed on the images to be analysed with the software MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html).

### Statistical analysis

The statistical analysis of the images was carried out under the general linear model (GLM), using SPM software. We defined a model for the comparison, using the GLM, of the groups (controls > group B, controls > group A and group B > group A). The model was adjusted by estimating the parameters to obtain the best approximation of the data to the model. We carried out a resolution of the model through Student's t-tests for two samples, which were applied independently for each voxel using contrasts (effects of interest); this was done to measure the interactions and, therefore, the possible differences between each pair of groups (controls > group B, controls > group A and group B > group A). Statistical significance was established by applying a correction for multiple comparisons in each case using the technique of ratio of false positives (False Discovery Rate, FDR)[27], which controls the proportion of false positives in the study and which corrects the potential problems of repeating a statistical test on hundreds of thousands of voxels. The thalamic metabolism of the two patient groups was thus compared with the control group and between the two groups of patients; the statistical significance level was set at $p < 0.05$.

The resolution of the statistical models was presented in the form of parametric probability maps, where the intensity or brightness of each voxel was determined by the corresponding t statistic.

## Results

There were significant differences in thalamic metabolism in the comparative studies between the three groups carried out by pairs. The study on patients in group B and control subjects (fig. 1A) showed that group B patients had lower thalamic metabolism than control subjects. The study conducted on patients in group A and control subjects (fig. 1B) showed that group A patients also had lower thalamic metabolism than controls, and with a greater difference than in the previous comparative study. In the study on the two groups of patients (fig. 1C), we observed that patients with a low degree of alertness also had a lower thalamic metabolism than patients with an adequate degree of alertness.

The analysis showed a lower metabolism in the thalamus (region of interest studied) in group A, followed by group B, while the group of control subjects showed the highest metabolism. The differences found in thalamic metabolism were much higher between group A and control subjects than in the other comparisons. This was observed in all comparisons using Student's t-test (table 1). The higher the value of the Student's t statistic obtained after the tests applied independently to each voxel, the more pronounced the difference in thalamic metabolism was. Figure 1 shows that each significant voxel has a brightness that is proportional to the difference between the two groups (which is reflected in the t value for that voxel). Student's t-test values increased with the gradient of the thalamus. Therefore, in the most external areas the Student's t value was lower, while in the centre of the thalamus the value was higher. The maps of results (fig. 1) show the values of the Student's t-tests applied to each voxel in the thalamus.

## Discussion

Since the first studies of brain metabolism on patients in vegetative states, we have known that patients with low level of consciousness show a reduction in overall brain metabolism that can reach up to 40-50% of normal values; even greater reductions can be observed in patients in whom this situation lasts for a long time[28-31]. The clinical significance of this isolated value in the evaluation of patients with low levels of perception has been challenged by the recent emergence of studies with new methods of image analysis that have shown global cerebral metabolism in the limits of normality in some of these subjects[19]. Some authors have even reported improvements in the degree of awareness and alertness of many of these patients, which have not been accompanied by an increase in the overall glucose consumption rates[32,33]. New image analysis techniques have been developed, such as fragmentation by regions of interest[26] and especially the development in recent years of VBM techniques that avoid the subjectivity of manual delineation of each region of interest and enable greater reproducibility.[20,34] The development of these techniques has allowed us to avoid general measurements and to specifically analyse the anatomical structures that appear to be more involved in maintaining alertness and

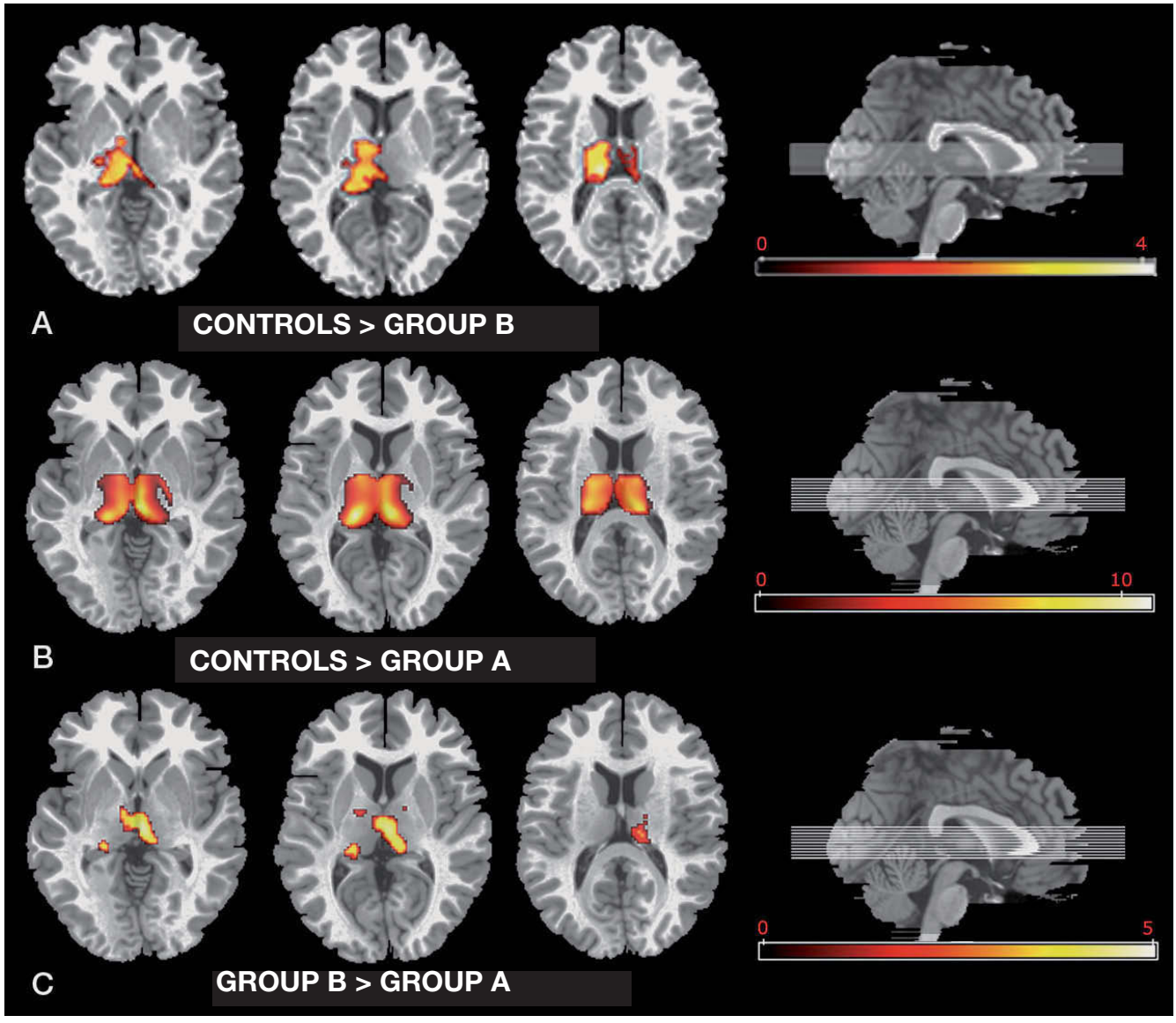


**Figure 1** Positron emission tomography image. Map of statistically significant differences in the target region of the thalamus. A: patients with an appropriate level of alertness compared to healthy subjects. B: patients with a low degree of alertness compared to healthy subjects. C: patients with a low degree of alertness compared to patients with an adequate degree of alertness.

**Table 1** Representation of the studies and significant values

| Groups | Corrected p | Ke (voxel number) | p, Student's t | Z | MNI coordinates (mm) | | |
|---|---|---|---|---|---|---|---|
| Controls > group B | 0.034 | 1,182 | 4.11 | 3.48 | 12 | −24 | 18 |
| | | | 3.51 | 3.08 | 4 | −24 | −2 |
| | | | 3.44 | 3.03 | 18 | −36 | 6 |
| Controls > group A | 0.005 | 2,877 | 10.78 | 5.51 | 14 | −28 | 6 |
| | | | 9.78 | 5.29 | −10 | −26 | 10 |
| | | | 9.47 | 5.22 | −6 | −24 | 0 |
| Group B > group A | 0.064 | 1,511 | 4.99 | 3.86 | −6 | −20 | 2 |
| | | | 4.08 | 3.36 | −14 | −28 | 12 |
| | | | 4.01 | 3.32 | −18 | −10 | 14 |

connection with the environment. Neuropathological description of the case series of patients in a vegetative state has shown that the thalamus (especially the intralaminar structures and thalamocortical projections) is essential in maintaining the level of consciousness[35,36]. Confirming this theory, a marked increase in the degree of interaction with the environment has been demonstrated in patients with low perceptual situation after electrical brain stimulation in thalamic intralaminar nuclei[38].

Cerebral metabolism studies conducted to date in posttraumatic brain conditions support this association between thalamic metabolism and degree of consciousness[39]. Specifically, VBM studies have reported a dysfunction of a broad network covering the polymodal association cortex and including the frontal and parietal-temporal cortices and thalamic nuclei[18,19,40]. These studies have shown, in turn, that the clinical recovery of decreased consciousness states is associated to a functional restoration of the connections between intralaminar thalamic nuclei and prefrontal cortex[17,32]. All these studies indicate that in the case of severe TBI, where the basic neuropathological substrate are DAD lesions, the process of loss and recovery of consciousness and, obviously, the rest of the skills lost after TBI should be interpreted as a continuum, which only expresses the diffuse loss and subsequent activation of lost brain connectivity. In this sense, it seems that the clinical process of recovery of each patient is associated, above all, to the ability to recruit progressively wider neural circuits, including areas structurally and functionally responsible for managing more complex information, rather than to the activation of a particular anatomical structure. In the case of the thalamus, given the functional relevance of its connections with the rest of cortico-subcortical structures, its metabolism (or in its absence its hypometabolism) should be interpreted as an alarm signal. Thalamus metabolism can warn us because it is a clear reflection of the degree of connectivity and, therefore, of the functionality of such networks. The visible clinical responses of each patient, from the coma phase up to the later stages of recovery, would be an expression of the degree of functionality of these connections[41].

Our results confirm the vulnerability of the thalamus to suffering the negative effects of the forces generated after a TBI[9,17,18,32,35,36,39,40,42,43]. Moreover, the increased thalamic involvement in the patients of our sample with worse functional status and the severity of hypometabolism in the deepest thalamic nuclei match the expectations according to the depth gradient theory; this theory proposes that the greater the intensity of the trauma, the greater the depth at which the lesions appear[9]. Our results are consistent with those of other studies that have shown a pattern of intensity of thalamus involvement that is directly proportional to the severity of the post-TBI clinical situation[16-18,32,39,41].

One aspect that has been questioned in previous studies is whether the metabolic decline observed in the subcortical structures in this group of patients is due to a direct effect of the TBI itself on the thalamus, a DAD deafferentation process on the white matter or a disconnection phenomenon due to a direct affectation by the TBI on cortical structures with which the thalamus is connected[16-19,32,39,41]. The absence of structural damage in the vast majority of our patients may indicate that the thalamic hypometabolism described here is due to a disconnection effect. However, it cannot be ruled out that the low sensitivity of the structural neuroimaging technique used (CT in 5 cases) or that the sample chronicity has prevented the detection of direct focal lesions, given the transient visibility of DAD lesions. Given that the present study did not analyse the metabolism of other cortical structures with which thalamic nuclei establish anatomical and functional connections, we cannot provide further evidence on this matter.

Our results highlight the special ability of functional neuroimaging techniques, particularly PET, as well as the usefulness of VBM techniques, in the detection of functional changes even in the absence of structural lesions. Specifically, only one patient in the sample studied here presented lesions in the thalamus identifiable by CT (interestingly, the patient belonged to the group with the highest level of consciousness). The prognostic importance of tests in posttraumatic brain injury has been known from TCDB studies, as has its classification of clinical severity into four degrees of diffuse involvement and two degrees of focal involvement[23]. With the advent of new functional neuroimaging techniques and the development of new analytical methods, in this decade we are going through a revolution in terms of our ability to examine brain structures noninvasively, which is helping us to understand the functioning of our brain better. Our results indicate that functional neuroimaging techniques offer us a clearer picture of the extent of brain dysfunction resulting after TBI. In addition, our results show that these techniques also present a vision of residual brain function and help us to understand possible pathophysiological mechanisms underlying many of the symptoms presented by these patients.

## Conflict of interests

The authors declare no conflict of interests.

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