Traumatic Brain Injury

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Traumatic Brain Injury: Nuclear Medicine Neuroimaging

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Abstract

This chapter provides an up-to-date review of nuclear medicine neuroimaging in traumatic brain injury (TBI). Although the role of FDG PET may be limited in the acute phase due to the more rapid availability of CT or MRI, ^{18}F-FDG PET could remain a valuable tool in researching complex mechanisms associated with early metabolic dysfunction in TBI, particularly in the absence of structurally apparent brain damage. $^{15}O_2$-PET is also a solid technique for research in acute TBI, but in contrast to ^{18}F-FDG PET, it is not widely available due to its high cost. In the chronic TBI phase, most ^{18}F-FDG PET studies converge to identify a diffuse cortical–subcortical hypometabolism involving key regions for cognitive function. In these cases, FDG PET may also be used for the evaluation of therapeutic interventions. More recently, research has focused on the imaging of specific pathological processes, such as neuroinflammation and accumulation of tau, as well as on distinct entities as chronic traumatic encephalopathy and the post-concussion syndrome. In this light, the in vivo demonstration of tau deposits in athletes exposed to repetitive head injury has gained special interest. These techniques may provide useful information, especially in situations where structural damage typically fails to show a pathologic substrate. Despite a paucity of recent research publications, SPECT may still be regarded a valid alternative for the study of TBI.

Abbreviations

AChE	Acetylcholinesterase
BP	Binding potential
BP_{ND}	Non-displaceable binding potential
BZR	Central-type benzodiazepine receptor
C-(R)-PK11195	1-[2-Chlorophenyl]-*N*-methyl-*N*-[1-methylpropyl]-3-isoquinoline carboxamide
CBF	Cerebral blood flow
C-MP4A	[Methyl-^{11}C]*N*-methylpiperidyl-4-acetate
CMRFDG	Cerebral metabolic rate of FDG
CMRglc	Cerebral metabolic rate of glucose
$CMRO_2$	Cerebral metabolic rate of oxygen
C-NMSP	^{11}C-*N*-methylspiperone
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
D_2	Dopamine receptor type 2
DAI	Diffuse axonal injury

DTI	Diffusion tensor imaging
FIQ	Full-scale intelligence quotient
FMZ	Flumazenil
GCS	Glasgow Coma Scale
GM	Gray matter
GOS	Glasgow Outcome Scale
L/N ratio	Lesion-to-normal contralateral ratio
MRI	Magnetic resonance imaging
NSC	Neural stem cell
OEF	Oxygen extraction fraction
OGR	Oxygen-to-glucose metabolic ratio
ROI	Regions of interest
SPM	Statistical parametric mapping
TBI	Traumatic brain injury
TSPO	Translocator protein
V/C ratio	Vermis-to-cerebellum ratio
WM	White matter

43.1 Introduction

Traumatic brain injury (TBI) is described as a traumatically induced disruption of the brain, in the presence of one of the following symptoms: loss of consciousness, anterograde or retrograde memory loss, alterations of the mental state at the time of the incident, or focal neurological deficits. The worldwide prevalence of TBI demands global attention and effective actions involving all levels of society. The annual incidence of TBI has been estimated to be up to 500 per 100,000 inhabitants in the European Union and the United States, causing 200 out of every 100,000 hospital admissions (Faul et al. 2010; Stryke et al. 2007; Tagliaferri et al. 2006). Worldwide incidence is growing mainly due to traffic accidents, with a higher increase in developing countries (WHO/OMS 2009). Not less important is the rise of the social and economic TBI burden because of military conflicts and civilian exposure in war zones. TBI as a consequence of sports practice and recreational activities should not be underestimated either. TBI has devastating effects on patients and their families due to death or chronic disabilities, with high socioeconomic cost throughout the world. Therefore, a widespread international effort is necessary to reduce TBI causes as much as possible and at the same time to increase knowledge on this complex disease that will allow mitigating or reverting short- and long-term outcomes.

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 (Zasler et al. 2007), which could be aggravated by systemic events, patient age, or preexisting chronic disease. In many cases, TBI may secondarily lead to epilepsy

(Frey 2003), and after aging, it is the most important nongenetic factor that increases the risk of dementia (McKee et al. 2009), including chronic traumatic encephalopathy.

Immediate clinical TBI consequences are directly related to the severity, mechanism, location, and duration of the impact (Maas et al. 2008). Conventional computed tomography (CT) is the technique of choice for the initial evaluation of TBI patients because it enables detection of fractures and helps to decide whether the patient requires an immediate surgical intervention, when focal injury with hematomas is suspected (Kubal 2012). When results on CT are unclear or negative, MRI may be performed to demonstrate occult traumatically induced injury, such as microhemorrhages (Haller et al. 2018). After the initial examination, secondary damage—indirect consequences of trauma—may contribute significantly to short- and long-term impairment, which is especially due to cell and inflammatory damage (Park et al. 2008). Secondary damage is a key concept, since it opens doors to treatment methods for preventing and limiting secondary injury. Neuroimaging using nuclear medicine techniques also has great potential for studying secondary damage and may serve as a guide to evaluate several therapeutic approaches.

In this chapter, a review of several relevant contributions of nuclear medicine neuroimaging toward improved understanding of TBI is presented, using both positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Various articles published in the last years, which summarize current knowledge on the roles of PET and SPECT, could be considered starting points for new research and clinical applications. The molecular basis of both techniques, especially PET, provides unique possibilities for studying complex cellular processes that take place in TBI, which are not yet fully understood.

43.2 PET

Despite the large number of studies using PET in TBI, in which the usefulness of this technique was shown in several clinical settings, there is no meta-analysis clarifying the importance of this technique either by itself or by complementary to structural neuroimaging. This is mostly due to the clinical heterogeneity and complexity of TBI, reflected in the diversity of studies published with regard to several aspects: first, differences in the time elapsed between the moment of injury and image acquisition; second, differences in patient characteristics with respect to TBI severity; third, differences in PET radiotracers; fourth, differences in methodological designs; and fifth, the use of different image analysis methodologies. In addition, no prospective randomized, blinded clinical trials have been conducted for obtaining major evidence, which can partly be explained by the high cost of such studies that require several years of follow-up. It is not surprising that such studies are scarce in medical imaging, including conventional CT and MRI (Medina et al. 2011).

43.2.1 ^{18}F-FDG PET in the Acute Phase of Brain Trauma

The first ^{18}F-FDG PET studies in TBI patients appeared in the 1980s and 1990s (Rao et al. 1984; Langfitt et al. 1986; Alavi 1989; Alavi et al. 1997; Tenjin et al. 1990; Yamaki et al. 1996; Fontaine et al. 1999). They pointed out that abnormalities detected by ^{18}F-FDG PET 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. In those years, PET was still restricted to very few centers in the world. This situation began to change after the beginning of the present century. One of the predominant issues from the 1990s to date has been the study of brain metabolism in the acute phase of TBI. Findings of Bergsneider et al. (1997, 2000, 2001) suggested the existence of a triphasic pattern in the cerebral metabolic rate of glucose (CMRglc) measured by ^{18}F-FDG PET. This pattern had been previously observed in animal models. The first and brief hyperacute phase is characterized by an increase of metabolic activity and followed by a second, relatively prolonged, period of reduced metabolism (for a month approximately), until a stable level within normal limits is achieved again. However, later studies have found that regional diffuse deficits may persist chronically (this will be discussed in Sect. 43.2). These studies also suggested that during the intermediate phase, there was disassociation between the global CMRglc and the level of consciousness measured by the Glasgow Coma Scale (GCS) (Bergsneider et al. 2000). The paper published by this group in 2001 is particularly interesting (Bergsneider et al. 2001). Fifty-four patients in acute phase (2–39 days post onset), with the three degrees of severity defined by the GCS (34 severe and 20 moderate or mild), were studied. ^{18}F-FDG PET scan was repeated in 13 patients during trauma evolution (6–15 months after the onset of injury). In the whole sample, the authors found the previously mentioned triphasic pattern, independent of the degree of TBI severity, suggesting that the degree of TBI severity does not affect the time course of CMRglc changes. In a follow-up study on 13 patients with ^{18}F-FDG PET, no relationship was found between CMRglc changes and neurological state changes measured by the disability rating scale. The authors concluded that ^{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 et al. (2003) 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 CMRglc, there was a direct association between level of consciousness measured by GCS and CMRglc 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 ^{18}F-FDG PET are related.

Three articles published by the UCLA group in 2004 made the role of ^{18}F-FDG PET in the acute phase of TBI even clearer (Hattori et al. 2004; Wu et al. 2004a, b). The first of these papers was a thorough characterization of brain tissue ^{18}F-FDG kinetics during the acute phase (Hattori et al. 2004). In this study, the authors characterized ^{18}F-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 $H_2{}^{15}O$-PET. 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}F-FDG uptake in pericontusional areas, probably associated with residual regional increase of hexokinase activity during the hyperacute 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 (Wu et al. 2004a) concerning the fact that gray matter (GM) to white matter (WM) contrast in ^{18}F-FDG PET images is reduced in patients with acute TBI, with or without focal damage, compared to normal healthy controls. Interestingly, this reduction was not observed in $H_2{}^{15}O$-PET 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}F-FDG PET, triple dynamic ^{15}O-PET ($C^{15}O$, $O^{15}O$, $H_2{}^{15}O$), and MRI were carried out. Initial GCS at onset and the Glasgow Outcome Scale (GOS) 12 months post onset were also evaluated. 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}F-FDG PET images was significantly reduced in the TBI group. Although a global reduction of CMRglc was observed in the patients, as expected from the previous study (Hattori et al. 2004), CMRglc 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 CMRglc in WM (or that it was increased with respect to the global CMRglc). 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 with DAI.

The third article of the UCLA group (Wu et al. 2004b) 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 and using the same image

acquisitions (PET and MRI). Five types of quantitative images were generated: CMRglc, CBF, cerebral metabolic rate of oxygen ($CMRO_2$), oxygen extraction fraction (OEF), and oxygen-to-glucose metabolic ratio (OGR). The results corroborated that CMRglc was reduced only in GM. CBF and OEF were preserved, while $CMRO_2$ was reduced in both 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 $CMRO_2$ depression, without parallel depression of CMRglc, suggesting a nonoxidative 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 multimodal 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 results published by the UCLA group between 2003 and 2004 (Hattori et al. 2003, 2004; Wu et al. 2004a, b), the state of coma was shown to involve a thalamocortical disconnection with a clearly defined metabolic substrate, and a prognostic value of ^{18}F-FDG PET was suggested (Wu et al. 2004a).

Complexity of metabolic dysfunction during the acute phase continues to be the object of current research and debate. Findings from the Cambridge University group, combining microdialysis and ^{18}F-FDG PET studies, did not support the hypothesis of nonoxidative metabolism associated with an increase in glucose cerebral metabolism in the acute phase (Hutchinson et al. 2009; O'Connell et al. 2005).

On the other hand, another study indicated that early dysfunction of nonischemic oxidative metabolism in the acute phase leads to chronic brain atrophy in TBI patients (Xu et al. 2010). This study showed that both cortical CMRglc and $CMRO_2$ 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 $CMRO_2$ and CBF, particularly in the frontal and temporal lobes ($N = 32$). CMRglc 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.

Another work carried out a longitudinal study in vivo that identified and traced the spatial and temporal metabolic and structural changes in an experimental TBI model in rats (Liu et al. 2010). Images were acquired 1 week and 1, 3, and 6 months post TBI by micro^{18}F-FDG PET and microMRI in 16 rats with lateral fluid percussion injury and 11 control rats (sham procedure). Using several methods of image analysis, including statistical parametric mapping (SPM), the authors found that regions with hypometabolism at 1 week and 1 month after TBI were essentially the same that subsequently showed progressive atrophy by microMRI. Hypometabolism was highest at 1 month but persisted in the study at 6 months in the ipsilateral amygdala. Disagreement was also found between structural and metabolic changes. Hypometabolism decreased or resolved at 6 months and preceded atrophy. Atrophy continued progressing for up to 6 months. Hippocampi changed shape with

reduction in volume, and both sides showed different patterns of change. The most interesting observation in this study was that both structural and functional changes seemed to consolidate between 3 and 6 months, suggesting that the temporal window to intervene and limit secondary neurodegenerative damage (atrophy) may be wider than expected.

In our view, ^{18}F-FDG PET will remain a valuable tool in researching complex mechanisms associated with early metabolic dysfunction in TBI, presently not well understood. Future research may benefit from more stringent inclusion of patients based on the timing and the type of trauma. From a clinical point of view, although appropriate clinical trials are still needed to provide more evidence, ^{18}F-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) failed to show damage explaining their neurological state. Of note, as has been addressed in a critical review in 2014, CMRglc values may be less reproducible in patients with traumatic brain injury, as the lumped constant—CMRFDG divided by CMRglc—could be altered after traumatic brain injury (Byrnes et al. 2014). With the growing number of hybrid PET–CT and PET/MRI systems and ^{18}F-FDG availability, combined studies of both structural and functional damage are now more feasible. This could facilitate acquisition of multicenter databases to carry out evidence-based imaging studies that enable demonstration of incremental validity of ^{18}F-FDG PET. Cost-effectiveness analysis is also necessary to compare ^{18}F-FDG PET with MRI-based techniques, such as diffusion tensor imaging (DTI), magnetization transfer imaging, magnetic resonance spectroscopy, and functional magnetic resonance (Hunter et al. 2012).

43.2.1.1 $^{15}O_2$-PET

TBI consequences are not only determined by primary injury but also by subsequent neuronal death due to secondary damage, which already starts during the acute phase. For this reason, the main strategy in TBI patient management, especially those in critical neurological state, is to prevent or limit secondary damage as much as possible (Park et al. 2008). Secondary damage can be initiated or aggravated by hypoperfusion, arterial hypotension, hypoxemia, autoregulation failure, as well as metabolic, immunologic, and biochemical changes. Although delayed ischemia is one of the routes of secondary damage, reperfusion can also take place, elevating intracranial pressure, reducing perfusion pressure, and finally reducing CBF again.

Triple dynamic $^{15}O_2$-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 articles have been published about triple $^{15}O_2$-PET studies that have allowed a deepened understanding of regional

ischemia mechanisms in acute TBI. Some studies have demonstrated significant regional ischemia in the first hours after TBI (Coles et al. 2004a; Coles and Fryer 2004; Abate et al. 2008), while in other studies, ischemia has been less evident (Wu et al. 2004b; Vespa et al. 2005; Kawai et al. 2008; Xu et al. 2010). This apparent contradiction could be due to the heterogeneity and complexity of TBI. Another explanation for these contradictory results has been provided by triple $^{15}O_2$-PET studies (Cunningham et al. 2005). The authors found that unlike classical acute ischemia (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 MR images that better identify regions with pan-necrosis. Studies using ^{11}C-flumazenil (FMZ) seem to corroborate this idea. ^{11}C-FMZ PET studies in TBI patients are examined in the next subsection of this chapter.

Other $^{15}O_2$-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 (Menon et al. 2004; Vespa et al. 2005; Robertson 2004). Other studies have proven useful to evaluate the impact of therapeutic interventions in critical state patients (Coles et al. 2004b, 2006; Johnston et al. 2005; Diringer et al. 2007, 2011; Nortje et al. 2008) and in animal models of TBI (Ley et al. 2009; Ley and Park 2010). $^{15}O_2$-PET studies also validated and refined bedside monitoring technologies, which facilitate continuous monitoring of cerebrovascular physiology (Hutchinson et al. 2002; Gupta et al. 2002; Coles et al. 2004b). Bedside monitoring has the advantage of continuous temporal monitoring of CBF, autoregulation, and metabolic state of the patient (Dagal and Lam 2011). The main difficulty is that it can only monitor a small area of the brain, unlike $^{15}O_2$-PET which allows studying the whole brain in a more quantitative way. The main disadvantages of $^{15}O_2$-PET are that continuous monitoring is not possible and the patient must be moved from the intensive care unit to the scanner and the high cost of the cyclotron. In our opinion, $^{15}O_2$-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. Also it presents a more logistical challenge, when compared to perfusion CT or MRI. Therefore, it is used mainly in research and less in clinical practice.

43.2.2 ^{18}F-FDG PET in the Chronic Phase of Brain Trauma

In the last years, there have been important advances in the care of neurocritical patients after TBI, resulting in a significant decrease of mortality (Bullock et al. 2007). However, TBI survivors frequently suffer from a wide variety of chronic cognitive, emotional, and behavioral disorders that hinder return to normal social and work life. Persistent vegetative state is the worst final outcome.

Neural networks connecting brain cortical and subcortical regions are crucial to maintain normal cognitive function (Bassett and Bullmore 2009). 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 of the UCLA group in acute TBI using ^{18}F-FDG PET already suggested a thalamocortical disconnection as the cause of coma (Hattori et al. 2004; Wu et al. 2004a, b). Cortical–subcortical disconnection may persist to a larger or lesser extent in many patients in the chronic phase after TBI. ^{18}F-FDG PET studies in chronic TBI patients have allowed characterization and unveiling of many aspects of this cortical–subcortical disconnection. The use of voxel-based image analysis methods, especially SPM (Friston 1994), is common in several of these studies. Unlike the methods based on regions of interest (ROI), SPM enables 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 ROI analysis. Table 43.1 summarizes the findings of FDG PET in the chronic phase of traumatic brain injury. Taken together, studies point toward the presence of corticothalamic deficits which carry an association with the neurological outcome, even without structural abnormalities. In addition to neuronal loss, altered ionic states, protein synthesis inhibition, CBF reduction, and alterations of the neurotransmitter systems could be involved to explain these findings (Marklund et al. 2009). Preliminary studies indicated that abnormalities at baseline may be monitored using FDG PET to evaluate the effectivity of treatment regimens. Kraus et al. (2005) evaluated the effects of amantadine. Amantadine is 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 ^{18}F-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 noncompetitive NMDA receptor antagonist (Kim et al. 2009, 2010). The study using donepezil (Kim et al. 2009) included two groups of patients with cognitive impairment after TBI (mean interval after injury = 5.2 months). The control group was treated only with rehabilitation ($N = 13$). The other group received rehabilitation plus donepezil medication ($N = 13$). In the donepezil-treated group, ^{18}F-FDG PET and neuropsychological test studies were carried out at treatment onset and completion. In the control group, only neuropsychological tests were performed. ^{18}F-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.

Table 43.1 FDG PET in chronic phase of traumatic brain injury

Authors	Subjects	Design/methods	Main results	Specifications
Nakayama et al. (2006)	Chronic TBI patients (higher dysfunction) ($N = 22$), minimally conscious state ($N = 13$), persistent vegetative state ($N = 17$), controls ($N = 30$)	Cross-sectional, SPM analysis	Bilateral hypometabolism pattern involving prefrontal medial region, medial frontobasal region, anterior and posterior regions of the cingulate gyrus, and thalamus	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
Kato et al. (2007)	Patients with clinical DAI ($N = 32$), controls ($N = 30$)	Cross-sectional, SPM, correlation analysis between regional metabolism and neuropsychological variables in the patient group	Full-scale intelligence quotient (FIQ) was found to correlate positively with metabolism in the right cingulate gyrus and the bilateral medial frontal region	
Nakashima et al. (2007)	DAI patients with neurological deficits ($N = 12$) and controls ($N = 32$)	Cross-sectional, SPM, case-by-case analysis using 3D stereotactic surface projection (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 (six patients)	
Lupi et al. (2007)	Chronic TBI ($N = 57$) and controls ($N = 57$)	Cross-sectional, visual and ROI analysis	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	The time elapsed between the acute phase and the ^{18}F-FDG PET was highly variable in the patient sample (15 days–4 years)
Lupi et al. (2011)			Strong correlation between V/C ratio and the severity of TBI as determined by cognitive and performance testings. Good correlation between V/C ratio determined shortly after TBI and the clinical outcome	Findings suggest that V/C ratio may be considered an index of brain suffering

(continued)

Table 43.1 (continued)

Authors	Subjects	Design/methods	Main results	Specifications
Zhang et al. (2010)	Chronic TBI patients ($N = 81$) and controls ($N = 68$), subgroups with ($N = 35$) and without ($N = 40$) structural abnormalities	Cross-sectional, SPM analysis.	Group comparison showed extensive bilateral hypometabolism in the cerebral cortex (including the frontal and temporal lobes) and the thalamus. 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
Lull et al. (2010)	Controls ($N = 10$), a group with minimally conscious or persistent vegetative state ($N = 17$), a group with posttraumatic amnesia ($N = 12$), and a group with patients emerging from posttraumatic amnesia ($N = 20$)	Cross-sectional, SPM	Hypometabolism in the thalamus was directly related to the neurological outcome	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
Garcia-Panach et al. (2011)	Same groups as Lull et al.	Cross-sectional, SPM	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	
Ito et al. (2016)	Patients with chronic mild/moderate traumatic brain injury ($N = 90$), with ($N = 50$) and without ($N = 40$) visible lesions on MRI	Cross-sectional, SPM	Significant decrease of metabolisms in the orbital gyrus, cingulate gyrus, and medial thalamus but increased in the parietal and occipital convexity in subjects with MRI abnormalities, but not in those without	

In the memantine study (Kim et al. 2010), a group of 17 TBI patients were evaluated (mean post-onset duration = 6.8 months). ^{18}F-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. ^{18}F-FDG PET image analysis was performed by SPM. Results showed that MMSE scores were significantly improved after memantine treatment. When ^{18}F-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.

Distinct mechanisms may be at play in two entities we will briefly address in the next two subsections: chronic traumatic encephalopathy and the post-concussion syndrome.

43.2.2.1 Chronic Traumatic Encephalopathy

Chronic traumatic encephalopathy is a neurodegenerative disease resulting from repetitive head injury, which involves the development of long-term neuropsychiatric sequelae. Since the neuropathological studies of Omalu et al. in American football players (Omalu et al., 2010)—which became the subject of the popular movie "Concussion"—the impact of repetitive head injury in sports and associated chronic traumatic encephalopathy has gained attention, both in research and in society. Symptoms vary according to the stage but may be related to behavior, mood, or cognition. Neuropathologically, it is characterized by deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles, astrocytic tangles, and neurites in clusters around small blood vessels of the cortex, preferentially located around small vessels in the depths of sulci (McKee et al. 2016). In recent years, tau PET ligands have become available allowing in vivo identification of tauopathies. Stern and colleagues demonstrated increased Standardized Uptake Value Ratios (SUVRs) using flortaucipir PET in the former American Football League players, a population particularly prone to CTE, primarily in the bilateral superior frontal, bilateral medial temporal, and left parietal regions (Stern et al. 2019). Takahata et al. using another tau ligand, ^{11}C-PBB3, determined the "binding capacity" in patients with a history of severe TBI of repetitive head injury ($n = 30$) and controls ($n = 16$). Binding capacity was significantly increased in widespread brain regions in patients, whereas clinical symptoms (diagnosis of traumatic encephalopathy syndrome) in the patient group were related to increased binding capacity in the white matter (Takahata et al. 2019). This group also demonstrated PBB3 binding to neurofibrillary tangles in cortical gray matter by means of PBB3 fluorescence labelling and immunofluorescence of autopsied TBI brains, albeit not in the same group of patients. These results seem to confirm the potential of PET to detect tauopathy in vivo in chronic TBI patients, although it is generally noted that the tau load is significantly less when compared to Alzheimer's disease. In the context of cognitive decline after repetitive head injury, additional amyloid positivity may be demonstrated using ^{11}C-PIB scanning (Okonkwo et al. 2019).

43.2.2.2 Post-concussion Syndrome

The "post-concussion syndrome" is a complex disorder in which symptoms—such as headaches and dizziness—may persist for weeks of months after a mild traumatic brain injury. These symptoms are often present in the absence of structural brain damage, which has also been described as "complicated" mild traumatic brain injury (Lange et al. 2009). Komura and colleagues studied 89 patients who suffered a single blunt mild traumatic brain injury without structural abnormalities and persistent mental and cognitive problems (Komura et al. 2019). Reduced metabolism was reported in the bilateral prefrontal area and significantly increased around the limbic system in the patient group compared with normal controls, which is different from patterns typically implicated in DAI. Mild chronic TBI due to cerebral concussion caused by repeated blast exposure in war zones has also been evaluated using ^{18}F-FDG PET (Peskind et al. 2011). The study included a group of Iraq war veterans ($N = 12$) and a control group ($N = 12$). The patient group showed hypometabolism in the cerebellum, vermis, pons, and medial region of the temporal lobe. The patients had mild cognitive dysfunction similar to that reported for patients with cerebellar lesions.

43.2.3 PET Imaging of Specific Cellular Process in Brain Trauma

Since the mid-2000s, 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}C-flumazenil (FMZ), which is a marker of central-type benzodiazepine receptor (BZR). FMZ binding, i.e., coupling of BZRs with GABA-A receptors, can be used as a marker of neuronal viability. The first study using $^{15}O_2$-PET and ^{11}C-FMZ PET (the binding potential of FMZ) investigated the relation between $CMRO_2$ abnormalities and loss of neuronal integrity in symptomatic patients with chronic TBI ($N = 10$), without structural abnormalities detected by MRI (Shiga et al. 2006). The study included a control group ($N = 10$). Image evaluation was done using ROI analysis. $CMRO_2$ abnormalities were observed in all patients, while reduced uptake in ^{11}C-FMZ BP images was only found in six patients. Reduced uptake in ^{11}C-FMZ BP images was accompanied by abnormalities in $CMRO_2$ images. In 15 lesions observed in $CMRO_2$ images, no abnormalities were found in ^{11}C-FMZ BP images, suggesting that ^{11}C-FMZ PET can be useful for differentiating hypometabolism caused by selective neuronal loss from hypometabolism caused by other factors. A more recent study using ^{11}C-FMZ PET aimed at identifying regional neuronal damage occurring in chronic diffuse TBI patients with neuropsychological impairment ($N = 8$) (Kawai et al. 2010). The study included a control group ($N = 20$). 3D SSP group comparisons showed significant bilateral reductions of ^{11}C-FMZ uptake in the frontal medial gyrus, anterior cingulate gyrus, and thalamus. Case-by-case analysis also found reduced ^{11}C-FMZ uptake in these regions, although the distribution and extent were different in each case. Furthermore, FIQ and performance IQ were negatively correlated with the degree of ^{11}C-FMZ BP

reduction in the right thalamus. Likewise, FIQ, verbal IQ, and performance IQ were negatively correlated with the degree of ^{11}C-FMZ BP 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 study was aimed at validating reference tissue kinetic modeling of ^{11}C-FMZ PET within a group of patients with TBI (Geeraerts et al. 2011). ^{11}C-FMZ PET imaging were performed on controls (N = 16) and patients (N = 11) at least 6 months after TBI. Regional non-displaceable binding potentials (BP_{ND}) were estimated from five reference tissue models and compared to BP_{ND} from arterial input models. Total distribution volume of the pons was not significantly different between controls and patients. BP_{ND} from all the reference tissue approaches significantly correlated with BP_{ND} from the plasma input models for control and patient groups. Thus this study demonstrated the validity of the pons as a reference region for calculating ^{11}C-FMZ BP in apparently normal and perilesional regions in patients with chronic TBI.

More recently, adenosine receptor imaging has been used in an effort to identify neuronal and axonal injury in patients in the chronic phase of DAI. Hayashi and colleagues used A_1 receptor (A1R) [1-methyl-^{11}C] 8-dicyclopropylmethyl-1-methyl-3-propylxanthine (MPDX) PET in ten patients in the chronic phase of DAI and reported increased BPs in the lower frontal lobe, posterior cingulate cortex, and rolandic cortex, without any apparent decreases in BP (Hayashi et al. 2018). These areas did not correlate with regions of decreased ^{11}C-FMZ binding in the same patients, suggesting that the observed alterations using MPDX PET reflect neuroprotective effects rather than neuronal loss.

Another specific cell process recently examined in chronic TBI is the activity of the cholinergic system (Östberg et al. 2011). 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). PET studies were performed with [methyl-^{11}C]*N*-methylpiperidyl-4-acetate (^{11}C-MP4A). ^{11}C-MP4A 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 size of the sample. Since the study sample only represents a certain type of TBI, we agree with the authors that it would be interesting to study larger and more varied samples. Moreover, it would be interesting to study what percentage of cases with TBI 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.

The outcome of ^{11}C-NMSP/^{18}F-FDG microPET studies aimed at evaluating the effects of neural stem cell (NSC) transplantation in a TBI model in rats was recently published (Zhang et al. 2008). ^{11}C-NMSP (^{11}C-*N*-methylspiperone) is a radioligand for the dopamine receptor subtype 2 (D_2). The combination of microPET and a

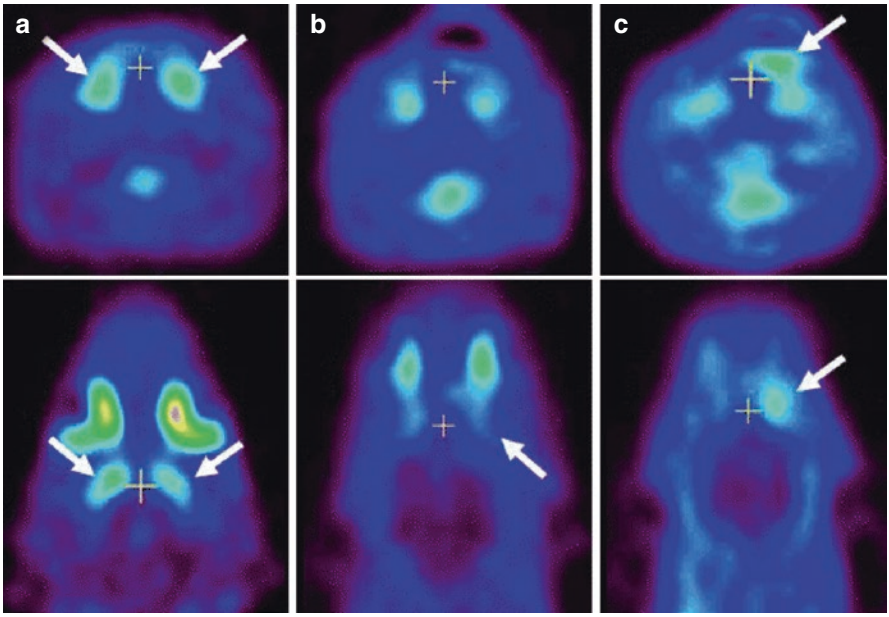

Fig. 43.1 Typical examples of ^{11}C-NMSP microPET imaging in various conditions. Coronal and axial sections of rat brain are shown. White cross markers in the coronal and axial sections indicate the same position in a scan. (**a**) Typical image of ^{11}C-NMSP microPET in normal rat brain showing high ^{11}C-NMSP accumulation in the striatum. (**b**) L/N ratio of ^{11}C-NMSP decreased after traumatic brain injury. (**c**) High accumulation of ^{11}C-NMSP indicated the existence of transplanted DRD2-positive NSCs. (From Zhang et al. (2008); with permission)

reporter gene system to track transplanted stem cells in animal experiments has allowed researchers to trace reporter gene carrying cells in vivo. The study was performed in a group of 18 rats with focal TBI in the right parietal lobe, later randomly assigned to a group that received a transplant ($N = 10$) and a control group ($N = 8$). In the former group, NSCs were transplanted in the brain lesion. ^{11}C-NMSP and ^{18}F-FDG microPET images were used to monitor changes in D_2 expression and glucose metabolism in the brain lesion before and after transplantation. Behavioral neurological function was also evaluated. Histological analysis identified viable NSCs at the transplantation site. The lesion-to-normal contralateral ratio (L/N ratio) of ^{11}C-NMSP in the brain lesion decreased from 97 to 68% after TBI, increasing to 137% 1 day after transplantation (Fig. 43.1) and later decreasing gradually. On the other hand, L/N ratio of glucose metabolism decreased to 35% in the brain lesion and then increased to 87% 2 weeks after transplantation (Fig. 43.2). The behavioral neurological function significantly improved in the transplanted group compared to the control group. Thus, this study demonstrates the feasibility of using microPET and a reporter gene system to evaluate NSC-induced D_2 expression in rat models, which could prove useful in future clinical trials of NSC transplantation therapy in TBI patients.

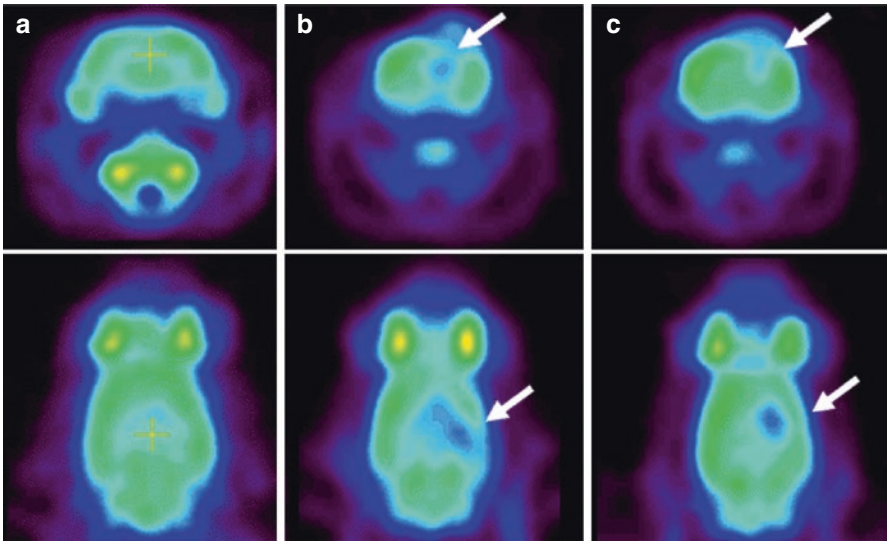

Fig. 43.2 Typical examples of ^{18}F-FDG microPET imaging in various conditions. Coronal and axial sections of rat brain are shown. (**a**) Typical image of ^{18}F-FDG microPET in normal rat brain. (**b**) As shown with *arrows*, the focal traumatic lesion appeared as a hypometabolic area in the right parietal cortex. (**c**) The regional glucose metabolism of the focal traumatic lesion recovered 14 days after NSC transplantation. (From Zhang et al. (2008); with permission)

43.2.3.1 PET Imaging of Neuroinflammation

Cellular processes that have received much attention lately are those involved in TBI neuroinflammation. Microglial, astrocyte, and neuron cells resident in the central nervous system begin to react in the acute TBI phase and eventually may be chronically activated. The role of activated microglia is to serve as the most important antigen-presenting cells and to synthesize inflammatory mediators and complement, which are crucial in the neuroinflammatory cascade after TBI. Microglia functions are very complex, since they have both neurotoxic and neuroprotective roles. In the acute phase, it may be involved in the restauration of the homeostasis in the brain. It has been hypothesized that chronic neuroinflammation may drive neurodegeneration after (repetitive) traumatic brain injury, which could be related to the release of pro-inflammatory cytokines, reactive oxygen species, nitrogen species, and excitatory neurotransmitters (Donat et al. 2017). Previous studies in TBI animal models have demonstrated that the inflammatory process may persist for at least a year, especially in the thalamus (Nagamoto-Combs et al. 2007, 2010). Human postmortem studies have also found microglial activation many years after TBI (Gentleman et al. 2004).

The neuroinflammatory response can be studied in vivo with PET using the radioligand ^{11}C-(R)-PK11195 (1-[2-chlorophenyl]-*N*-methyl-*N*-[1-methylpropyl]-3-isoquinoline carboxamide), which is a selective marker for activated microglia.

(R)-PK11195 binds to the 18 kDa translocator protein (TSPO), expressed in the mitochondria of activated microglia. ^{11}C-(R)-PK11195 PET has previously been used to study neuroinflammation in several neurodegenerative diseases.

The first studies using ^{11}C-(R)-PK11195 PET in TBI patients have been published recently (Folkersma et al. 2011; Ramlackhansingh et al. 2011). In the paper by Folkersma and coworkers, a patient group in chronic stage with moderate or severe TBI ($N = 8$) and a control group ($N = 7$) were studied. ^{11}C-(R)-PK11195 PET and MR images were acquired 6 months after TBI. ^{11}C-(R)-PK11195 BP_{ND} parametric images were generated. To generate a reference tissue input, the authors used supervised cluster analysis (Boellaard et al. 2008). Evaluation of the ^{11}C-(R)-PK11195 BP_{ND} was done in the whole brain and regionally. Group comparisons showed a significant increase of whole-brain ^{11}C-(R)-PK11195 BP_{ND} in the TBI group. This increase was not only observed in structurally affected brain regions (MRI) but also in apparently normal regions. On the other hand, there was no correlation between TBI severity (GCS) or neurological outcome (GOS) and whole-brain ^{11}C-(R)-PK11195 BP_{ND}. Although microglial activation is mostly a diffuse event in TBI, brain regions showing significant increases of ^{11}C-(R)-PK11195 BP_{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-(R)-PK11195 BP_{ND} was maximal in the thalamus in six out of eight patients.

The study by Ramlackhansingh et al. (2011) investigated whether the inflammatory response persists in patients with chronic TBI and if this response was related to structural abnormalities and cognitive dysfunction. This paper included a group of patients with moderate to severe chronic TBI ($N = 10$). Five patients had focal damage visible in MR images, while the other five did not show abnormalities. ^{11}C-(R)-PK11195 PET was performed on all patients at least 11 months after TBI. Like in the previous study, ^{11}C-(R)-PK11195 BP_{ND} parametric images were generated using supervised cluster analysis. Volumetric MRI and DTI were done to evaluate focal damage and the disruption of WM. Cognitive function was also evaluated. Group comparisons showed that ^{11}C-(R)-PK11195 BP_{ND} was increased in the thalami, putamen, occipital cortices, and posterior limb of the internal capsules in the patient group compared with controls (Fig. 43.3). Unlike the study by Folkersma and coworkers, they found no increase in ^{11}C-(R)-PK11195 BP_{ND} 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-(R)-PK11195 BP_{ND} in the thalamus and the degree of cognitive impairment. ^{11}C-(R)-PK11195 BP_{ND} increase was not associated with structural damage found by volumetric MRI and DTI or the time elapsed after TBI. Like in the article by Folkersma, persistent microglial activation in chronic TBI patients was confirmed especially in subcortical regions. Taking into account the long intervals after injury in the patient sample, this paper also suggests that therapeutic interventions can be beneficial even for a long time after TBI.

Over the past decades, new TSPO PET ligands have been developed with higher signal-to-noise ratios, including second- and third-generation ligands. After it

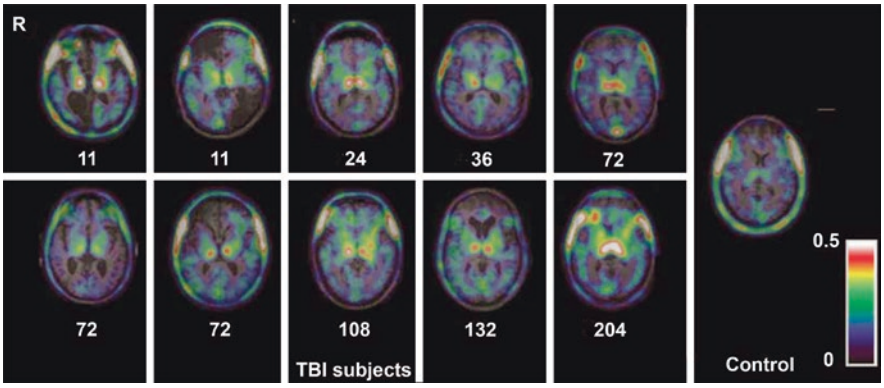

Fig. 43.3 Chronic microglial activation is present following traumatic brain injury (*TBI*). Overlay images of the transverse T1 magnetic resonance imaging at the level of the thalamus superimposed with ^{11}C-(R)-PK11195 (*PK*) images of all TBI subjects and a representative control subject. Numbers indicate time in months from the time of TBI to positron emission tomography scanning. Images illustrate the greater binding of PK in the thalami of all TBI subjects. *R* right. (From Ramlackhansingh et al. (2011); with permission)

became apparent that the binding of second-generation ligands was influenced by the rs6971 polymorphism (Ala147Thr) in the TSPO gene, efforts using third-generation ligands have shown promise to reduce this issue (Ikawa et al. 2017). Although its clinical value still has to be determined, these developments may eventually facilitate the use of TSPO PET as a biomarker after traumatic brain injury.

43.3 Single-Photon Emission Computed Tomography (SPECT)

Perfusion SPECT using ^{99m}Tc-hexamethyl-propyleneamine oxime (HMPAO) or ^{99m}Tc-ethylene cysteine dimer (ECD) has been extensively used in TBI. Reviews of this neuroimaging modality have appeared regularly in the last years (Davalos and Bennett 2002; Cihangiroglu et al. 2002; Belanger et al. 2007; Tikofsky 2010; Tong et al. 2011). These reviews coincide in pointing out that perfusion SPECT has high negative predictive value during the acute phase in mild TBI. 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. Abnormalities detected by perfusion SPECT are more extensive than those observed by structural neuroimaging. A recent study shows that the combination of structural neuroimages, such as CT, with perfusion SPECT using ^{99m}Tc-ECD is useful to determine the extent and severity of TBI lesions and tissue viability in core, edema, and perilesional tissue (Pifarré et al. 2011). Figure 43.4 shows CT and SPECT perfusion imaging of a patient with left frontal primarily brain trauma.

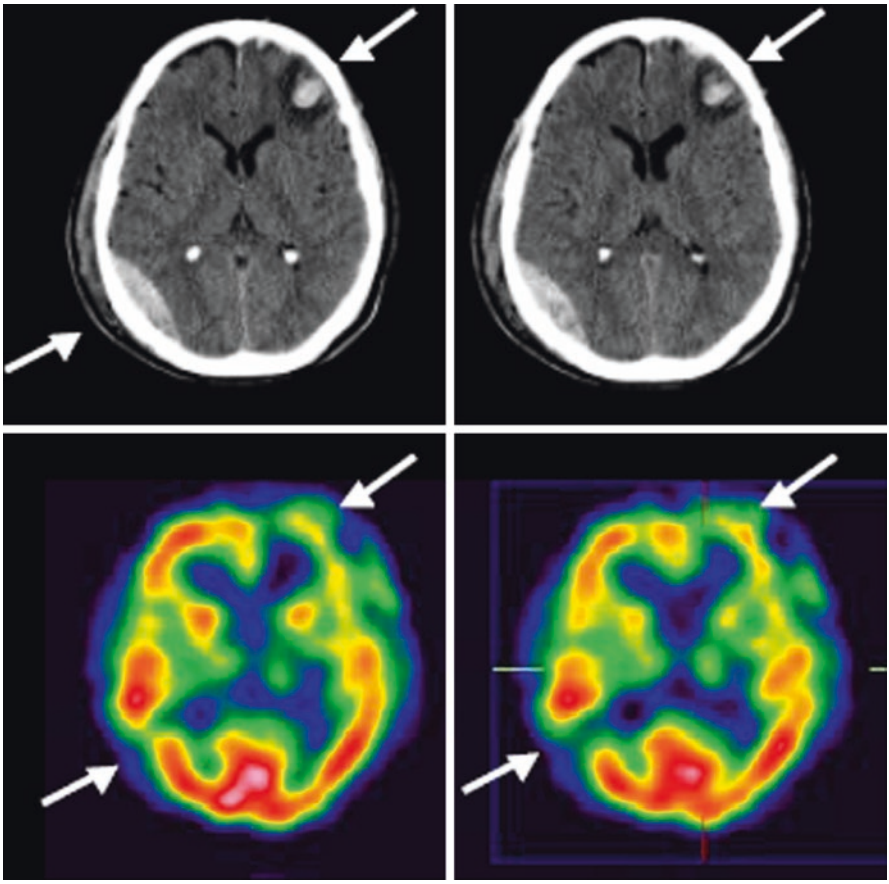

Fig. 43.4 CT and SPECT perfusion imaging of a patient with left frontal primarily brain trauma. In the hemorrhagic lesion seen on the CT in the right posterior temporal region, SPECT images show an absence of perfusion. (From Pifarré et al. (2011))

Furthermore, using SPECT, it is possible to study cell-specific processes related to TBI pathophysiology. Studies combining ^{123}I-2-β-carbomethoxy-3-β-(4-iodophenyl) tropane (β-CIT) and ^{123}I-iodobenzamide (IBZM) found nigrostriatal dysfunction in TBI patients, although the striatum was structurally relatively preserved, suggesting these studies may be useful in the evaluation of therapies directed toward reducing parkinsonian symptoms in TBI patients (Donnemiller et al. 2000). Another very recent animal study used *N*′,*N*′-diethyl-6-chloro-(4′-[^{123}I]iodophenyl) imidazo[1,2-*a*]pyridine-3-acetamide (^{123}I-CLINDE) for the in vivo monitoring of neuroinflammation by SPECT (Mattner et al. 2011). ^{123}I-CLINDE is a highly specific radioligand for TSPO. A recent perfusion SPECT activation study investigated cognitive fatigue mechanisms in patients with mild TBI (Hattori et al. 2009). In this study, it was possible to show that there is a frontocerebellar dissociation in patients with mild TBI that may explain cognitive impairment and cognitive fatigue in the chronic phase.

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 a valid alternative for the study of TBI, both for clinical practice and for research. Nevertheless, like ^{18}F-FDG PET, 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 and is still more widely available on a worldwide scale in comparison to PET.

43.4 Conclusions

In the acute TBI phase, ^{18}F-FDG PET seems to be more useful and has prognostic value in patients whose neurological state cannot be explained by structural neuroimages. However, evidence-based imaging studies are necessary to demonstrate the incremental validity of ^{18}F-FDG PET together with cost-effectiveness analysis to appropriately compare ^{18}F-FDG PET with other neuroimaging techniques. Whichever the results of these studies, ^{18}F-FDG PET and $^{15}O_2$-PET will remain very valuable tools for research of the complex and not yet fully understood pathophysiology of acute-phase TBI. In chronic TBI patients, most of the ^{18}F-FDG PET studies coincide in indicating a diffuse cortical–subcortical pattern of hypometabolism associated with cognitive impairment, even in patients without evident structural abnormalities. Preliminary studies also suggest the usefulness of ^{18}F-FDG PET for the evaluation of different therapeutic approaches for improving cognitive function in chronic TBI. In recent years, interest in studying cell-specific processes involved in TBI pathophysiology with PET is growing. Most considerably, tau PET ligands became available, which have allowed in vivo imaging of tauopathy in subjects who were exposed to (repetitive) traumatic brain injury. Another interesting application has been the imaging of markers of neuroinflammation using TSPO PET. Neuroinflammation imaging could become very attractive for detecting secondary damage after TBI, possibly with higher sensitivity than ^{18}F-FDG PET. Furthermore, it could serve in the evaluation of different therapeutic approaches, especially with the arrival of more sensitive third-generation TSPO ligands Finally, SPECT is a valid alternative for the study of TBI. However, as with PET, evidence-based imaging studies are required to demonstrate its incremental validity. SPECT is much less expensive and more widely available on a global scale.

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