Nuclear Medicine Imaging in Traumatic Brain Injury

Adapted from:


Abstract

This chapter provides an up-to-date review of nuclear medicine neuroimaging in traumatic brain injury (TBI). Although evidence-based imaging studies are needed, $^{[18\textnormal{F}]}$FDG PET is a valuable tool in researching complex mechanisms associated with early metabolic dysfunction in TBI, and in the acute phase appeared to be useful in those patients in whom structural neuroimage fail to show abnormalities explaining their neurological state. While in the chronic TBI phase, most $^{[18\textnormal{F}]}$FDG PET studies converge to identify a diffuse cortical–subcortical hypometabolism involving key regions for cognitive function, such as thalamus. In addition, recent studies suggested the usefulness of $^{[18\textnormal{F}]}$FDG PET for the evaluation of therapeutic interventions in chronic TBI patients with cognitive deficits. Moreover, the use of other PET and SPECT radioligands as markers of specific cellular process, are an attractive tool for detecting the secondary neuronal damage involved in the pathophysiology of TBI, and for the evaluation of different therapeutic approaches.
Introduction

The worldwide prevalence of traumatic brain injury (TBI) demands global attention and effective actions involving all levels of society. Recent studies have estimated annual TBI incidence to be 230 per 100,000 inhabitants in the European Union, and of about 500 per 100,000 inhabitants in the United States; with about 70-80% of these cases accounted for as mild TBI (mTBI), which is defined as loss of consciousness lasting <30 min, and initial Glasgow Coma Score (GCS) of 13-15, and post-traumatic amnesia lasting <24 h. The estimated cost of TBI in the United States is of US$17 billion per year. Falls and motor related vehicle accidents are the most common causes of TBI, and its worldwide incidence is growing mainly due to traffic accidents, with a higher increase in developing countries. TBI as a consequence of sports practice and recreational activities should not be underestimated either, especially in children and adolescents where the rate of emergency department visits for sport- and recreation-related TBIs rose 57% in the last decade among persons aged ≤19 years, and with and increased annual rate of 16.5% in mTBI related with high school sports over the past 10 years. Not less important is the rise of the social and economic TBI burden consequence of military conflicts and civilian exposure in war zones: about 20% of the veterans from the Iraq or Afghanistan wars have experienced mTBI. These trends have substantially modified epidemiological and clinical patterns of TBI.

TBI includes a wide and heterogeneous spectrum of pathologies ranging from focal damage caused by contusion (with or without cranial fracture) to diffuse axonal injury (DAI), including complex secondary pathophysiological processes that could be aggravated by systemic events, patient age or preexisting chronic diseases. In many cases, TBI may secondarily lead to epilepsy and, after aging, it is the most important non-genetic factor that increases the risk of dementia.

Immediate clinical TBI consequences are directly related to the severity, mechanism, location and duration of the impact. But even in the mild cases about 85% of the patients report one or more symptoms the day after the accident, which generally recovers within 3 months to a level comparable to healthy population.

Conventional computed tomography (CT) is the technique of choice for initial evaluation of TBI patients, because it enables to decide whether the patient requires an immediate surgical intervention, when focal injuries with hematomas are suspected. However, and despite the advances of conventional CT and magnetic resonance imaging (MRI) in the last years,
these techniques cannot be used to predict neurocognitive functional deficits at any stage of TBI, as even if any structural abnormality is shown with these tools, they do not image the functional pathology important for the neurocognitive outcome.20–22

It is in these cases that functional neuroimaging using nuclear medicine techniques, such as single-photon emission tomography (SPECT) or positron emission tomography (PET), have a great potential to provide insight into the underlying metabolic changes that arise from TBI and to reveal the secondary damage that contributes to short- and long-term impairment.

In this chapter a review of several relevant contributions of nuclear medicine neuroimaging towards improved understanding of TBI is presented, using both positron emission tomography (PET) and single photon emission computed tomography (SPECT), with an special focus on the mild traumatic brain injuries common in sports.

**Concussive head injuries in sports**

Contact sports are especially prone to mild TBI, commonly termed as concussion. From these sports, ice hockey shows the highest incidence of concussion amongst team sports (e.g. American football, ice hockey, rugby and soccer). It seems that the over-reliance on protective equipment in some of these sports, such as in ice hockey and American football, may induce the athletes to be even more aggressive, and then indeed have a higher incidence of concussion. On the other hand, in individual sports it is boxing which shows the highest frequency of concussion at the recreational and competitive level.23

Boxing and other forms of unarmed combats are probably as old as human species. Not surprisingly, the link between repetitive concussions and cognitive or behavioral impairments later in life was originally noted in boxers. These clinical characteristics were first described in 1928 by Martland as the “punch drunk syndrome”,24 who hypothesized that the clinical spectrum of abnormalities observed in boxers were the result of repeated blows to the head. Later in 1937, Millspaugh introduced to the condition the more formal term of “dementia pugilistica”, a term that has survived until today.25

Concussed athletes can experience a variety of symptoms including headache, fatigue, dizziness, anxiety, abnormal balance and postural instability, impaired memory or cognitive deficits among others. These symptoms, when prolonged in time, are frequently referred as post-concussive syndrome (PCS),26 which is manifested in 15% of those suffering a concussion27–30 even
in the absence of relevant pathology.\textsuperscript{31}

The common experience is that recovery following a single sport-related concussion is rapid and complete, i.e. without residual deficits or long lasting structural changes. However, there is growing evidence of the clinical and neuropathological consequences of repetitive concussions. Several brain changes are potentially associated with repetitive head impacts\textsuperscript{32} including hippocampal atrophy, cavum septum pellucidum, dilated perivascular spaces, diffuse axonal injury, cerebral atrophy, increase in lateral ventricular size, pituitary gland atrophy, contusions, arachnoid cyst, hemosiderin deposition from prior hemorrhage, and vascular injury.

Moreover, repetitive concussions have been linked with an increased risk of depression,\textsuperscript{33} Alzheimer’s disease,\textsuperscript{34} chronic traumatic encephalopathy (CTE),\textsuperscript{14} and neurodegenerative diseases.\textsuperscript{35,36} CTE is a distinct form of the acute symptoms of concussion, and it is not merely a prolonged PCS.\textsuperscript{37} Symptoms of CTE typically do not present until years after the trauma, and include dementia, impaired mental function and coordination, tremors, impulsive behavior and cognitive impairment.\textsuperscript{38,39}

With the highest rates of sport-related brain injuries during the adolescence and young adulthood it is important to make an effort to fully understand the short- and long-term consequences of repetitive concussions. Thereby, appropriate guidelines can be created for clinical evaluation and to address the return to exercise and athletic participation.

**Neuropathology of concussion**

To understand the relevance of nuclear imaging in the context of concussion in sport, it is necessary to start with an overview on the metabolic cascade of reactions that take place after an mTBI.\textsuperscript{40} It is generally accepted that a concussion results from rotational or angular accelerations in the brain. The maximal rotational forces, which are a consequence of the head impact, are exerted in the midbrain and diencephalic region, creating a disruption of the electrophysiological and subcellular activities of neurons and glial cells. Contrary to common belief, the initial transmitted tension does not result in shearing of the axons, which can be stretched and twisted without being sheared or torn.\textsuperscript{28} In fact, the neuropathology of concussion is the result of a complex process and not an instant, consequence of the “neurometabolic cascade” that follows the head trauma.\textsuperscript{41} This process is shown with more detail in Figure 1 and Figure 2.

Immediately after the mechanical injury of the brain, there is a cellular response with a widespread release of excitatory neurotransmitters (i.e.
Figure 1. Neuromembrane events in TBI. The complex cellular and vascular pathological interactions that occur following TBI, and the central role of mitochondrial failure.

Figure 2. Neurometabolic cascade following experimental concussion. $K^+$, potassium; $Ca^{2+}$, calcium; CMR$_{gluc}$, oxidative glucose metabolism; CBF, cerebral blood flow.
glutamate) and an uncontrolled ion flux. The binding of glutamate to its receptors leads to further neuronal depolarization, with efflux of potassium (K\(^+\)) and influx of calcium (Ca\(^{2+}\)), sodium (Na\(^+\)), and chloride (Cl\(^-\)). This ionic shift causes a failure to generate and propagate action potentials, leading to acute and subacute changes at cellular level. This process will end in a secondary axotomy 4 hours to 12 weeks after the mTBI (with a minimum of 2 hours in animals and 12 hours in human beings).

In the acute stage, the sodium-potassium (Na\(^+\)-K\(^+\)) pumps increase their function in an effort to restore the neuronal membrane potential, with the corresponding increment in production of adenosine triphosphate (ATP). The trigger of the glucose metabolism into a diminished cerebral flow state creates a mismatch between glucose supply and the demand of energy that ends in a cellular energy crisis and failure of the ATP dependent membrane pumps.

In the subacute phase, after the initial period of increased glucose consumption, the brain undergoes a period of depressed metabolism. The reduction in ATP production creates a failure in ATP dependent membrane pumps, with a reverse pumping of Na\(^+\)/Ca\(^{2+}\) exchangers. This leads to a marked increase of Ca\(^{2+}\) concentration in the cytoplasm, which is sequestered by the mitochondria, causing damage to it and worsening the energy crisis. This process starts a cascade of reactions that include oxygen radical production, disruption of protein phosphorylation, formation of proteases and free fatty acids (e.g. arachidonic acid), depolymerization of microtubules, collapse and loss of neurofilaments, and the separation of myelin lamellae in later stages.

It is important to understand that this complex pathophysiologic sequence of events and metabolic changes occurs prior to what can be visualized using conventional CT and MRI, while it can be the target of the more specific nuclear imaging techniques aiming to visualize particular metabolic processes.

**Positron emission tomography (PET)**

One of the main advantages of PET over SPECT is its higher sensitivity that allows generating images of greater resolution, and the usefulness of this technique in the study of traumatic brain injuries was shown in several clinical settings. However, no meta-analyses have clarified its importance due to the heterogeneity of the published studies (differences in the time elapsed between trauma and image acquisition, in the TBI classification, in radiotracers, or in methodological designs). Despite the large number of these studies including moderate and severe injuries, not much research has been done to address expressly the mild injuries or the concussions in sports.
Aside from PET cameras availability and the need for a near-by cyclotron, the absence of studies can also be explained by the high cost of each PET exams, usually ranging between US $1000 and $3000.\textsuperscript{42}

**Metabolism and perfusion in the acute phase of brain trauma**

**[\textsuperscript{18}F]FDG PET**

The most common radiotracer used in clinical PET imaging is [\textsuperscript{18}F]FDG (2-deoxy-2[\textsuperscript{18}F]-fluoro-D-glucose), with its first studies applied to TBI patients dating back to the 1980s and 1990s.\textsuperscript{43–49} In these studies, it was pointed out that abnormalities detected by [\textsuperscript{18}F]FDG were more extensive than those observed by CT, and that it was possible to detect them very early when structural modalities could still be negative. The brain metabolism in its acute phase after the trauma has been since then one of the main topics of research in TBI. Findings of Bergsneider and co-workers\textsuperscript{50–52} suggested the existence of a triphasic pattern in the cerebral metabolic rate of glucose (CMR\textsubscript{glc}). These phases, observed also in animal models, can be divided in:

1. Hyper-acute increase of metabolic activity;
2. Prolonged period of reduced metabolism, of about a month; and
3. Recovery of stable levels within normal limits.

In the paper published by this group in 2001,\textsuperscript{52} fifty four TBI patients in acute phase (2-39 days post onset) were studied with [\textsuperscript{18}F]FDG, and in 13 of those patients the scan was repeated after 6-15 months. The presence of this triphasic pattern was found to be independent of the TBI severity and the level of consciousness, measured by the GCS. No relationship was found between the CMR\textsubscript{glc} changes and the neurological alterations measured by the disability rating scale. The authors concluded that [\textsuperscript{18}F]FDG PET should not be used as a surrogate marker to estimate the degree of functional recovery following TBI.

On the other hand, Hattori and coworkers\textsuperscript{53} using a new generation of PET scanners with better spatial resolution, capable of identifying smaller brain regions, demonstrated in 23 acute phase patients (5 days post onset) that, unlike global CMR\textsubscript{glc}, there was a direct association between level of consciousness measured by GCS and CMR\textsubscript{glc} values for the thalamus, brain stem, and cerebellum. This study significantly contributed to a better understanding of how the level of consciousness and brain glucose metabolism, measured by [\textsuperscript{18}F]FDG, are related.

Three other studies made the role of [\textsuperscript{18}F]FDG in the acute phase of TBI even more clear.\textsuperscript{54–56} The first of these papers was a thorough characterization of brain tissue [\textsuperscript{18}F]FDG kinetics during the acute phase.\textsuperscript{54} In this study, the
authors characterized \[^{18}\text{F}]\text{FDG}\) uptake, transport, and hexokinase activity using kinetic modeling. The study group comprised 21 TBI patients with cerebral contusions. Cerebral blood flow (CBF) was also evaluated by dynamic \[^{15}\text{O}]\text{H}_2\text{O}\) PET scan. Results demonstrated that hexokinase activity was reduced in the entire brain, including apparently undamaged brain cortex, while glucose transport and CBF were reduced only in pericontusional areas. Seven patients showed regionally increased \[^{18}\text{F}]\text{FDG}\) uptake in pericontusional areas, probably associated with residual regional increase of hexokinase activity during the hyper acute phase (first phase of the triphasic pattern). Hypotheses taken into account to explain focal pericontusional hyperglycolysis were anaerobic glycolysis, ionic disturbance, release of excitatory amino acids and glycolysis due to increased glutamate activity. Bearing in mind that glycolysis takes place mainly in glial cells; authors suggested that an increase in glial metabolic activity was a possible cause of hyperglycolysis.

The following study was inspired by an important observation concerning the fact that gray matter (GM) to white matter (WM) contrast in \[^{18}\text{F}]\text{FDG}\) PET images was reduced in patients with acute TBI, with or without focal damage, compared to normal healthy controls.\(^5\)\(^5\) Interestingly, this reduction was not observed in \[^{15}\text{O}]\text{H}_2\text{O}\) PET images of CBF in the same patients. For this reason, the authors hypothesized that changes of glucose metabolism in the acute phase were different in GM and WM. They studied 14 patients with severe to moderate TBI (0-4 days post onset), all with structural focal abnormalities by CT. In all subjects, \[^{18}\text{F}]\text{FDG}\) PET, triple dynamic \[^{15}\text{O}]\text{PET}\) (\[^{15}\text{O}]\text{CO}, \[^{15}\text{O}]\text{O}, \[^{15}\text{O}]\text{H}_2\text{O}\) and MRI were carried out. Initial GCS at onset and the Glasgow outcome scale (GOS) 12 months post onset were also evaluated, and peri-hemorrhagic regions were excluded from the analysis. For comparison, a control group of 18 healthy subjects was studied. The results showed that the GM-to-WM ratio in \[^{18}\text{F}]\text{FDG}\) PET images was significantly reduced in the TBI group. Although a global reduction of \(\text{CMR}_{\text{glc}}\) was observed in the patients, as expected from the previous study,\(^5\)\(^4\) \(\text{CMR}_{\text{glc}}\) and hexokinase activity were selectively reduced in the GM and not in the WM. Significant changes of global CBF were not found in GM or in WM, corroborating that glucose supply to the brain was not limited. Even more interesting was the finding that the GM-to-WM ratio was positively correlated with the initial GCS and patients with higher GM-to-WM ratio showed better recovery (GOS) after 12 months. Before this study, physiological changes occurring in WM after TBI had received less attention compared to changes in GM. Based on prior observations in animal models, the authors considered several hypotheses to explain the unexpected finding that there were no significant changes in \(\text{CMR}_{\text{glc}}\) in WM (or that it was increased with respect to the global
One of these hypotheses is that in WM there was a combination of infiltration of inflammatory cells and reactive gliosis after TBI, which was probably associated to DAI.

The following article was a direct consequence of the aforementioned study. The authors examined the relationship between glucose and oxygen metabolism in WM in the acute phase, to determine the nature, extension, and degree of abnormalities in regions remote from hemorrhagic lesions. The study sample was essentially the previous one, but triple dynamic [15O] PET and MRI studies were carried out as well. Five types of quantitative images were generated: CMRg, CBF, cerebral metabolic rate of oxygen (CMRO2), oxygen extraction fraction (OEF) and oxygen-to-glucose metabolic ratio (OGR). The results corroborated that CMRg was reduced only in GM. CBF and OEF were preserved, while CMRO2 was reduced both in GM and WM. The main result was that OGR was selectively reduced in WM. Thus, this study showed that acute metabolic changes in WM had a particular feature, characterized by CMRO2 depression, without parallel depression of CMRg, suggesting a non-oxidative use of glucose in this region during the acute phase. These findings were present throughout WM, even in regions without evidence of DAI based on conventional MRI images, thus suggesting that DAI detected by multi-modal PET was much more extensive and subtle than that detected by conventional MRI. As possible explanations for these findings, authors indicated an increase in inflammatory cells during the acute phase, especially in the WM, which are more prone to anaerobic glycolytic metabolism. Combining the results obtained from these studies, it can be concluded that the state of coma involves a thalamus-cortical disconnection with a clearly defined metabolic substrate, and that [18F]FDG PET has a prognostic value.

However, the metabolic dysfunction in the acute phase continues to be object of research and debate. Findings from the Cambridge University group, combining microdialysis and [18F]FDG PET studies did not support the hypothesis of non-oxidative metabolism associated with an increase in glucose cerebral metabolism in the acute phase. On the other hand, a recent study indicated that early dysfunction of non-ischemic oxidative metabolism in the acute phase leads to chronic brain atrophy in TBI patients. This study showed that both cortical CMRg and CMRO2 were reduced in the acute phase, even in apparently normal areas by MRI. However, the extent of regional brain atrophy 6 months after TBI correlated better with CMRO2 and CBF, particularly in the frontal and temporal lobes (n=32). CMRg correlated with atrophy only in the frontal lobe. They also found that OEF was not in the ischemic range and did not correlate with chronic brain atrophy. These results emphasized the fact that chronic brain atrophy is related with early
metabolic changes, especially in brain areas not directly damaged during TBI.

In our view, from a clinical point of view, although appropriate clinical trials are still needed to provide more evidence, \([^{18}\text{F}]\text{FDG PET}\) in the TBI acute phase appeared to be more useful and to show incremental validity (prognostic information) in those patients in whom CT or MRI fails to show damage explaining their neurological state. With the growing number of hybrid PET-CT systems and \([^{18}\text{F}]\text{FDG availability}\), combined studies of both structural and functional damage are now more feasible. This could facilitate acquisition of multi-center databases to carry out evidence-based imaging studies to evaluate the incremental validity of \([^{18}\text{F}]\text{FDG PET}\). Cost-effectiveness analysis is also necessary to compare \([^{18}\text{F}]\text{FDG PET scans}\) with other emerging MRI-based techniques, such as diffusion tensor imaging, magnetization transfer imaging, magnetic resonance spectroscopy and functional magnetic resonance.\(^{60}\)

\(\text{[^{15}\text{O}] PET}\)

TBI consequences are not only determined by primary injury, but also by subsequent neuronal damage due to secondary processes, which already starts during the acute phase. For this reason, the main strategy in TBI patient management, especially for those in critical neurological state, is to prevent or limit secondary damage as much as possible.\(^{61}\) Secondary damage can be initiated or aggravated by hypoperfusion, arterial hypotension, hypoxemia, auto-regulation failure, as well as metabolic, immunologic and biochemical changes. Although delayed ischemia is one of the routes of secondary damage, re-perfusion can also take place, elevating intracranial pressure, reducing perfusion pressure and finally reducing CBF again.

Triple dynamic \(\text{[^{15}\text{O}] PET}\) is the best technique for determining true ischemia because it is the only one that can simultaneously measure CBF, CMRO\(_2\) and OEF globally and regionally. To demonstrate true ischemia, it is not enough to demonstrate that CBF is reduced, since this could be a response to CMRO\(_2\) decrease (flow-metabolism coupling). Therefore, it is essential to demonstrate that CBF is also inadequate for the oxygen demand, which means confirming a significant OEF increase in the ischemic range.

Since the beginning of this century several triple \(\text{[^{15}\text{O}] PET studies}\) have allowed a better understanding of regional ischemia mechanisms in acute TBI. Some studies have demonstrated significant regional ischemia in the first hours after TBI,\(^{62-65}\) while in other studies ischemia has been less evident.\(^{56,59,66,67}\) This apparent contradiction could be due to the heterogeneity and complexity of TBI. Another explanation for these contradictory results has been provided by triple \(\text{[^{15}\text{O}] PET studies,}\(^{68}\) were was found that
unlike classical acute ischemia (i.e. stroke), the quantitative CBF threshold that defines irreversible ischemia did not discriminate correctly between surviving and irreversibly damaged tissue acutely post TBI \( (n=14) \). Although the quantitative CMRO\(_2\) threshold was comparable to the threshold reported for brain infarction, extensive overlapping was found for both tissues. From this study, the hypothesis emerged that selective neuronal death could be present in apparently surviving regions, which are not visible in conventional MRI images that better identify regions with pan-necrosis. Later studies using \([^{11}C]\)flumazenil seem to corroborate this idea.

Other \([^{15}O]\) PET studies have allowed examination of new hypotheses about additional mechanisms of hypoxia and energetic failure, such as metabolic suppression, mitochondrial dysfunction and microvascular disease in the acute phase of TBI.\(^{66,69,70}\) Some studies have been proven useful to evaluate the impact of therapeutic interventions in critical state patients\(^{64,71–75}\) and in animal models of TBI.\(^{76,77}\) \([^{15}O]\) PET studies also validated and refined bedside monitoring technologies, which facilitate continuous monitoring of cerebrovascular physiology.\(^{71,78,79}\) Bedside monitoring has the advantage of continuous temporal monitoring of CBF, auto-regulation and metabolic state of the patient.\(^{80}\) The main difficulty is that it can only monitor a small area of the brain, unlike \([^{15}O]\) PET which allows studying the whole brain in a more quantitative way. The main disadvantages of \([^{15}O]\) PET are that continuous monitoring is not possible, the patient must be moved from the intensive care unit to the scanner and the high cost of the cyclotron. In our opinion, \([^{15}O]\) PET is a solid technique for research into the complex pathophysiology of acute TBI, but in contrast to \([^{18}F]\)FDG PET it is not widely available due to its high cost. Therefore, it is used mainly in research and less in clinical practice.

**Metabolism in the chronic phase of brain trauma**

In the last years there have been important advances in the care of neuro-critical patients after TBI, resulting in a significant decrease of mortality.\(^{81}\) However, TBI survivors frequently suffer of a wide variety of chronic cognitive, emotional and behavioral disorders that hinder return to normal social and work life, being persistent vegetative state the worst final outcome.

Neural networks connecting brain cortical and subcortical regions are crucial to maintain normal cognitive function.\(^{82}\) TBI damages, both primary and secondary, can impair not only particular nodes of these networks (focal damage) but also the wiring (DAI). Focal damage is easily identifiable both in structural and functional neuroimages, unlike DAI which can be underestimated by routine structural imaging in many patients. Findings in acute TBI using \([^{18}F]\)FDG PET already suggested a thalamus-cortical
disconnection as the cause of coma.\textsuperscript{54–56}

However, cortical – subcortical disconnection may persist to a larger or lesser extent in many patients in the chronic phase after TBI. \textsuperscript{[18F]}FDG PET studies in chronic TBI patients have allowed characterization and unveiling of many aspects of this cortical – subcortical disconnection. Several of these studies have in common the use of voxel-based image analysis methods, especially SPM.\textsuperscript{83} Unlike the methods based on volumes of interest (VOI), SPM enables the analysis of the whole-brain volume voxel by voxel, without prior spatial hypothesis. In this regard, the exploration range is considerably broadened, giving in many cases unexpected results that reveal subtle information contained in the images, which are very difficult to extract using the visual qualitative method or VOI-based analysis.

Nakayama and coworkers,\textsuperscript{84} using \textsuperscript{[18F]}FDG PET and SPM analysis studied the differences between control individuals (\(n=30\)) and chronic TBI patients divided into three groups: a group with higher brain dysfunction (\(n=22\)), a second group with minimally conscious state (\(n=13\)) and a third group in persistent vegetative state (\(n=17\)). The patients selected did not have focal lesions evidenced by CT or MRI at onset. Results showed that the three groups had a bilateral hypometabolism pattern involving prefrontal medial region, medial frontobasal region, anterior and posterior regions of the cingulate gyrus and thalamus. These brain regions are an essential part of the cognitive networks. This pattern was more extensive and prominent in the group in persistent vegetative state and less in the group with higher brain dysfunction, with an intermediate level in the group with minimally conscious state. Thus, this study identified a common cortical – subcortical regional pattern of hypometabolism in patients with chronic TBI, where the extent and severity was associated to the level of consciousness. The results obtained fitted the concept of thalamo-cortical disconnection due to DAI. Two subsequent studies corroborated and extended these findings in patients with clinical diagnosis of DAI and chronic neuropsychological deficit.\textsuperscript{85,86} Kato and coworkers performed group comparison analysis by SPM between controls (\(n=30\)) and patients with DAI (\(n=32\)), and carried out correlation analysis between regional metabolism and neuropsychological variables in the patient group. Group comparison showed similar findings to those reported by Nakayama and coworkers. In addition, a metabolic deficit was also found in both temporal lobes and the right cerebellum. Full-scale Intelligence Quotient (FIQ) was found to correlate positively with metabolism in the right cingulate gyrus and the bilateral medial frontal region. Nakashima and coworkers\textsuperscript{86} carried out a group comparison between controls (\(n=32\)) and DAI patients with neuropsychological deficit (\(n=12\)), and case by case analysis. They used another voxel-based method.
known as 3D stereotactic surface projection (3D-SSP). Group comparison revealed hypometabolism in the cingulate, lingual and cuneus gyrus. Case by case analysis showed differences regarding the site and extension of hypometabolism in the cingulate gyrus, although hypometabolism was more frequent in the medial region of the cingulate gyrus (6 patients).

Another interesting study looked into the incidence of increased $[^{18}F]$FDG uptake in the cerebellar vermis in TBI patients. This study comprised a TBI group ($n=44$) and a control group ($n=57$). The time elapsed between the acute phase and the $[^{18}F]$FDG PET was highly variable in the patient sample (15 days – 4 years). Image evaluation was done visually and using VOI analysis to calculate the vermis to cerebellum ratio (V/C) in patients and controls. Results showed that in most patients there was visually increased $[^{18}F]$FDG uptake in the cerebellar vermis. V/C also showed a significant increase in the patients compared to controls. One of the limitations of this study is the high variability of the time elapsed between the acute phase and the $[^{18}F]$FDG PET study. Curiously, previous and later studies using SPM analysis have not detected increased $[^{18}F]$FDG uptake in the cerebellar vermis in TBI patients. Recently, Lupi and coworkers have reported a strong correlation between V/C ratio and the severity of TBI as determined by cognitive and performance tests, suggesting that the V/C ratio may be considered an index of brain suffering. They also found a good correlation between V/C ratio determined shortly after TBI and the clinical outcome.

A more recent study using $[^{18}F]$FDG PET and SPM evaluated differences at group and individual case level in chronic TBI patients ($n=81$) and controls ($n=68$). Group comparison analysis considered the entire patient group and also a division into two subgroups depending on whether ($n=35$) or not ($n=40$) they showed structural abnormalities by CT or MRI at onset. Structural images were not available in 6 cases. The authors also evaluated $[^{18}F]$FDG PET in each individual by cluster counting analysis to identify abnormal clusters, which deviate 2 or more standard deviations from the mean of the controls. Group comparison showed extensive bilateral hypometabolism in the cerebral cortex (including the frontal and temporal lobes) and the thalamus. The findings were also similar in the two subgroups examined. Cluster counting analysis showed that patients with TBI (with or without structural lesion) had a higher proportion of large clusters of hypometabolism, and they were closer to the brain edge when compared with controls. One of the most interesting findings was that the cortical–subcortical hypometabolism was similar in patients with or without structural lesion, suggesting that abnormal patterns of metabolism are similar in patients with focal or diffuse TBI.
Two other recent studies have confirmed and extended the previously described findings.91,92 Lull and coworkers using [18F]FDG PET studied the differences between controls (n=10) and chronic TBI patients divided into three groups: one with minimally conscious or persistent vegetative state (n=17), a second with post traumatic amnesia (n=12), and a third with patients emerging from post-traumatic amnesia (n=20). In the three groups there were patients with and without structural lesions by CT or MRI (the percentage of cases with lesions was similar for all three groups). Results demonstrated that hypometabolism in the thalamus was directly related to the neurological outcome and that this region was the most sensitive structure when patients in different neurological states were compared, despite the small percentage of patients with structural thalamic lesions in the three groups. A subsequent study by these authors aimed at investigating whether the integrity of connections between cortical regions and the thalamus was related to neurological outcome.92 The study groups were the same as used in the previous study. The authors found a significant correlation between neurological outcome and glucose metabolism in all brain regions analyzed (precuneus, frontal and temporal lobes and thalamus); there was also a direct relationship between hypometabolism and disease severity. Furthermore, they found a functional correlation between the four regions examined. Consequently, the authors suggested that damage to the thalamus-cortical connectivity, as a result of TBI, is directly related to the neurological outcome.

In summary, despite the fact that several of the studies described above were done in relatively small and heterogeneous patient samples and have used different methodological designs, most of them converge to identify a diffuse cortical-sub cortical hypometabolism pattern in the chronic TBI phase, with or without structural lesion, involving key regions for cognitive function. A recent study reviewed mechanisms that could explain this chronic hypometabolism.93 In addition to neuronal loss, altered ionic states, protein synthesis inhibition, CBF reduction and alteration of the neurotransmitter systems could be involved.

On the other hand, [18F]FDG PET seems to have also great potential for in vivo evaluation of therapeutic drugs, acting on the neurotransmitter systems in chronic TBI patients with cognitive deficit. Kraus and coworkers94 evaluated the effects of amantadine, a dopaminergic agent and N-methyl-D-aspartate (NMDA) receptor antagonist. The results showed significant improvement of the executive function in a group of patients after amantadine therapy (n=22). Analysis of [18F]FDG PET images also showed a significant increase in the metabolism of the left prefrontal cortex. This region correlated positively with the executive function in the patient group.
Two more recent studies evaluated the effects of donepezil, an acetylcholinesterase inhibitor, and memantine, a non-competitive NMDA receptor antagonist. The study using donepezil included two groups of patients with cognitive impairment after TBI (mean interval after injury of 5.2 months). The control group was treated only with rehabilitation (n=13), while the other group received rehabilitation plus donepezil medication (n=13). In the donepezil treated group [18F]FDG PET and neuropsychological tests studies were carried out at treatment onset and completion. In the control group only neuropsychological tests were performed. [18F]FDG PET images were analyzed by SPM. At the beginning of the study, no significant differences in cognitive function of both groups were observed. At the end, the group given donepezil showed a significant improvement in cognitive functions compared with controls and a significant bilateral increase of cortical metabolism in the frontal, parietal, occipital and temporal regions.

In the memantine study, TBI patients (n=17) were evaluated (mean post onset duration = 6.8 month). [18F]FDG PET was done at the beginning and after completion of the treatment. Furthermore, a covariance analysis was performed to assess if metabolic enhancement correlated with increases in Mini-Mental Status Examination (MMSE) scores. [18F]FDG PET image analysis was performed by SPM. Results showed that MMSE scores were significantly improved after memantine treatment. When [18F]FDG PET data acquired before and after treatment were compared, a significant increase of metabolism in the prefrontal region and the parietal association cortex was observed. A significant correlation was also found between MMSE and metabolism in the prefrontal regions and the association parietal cortex of the left hemisphere.

These studies suggest usefulness of [18F]FDG PET for evaluation of different therapeutic interventions in chronic TBI patients with cognitive deficits. However, these are preliminary findings and studies in larger patient samples using more refined methodological designs are required.

**Metabolism in mild traumatic brain injuries**

Only few studies have focused on mTBI, and most of them report similar diffuse cortical-to-subcortical abnormal patterns as those presented previously in moderate and severe trauma. This includes alterations in glucose metabolism in frontal, temporal and parietal lobes, prefrontal cortex and cingulate gyrus.

A recent study had examined the effects of repetitive head injuries on brain metabolism, in a group of boxers (n=19) compared with controls (n=7) subjects. Images were analyzed by SPM and VOI analyses, and both methods showed that boxers have bilateral hypometabolism in posterior cingulate
cortex, parieto-occipital cortex, frontal lobes, and cerebellum (Figure 3). While these results present a unique pattern of decreased metabolism, the authors suggest that this could be the result of a singular signature of brain injury in boxing. These results partially overlap with the findings of hypometabolism in cerebellum, vermis, pons, and medial temporal lobe after repeated blast exposure in Iraq war veterans ($n=12$), when compared with control volunteers ($n=12$).\textsuperscript{98} Besides, the reported hypometabolism in the parieto-occipital region interestingly matches with the finding often seen in whiplash injury.\textsuperscript{99,100}

**PET imaging of specific cellular process in TBI**

*Neuronal integrity*

In the last years, several papers of great interest using other PET radiotracers to study specific cellular processes in TBI pathophysiology have been published. An example of these is $[^{11}\text{C}]$flumazenil, a marker of central-type benzodiazepine receptor (BZR). $[^{11}\text{C}]$flumazenil binding, i.e. coupling of BZRs

![Figure 3. $[^{18}\text{F}]$FDG PET imaging of chronic traumatic brain injury in boxers. Statistical parametric mapping analysis showing the group differences between boxers and controls. Regions of decreased $[^{18}\text{F}]$FDG uptake displayed on a glass brain are seen in the posterior cingulate cortex and the cerebellum, parieto-occipito, and frontal lobes bilaterally (shaded areas)\textsuperscript{97}](image)
with GABA<sub>A</sub> receptors, can be used as a marker of neuronal viability. The first study using [¹⁵O] PET and [¹¹C]flumazenil PET investigated the relation between CMRO<sub>2</sub> abnormalities and loss of neuronal integrity in symptomatic patients with chronic TBI (n=10), without structural abnormalities detected by MRI, compared with a control group (n=10). Image evaluation was done using VOI analysis. While CMRO<sub>2</sub> abnormalities were observed in all patients, a reduced uptake in [¹¹C]flumazenil binding potential was only found in 6 patients and was accompanied by abnormalities in CMRO<sub>2</sub> images. In 15 lesions observed in CMRO<sub>2</sub> images no abnormalities were found in [¹1C]flumazenil binding potential images, suggesting that [¹¹C]flumazenil PET can be useful for differentiating hypometabolism caused by selective neuronal loss from hypometabolism caused by other factors.

A more recent study using [¹¹C]flumazenil aimed at identify regional neuronal damage occurring in chronic diffuse TBI patients with neuropsychological impairment (n=8), compared with control subjects (n=20). A significant bilateral reductions of [¹¹C]flumazenil uptake was shown in frontal medial gyrus, anterior cingulate gyrus, and thalamus. Case by case analysis also found reduced [¹¹C]flumazenil uptake in these regions, although the distribution and extent was different in each case. Furthermore, FIQ and performance IQ (PIQ) were negatively correlated with the degree of [¹¹C] flumazenil binding potential reduction in the right thalamus. Likewise, FIQ and verbal IQ and PIQ were negatively correlated with the degree of [¹¹C] flumazenil binding potential reduction in the left frontal medial gyrus.

We consider that even though these results are promising for detection of selective neuronal loss in patients with chronic diffuse TBI, they still require validation in larger patient samples and improvement of quantification methods. A recent tissue kinetic modeling study demonstrated the validity of the pons as a reference region for calculation of [¹¹C]flumazenil binding potential in apparently normal and perilesional regions in patients with chronic TBI.

Cholinergic system

Another specific cell process recently examined in chronic TBI was the activity of the cholinergic system. This preliminary study was carried out in a group of patients with chronic diffuse TBI with cognitive deficit (n=17) and a control group (n=12). The PET studies were performed with [¹¹C]MP4A ([methyl-¹¹C] N-methylpiperidyl-4-acetate), which reflects acetylcholinesterase (AChE) activity. Group comparisons by SPM showed a significant bilateral reduction of AChE in several areas of the neocortex in the TBI group, more pronounced in the parietal-occipital regions. ROI analysis also showed a significant reduction of AChE in all ROIs examined, except
in the medial temporal region, probably associated with the relatively small sample size. Since the study sample only represents a certain type of TBI, it would be interesting to study larger and more varied samples. Moreover, it would be interesting to study what percentage of TBI cases shows cholinergic dysfunction and whether this dysfunction correlates with clinical symptoms and outcome. This methodology could also be useful to clarify differences between patients with chronic TBI who respond to treatment with AChE inhibitors and those that do not respond.

Neuroinflammation

Microglial and astrocyte cells resident in the central nervous system begin to react in the acute TBI phase and may become chronically activated subsequently. One main role of activated microglia is to serve as the antigen presenting cells and to synthesize inflammatory mediators, which are crucial in the neuroinflammatory cascade after TBI. Microglia functions are very complex, since they have both neurotoxic and neuroprotective roles. Several researchers have suggested that the neuroinflammatory response may explain the great variability in long-term clinical course after TBI. Previous studies in TBI animal models have demonstrated that the inflammatory process may persist for at least a year, especially in the thalamus, and human post mortem studies have also found microglia activation many years after TBI.

The neuroinflammatory response is frequently studied in vivo with PET using the radioligand $[^{11}\text{C}]$PK11195 (1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide), which is a selective marker for activated microglia. $[^{11}\text{C}]$PK11195 binds to the 18 kDa translocator protein (TSPO), expressed in mitochondria of activated microglia, and has been used previously to study neuroinflammation in several other neurodegenerative diseases.

In a recent study on chronic TBI, patients with moderate or severe TBI ($n=8$) were compared with a control group ($n=7$). $[^{11}\text{C}]$PK11195 PET and MRI images were acquired 6 months after the trauma, and $[^{11}\text{C}]$PK11195 BP$_{\text{ND}}$ (non-displaceable binding potential) parametric images were generated, using a supervised cluster analysis to generate a reference tissue input. Group comparisons showed a significant increase of whole-brain $[^{11}\text{C}]$PK11195 BP$_{\text{ND}}$ in the TBI group, which was not related with structurally affected brain regions (MRI), present in apparently normal regions. On the other hand, there was no correlation between TBI severity (GCS) or neurological outcome (GOS) and whole-brain $[^{11}\text{C}]$PK11195 BP$_{\text{ND}}$. Brain regions showing significant increases of $[^{11}\text{C}]$PK11195 BP$_{\text{ND}}$ were the left and right frontal lobe, left and right thalamus, left parietal lobe, right temporal lobe, hippocampus...
and putamen, midbrain, and pons. An interesting finding was that $^{[11]}$C PK11195 $\text{BP}_{\text{ND}}$ was maximal in the thalamus in 6 out of 8 patients.

A different study investigated whether the inflammatory response persists in patients with chronic TBI, and if this response was related to structural abnormalities and cognitive dysfunction.\textsuperscript{110} This paper included a group of patients with moderate to severe chronic TBI ($n=10$). Five patients presented a focal damage visible in MRI images, while the other five did not show abnormalities. $^{[11]}$C PK11195 PET was performed on all patients at least 11 months after TBI, and like before, $^{[11]}$C PK11195 $\text{BP}_{\text{ND}}$ parametric images were generated using the supervised cluster analysis approach. Volumetric MRI and diffusion tensor imaging (DTI) were done to evaluate focal damage and disruption of WM; and cognitive function was also evaluated. Group comparisons showed that $^{[11]}$C PK11195 $\text{BP}_{\text{ND}}$ was increased in the thalamus, putamen, occipital cortices, and posterior limb of the internal capsules in the patient group compared with controls. Unlike the previous study, no increase in $^{[11]}$C PK11195 $\text{BP}_{\text{ND}}$ was found at the original site of focal brain injury, which is probably due to the different intervals which had elapsed after TBI in both studies. In the patient sample, a positive correlation was observed between $^{[11]}$C PK11195 $\text{BP}_{\text{ND}}$ in the thalamus and the degree of cognitive impairment. $^{[11]}$C PK11195 $\text{BP}_{\text{ND}}$ increase was not associated to structural damage found by volumetric MRI and DTI, or the time elapsed after TBI. Taking into account the long intervals after injury in the patient sample, this paper also suggests that therapeutic interventions can be beneficial even long time after TBI.

Although longitudinal studies are required in larger patient samples, the results of both studies indicate that $^{[11]}$C PK11195 PET could become an attractive method for detecting secondary damage after TBI, and could serve as guide for the evaluation of interventions directed towards manipulating the inflammatory cascade.

It is important to notice that, in recent years, there have been great efforts to develop other selective radioligands for neuroinflammation,\textsuperscript{113,114} in order to overcome the limitations of $^{[11]}$C PK11195.\textsuperscript{113,115} Among these limitations are the poor signal-to-noise ratio (mainly due to its low binding potential to TSPO and high level of non-specific binding), highly variable kinetic behavior, and the apparent lack of sensitivity to detect low levels of microglial activation.

**Dopaminergic system**

A couple of studies have examined the effect of multiple head injuries in the dopaminergic system. In the first study six patients (five boxers and one jockey), who were presumed to have post-traumatic parkinsonism, were investigated with $^{[18]}$F DOPA.\textsuperscript{116} Results were compared with a healthy group
(n=32), and a group of patients with idiopathic Parkinson’s disease without history of head trauma (n=18). In the post-traumatic group a 40% reduction of mean $[^{18}F]$DOPA uptake was found in caudate and putamen compared with controls. Their mean putamen uptake was significantly higher than in the Parkinson’s disease group; while mean caudate uptake was lower (Figure 4). The authors concluded that – although post-traumatic parkinsonism shares clinical features with idiopathic Parkinson’s disease – the uniform loss of nigrostriatal dopaminergic function in the post-traumatic subject suggests a different underlying pathology.

In a more recent publication, the dopaminergic function of three retired Thai boxers with parkinsonism was compared with another three patients with idiopathic Parkinson’s disease, having no history of significant head injury.\textsuperscript{117} In the post-traumatic parkinsonism patients a higher uptake in putamen was found compared with the Parkinson’s disease group. Furthermore, boxers had a significantly lower uptake in the ipsilateral anterior putamen and the contralateral posterior putamen than the Parkinson’s disease group (considering the side of predominant symptoms). However, no differences

\textbf{Figure 4.} Dopaminergic function in post-traumatic parkinsonism. Transaxial images of striatal $[^{18}F]$DOPA activity accumulated over the last 60 minutes of the study in a control subject, a patient with Parkinson’s disease, and a patient with post-traumatic parkinsonism. Note that putamen uptake is impaired in both patients while the post-traumatic parkinsonism patient also shows reduced uptake in caudate\textsuperscript{116}
were observed in the caudate nucleus of the two groups. These different findings compared with the previous study, where lower uptake was found in the boxers group compared to the Parkinson’s disease group, was explained by the shorter disease duration of the post-traumatic parkinsonism in the Thai boxers (range 1-3 years compared to 6 years in the previous study). While both studies support the idea that cumulative chronic head trauma in boxers is an additional insult to the dopaminergic system, more research needs to be done in this context.

**Single photon emission tomography (SPECT)**

### SPECT in TBI

Perfusion SPECT using $[^{99m}Tc]$HMPAO (hexamethyl-propyleneamine oxime) or $[^{99m}Tc]$ECD (ethylene cysteine dimer) has been extensively used in TBI. From the aforementioned SPECT perfusion tracers, $[^{99m}Tc]$ECD has been proven to distinguish more and especially smaller functional deficits in mTBI than $[^{99m}Tc]$HMPAO. Reviews of this neuroimaging modality have appeared regularly in the last years. These reviews coincide in pointing out that perfusion SPECT has high negative predictive value during the acute phase in mTBI. They also agree that perfusion SPECT, like $[^{18}F]$FDG PET, is more sensitive than CT for identifying abnormalities in TBI during the first hours, detecting them in very early stages, when CT or MRI scans may still be negative.

Furthermore, the use SPECT can be extended to other cell-specific processes related to TBI pathophysiology. Studies combining $[^{123}I]$$\beta$-CIT ($[^{123}I]$2-β-carbomethoxy-3-β-(4-iodophenyl) tropane) and $[^{123}I]$IBZM ($[^{123}I]$iodobenzamide) found nigrostriatal dysfunction in TBI patients, although the striatum was structurally relatively preserved, suggesting that these studies may be useful in the evaluation of therapies directed towards reducing parkinsonian symptoms in TBI patients. Another recent perfusion SPECT study investigated cognitive fatigue mechanisms in patients with mTBI, showing that there is frontocerebellar dissociation in patients with mTBI that may explain cognitive impairment and cognitive fatigue in the chronic phase.

Other radiopharmaceuticals have also been used in the study of concussion. CBF measures with $[^{123}I]$IMP ($[^{123}I]$N-isopropyl-p-iodoamphetamine), in conjunction with $[^{123}I]$IMZ ($[^{123}I]$iomazenil) to measure neuronal integrity by binding to BZRs, was used to study nine chronic mTBI patients. In all of these a significant increase in BZR uptake of the prefrontal cortex could be shown as compared with matched control subjects. In another study, $[^{57}C]$Cl$_2$ ($[^{57}C]$chloride) SPECT, which is suggested to target calcium in the brain, was
performed in 8 mTBI patients two days after the injury. In this study, $^{[57}]$Cl accumulation in frontal and temporal lobes, with additional accumulation in the posterior parietal occipital region, was shown in accordance with hypoperfusion measured by $^{[99mTc]}$HMPAO. By contrast, CT and EEG did not detect lesions in any of these cases. Moreover, a recent animal study used $^{[123I]}$CLINDE (N′,N′-diethyl-6-chloro-(4′-$^{[123I]}$iodophenyl)imidazo [1,2-a]pyridine-3-acetamide) for the in vivo monitoring of neuroinflammation by SPECT. This tracer was presented as alternative of $^{[11C]}$PK11195 PET tracer for the imaging of neuroinflammatory processes, and may be consider for future studies by SPECT.

Technological advances in SPECT detector systems, hybrid SPECT-CT, continuous development of new gamma-emitting radioligands and the application of modern methods of image analysis make the SPECT technique an alternative for the study of TBI, both for clinical practice and for research. Nevertheless, evidence-based imaging studies are required to demonstrate its incremental validity in TBI. The main advantage of SPECT is that it is much less costly (about US $800) and is widely available on a worldwide scale in comparison to PET.

**SPECT in sport-related head injuries**

Although SPECT on concussion in the acute stages of sport-related head injuries are not available to date, some studies have explored the chronic stages of repetitive concussions in boxing and American football. In a $^{[99mTc]}$HMPAO SPECT study, Kemp and colleagues have compared the CBF between active amateur boxers ($n=34$) and a control group of healthy athletes ($n=34$). They reported that 14 (41%) of the boxers had abnormal cerebral perfusion when compared with an “atlas of normality” (database of images obtained from healthy controls), while abnormalities were observed only in 5 (14%) of the controls. They also reported significant correlations between behavior deficits and abnormalities seen by SPECT. The same group of amateur boxers was reanalyzed, including other groups (undersea divers, schizophrenic patients and Alzheimer’s disease patients) for comparison. Boxers exhibited large regional CBF abnormalities (1.05% of cortical voxels) and presented at least one large lesion (>10 voxels, each with a side length of 0.64 cm) in eight of the nine regions of interest, including left and right frontal, parietal, and inferior temporal lobe, right inferior frontal lobe, and occipital region.

More recently, three studies by Amen and colleagues have investigated the chronic stages of repetitive concussion in retired American football players. In their first experiment 100 subjects were recruited from the National Football League (NFL), representing different teams and all positions, and compared
with healthy matched controls.\textsuperscript{131} The study, using $[^{99}\text{m}Tc]$HMPAO, revealed a global decrease in CBF, especially in prefrontal, temporal, and occipital lobes, anterior and posterior cingulate gyrus, hippocampus, and cerebellar region (Figure 5). The use of Z scores to analyze the results, instead of the generally used number of hypoperfusion regions, makes it difficult to compare the data with other SPECT studies.\textsuperscript{121} However, their findings seem to correspond with CBF changes found in other general studies about mTBI.

In a second study, 30 retired NFL players were examined before and after an intervention based on weight loss and multiple supplements, such as fish oil, vitamins, ginkgo biloba, acetylcholine and antioxidants.\textsuperscript{132} Initial SPECT scans were compared with the follow-up scans using a paired t-test. They found increased brain perfusion in the prefrontal cortex, parietal and occipital lobes, anterior cingulate gyrus, and cerebellum. Unfortunately, there was no control group and no randomization in the study, so it is rather difficult to answer the question of whether or not the results are due to the intervention.

Figure 5. Global brain $[^{99}\text{m}Tc]$HMPAO SPECT decrease in NFL players versus healthy subjects. Light areas indicate decreased perfusion in the NFL players versus healthy-brain comparison subjects at $p<0.0001$, family-wise error. No increases were seen\textsuperscript{131}
In the last study that uses the same data pool, the CBF of 38 overweight (waist-to-height ratio = 58.7±4.7) retired NFL players was compared with the same number of normal-weight players (49.34±2.8). The study revealed that overweight athletes present a decreased CBF in the dorsolateral prefrontal cortex, the anterior prefrontal cortex, and the left temporal pole. These brain regions are involved in attention, reasoning and executive function.

Conclusions

It is more than two decades since the first SPECT and PET studies on traumatic brain injury. However, not much is known about its pathophysiology. Research focused in mTBI, the most frequent diagnosis of TBI, and its long term consequences has been almost neglected during this time. For example, most of the guidelines for the assessment of concussion in sports are constructed based on the neuropsychological assessments without the support of any neuroimaging techniques, e.g. the 4th International Conference on Concussion in Sport 2012. Conventional structural imaging (CT or MRI) contributes little to the diffuse axonal injury frequently associated with TBI, and PET or SPECT techniques are still in the early stages to be recommended in a different setting than research. Nevertheless, nuclear imaging techniques with access to specialized ligands having the potential to bind to specific receptors involved in the pathophysiology of TBI lies ahead us for an exciting future.

Some conclusions can be drawn from the research conducted so far in TBI, and extrapolated to some extent to the most frequent mTBI. First, in the acute phase of the concussion there is a global decrease of brain perfusion, which is not related to the level of consciousness; while CMRglc in thalamus, brain steam and cerebellum do relate with consciousness measured with GCS. Therefore, the severity of a concussion and the related clinical decisions cannot be solely decided by the loss of consciousness, as this does not represent the severity of the injury. This is especially relevant in sports for the evaluation athletes, and if they must be removed or not from playing after head trauma. In the same context, the absence of structural abnormal findings in CT or MRI does not reflect the long term characteristics of the TBI, while \(^{18}\text{F}\)FDG PET seems to be more useful to explain neurological states. However, still remains to be demonstrated the cost-effectiveness validity of \(^{18}\text{F}\)FDG PET over other neuroimaging techniques or neuropsychological assessments. Moreover, the alterations found with functional imaging, which involve hypometabolism (\(^{18}\text{F}\)FDG), decrease of neuronal viability (\(^{11}\text{C}\) flumazenil), and increase of neuroinflammatory response (\(^{11}\text{C}\)PK11195) are mostly located in midbrain and thalamus. These structures are known to be especially susceptible of damage due to the biomechanical characteristics of
the concussion. Additionally, other brain areas like prefrontal and cingulate cortices were shown to be damaged or have an abnormal function in different studies. All of these areas are part of a common emotional network, and its dysfunction can be related to some of the cognitive impairments shown by these patients.

As mentioned previously, a great advantage of nuclear imaging techniques is the possibility to develop specific radioligands capable to address specific characteristics of a metabolic process. Therefore, there is a bright future of PET and SPECT in TBI, helping to better understand the cascade of reactions taking place after the injury.
References


