

The role of PET imaging in the management of patients with central nervous system disorders

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PET has been widely used in the study of various central nervous system (CNS) disorders. A number of different radiopharmaceuticals labeled with positron-emitting isotopes, such as carbon-11 ($[^{11}\text{C}]$), fluorine-18 ($[^{18}\text{F}]$), and nitrogen-13 ($[^{13}\text{N}]$), have been developed for measuring cerebral blood flow (CBF), cerebral metabolism, and neurotransmitter systems [1,2]. In fact, virtually every aspect of brain physiology can be evaluated by a PET radiopharmaceutical. Perhaps the most commonly used radiopharmaceutical for both research and clinical purposes is $[^{18}\text{F}]$ -fluorodeoxyglucose (FDG). FDG-PET allows for the evaluation of cerebral glucose metabolism and has physical characteristics that make it relatively easy to produce and use, and provide high-resolution images of cerebral metabolism (Fig. 1). PET, along with its available radiotracers, has been used to study many pathologic states in the brain and assist with the management of these disorders. Specific CNS disorders in which PET studies may influence the management of the patient include seizures, brain tumors, movement disorders [3,4], dementia [5], head trauma, and depression.

Alzheimer's disease

Perhaps the most important use for PET imaging in the work-up of the dementia patient is to aid in

making an accurate diagnosis as early in the course of Alzheimer's disease (AD) as possible. The criteria for the diagnosis of AD were defined by the Working Group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association in 1984 [6] and require evidence of progressive, chronic cognitive deficits in middle-aged and elderly patients with no identifiable underlying cause. Unfortunately, although it is possible to make an accurate diagnosis of dementia in most patients with severe disease, it is very difficult to differentiate between AD and other dementing disorders in patients with mild cognitive impairment [7,8]. It is believed that functional imaging studies, such as PET, might help in making the diagnosis of AD and elucidating the mechanisms underlying the disorder.

Since 1980, a large number of studies have used PET in the assessment of patients with AD. Initial $[^{18}\text{F}]$ -FDG PET studies, comparing CMRGlC in patients with AD with age-matched, healthy controls, showed that there is a 20% to 30% decrease in whole-brain CMRGlC values in patients with AD when compared with healthy age-matched controls [9]. Other studies showed that patients with AD have decreased whole brain glucose metabolism (CMRGlC), whereas the bilateral parietal and temporal lobes are particularly affected [10–13]. This parietal hypometabolism (Fig. 2) is often referred to as representing the typical pattern of AD and may be particularly pronounced in patients with an age less than 65 years [14]. Although the bilateral parietal pattern is highly predictive of AD [15,16], the pattern is not pathognomic for AD and may be seen in patients with

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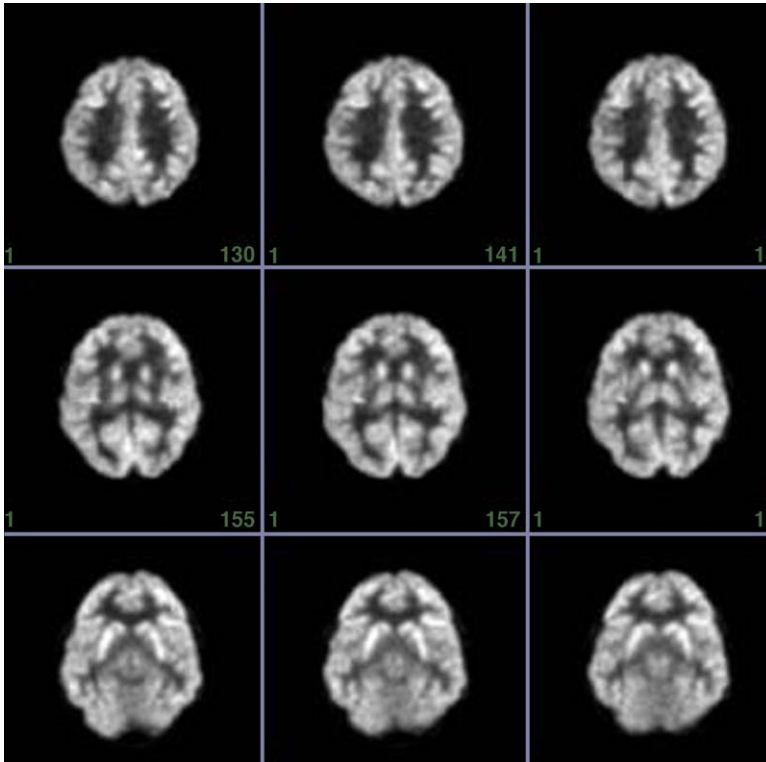


Fig. 1. FDG-PET image of normal subject using a high-resolution gadolinium orthosilicate PET camera. The resolution of 2.5 to 3mm is superior to prior PET cameras and demonstrates significant cortical and subcortical detail.

Parkinson’s disease (PD), bilateral parietal subdural hematomas, bilateral parietal stroke, and bilateral parietal radiation therapy ports [17].

In patients with AD of varying severity, the magnitude and extent of hypometabolism correlates

with the severity of the dementia symptoms [18–20]. Usually, there are only minor decreases in the parietal lobes in patients with early mild AD. Moderately affected patients show significantly decreased metabolism in the left midfrontal lobes, bilateral parietal

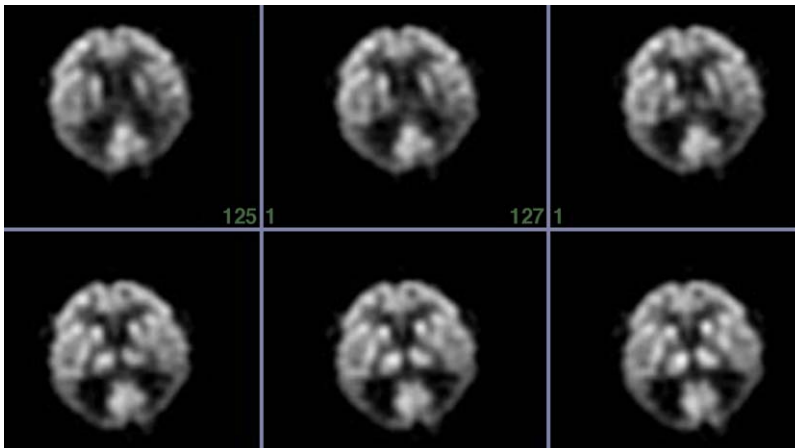


Fig. 2. FDG-PET scan of a patient with moderately advanced Alzheimer’s disease. The findings demonstrate significant bilateral temporoparietal hypometabolism.

lobes, and the superior temporal regions. In patients with severe AD, the same regions are affected, but the hypometabolism is much more pronounced with sparing only of the sensorimotor, visual, and sub-cortical areas (Fig. 3). Longitudinal studies have shown that CMRGlC values decrease more rapidly over time in patients with AD than age-matched control subjects and particularly affect the temporal, parietal, and frontal lobes [21]. The authors' research group has also developed a semiquantitative subjective scoring system designed to assess for disease severity in AD patients [18]. Such a scoring system, which weighs metabolic values according to the areas particularly involved in AD, such as the parietal, temporal, and frontal lobes, may be beneficial for routine clinical use and future research studies of therapeutic interventions.

PET imaging also provides the ability to measure changes in neurotransmitter systems that might be affected in AD. One study demonstrated significant decreases in acetylcholinesterase activity in the neocortex, hippocampus, and amygdala of all patients with AD, suggesting a loss of cholinergic innervation in the basal forebrain [22]. The temporal and parietal cortices were the most affected, although reductions were relatively uniform in the cerebral neocortex. PET can also play an important role in the evaluation of therapeutic interventions for AD. The relatively recent development of several pharmaceuticals for

AD provides an important area for PET imaging. For example, patients treated with donepezil were found to have relatively similar cerebral metabolism at 24 weeks compared with the placebo group that was observed to have a 10% decline [23]. In terms of the exact pharmacologic mechanism, one PET study explored how donepezil affected acetylcholinesterase activity [24]. Donepezil hydrochloride reportedly provides nearly complete inhibition of cerebral cortical acetylcholinesterase activity in patients with AD. This study, however, demonstrated an average of only 27% inhibition of acetylcholinesterase activity. More recent studies have suggested that the therapeutic response of drugs, such as donepezil and rivastigmine, is associated with acetylcholinesterase activity primarily in the frontal lobes [25].

PET continues to play a major role in the study and diagnosis of AD. It has the ability to aid in the diagnosis and the determination of the course and severity of the disease. With improved methods for quantitative analysis of specific regions, such as the hippocampus, PET may help further unravel the pathophysiologic changes in AD. The role of PET imaging will be significantly enhanced as successful therapeutic interventions evolve in the treatment of AD. This is of particularly great importance in the management of patients with early AD.

Pick's disease

Pick's disease is a neurodegenerative dementia with a predilection for the frontal and temporal lobes where Pick's bodies are noted on histopathologic examination. The disease is associated with cognitive and language dysfunction, and behavioral changes. The most common finding in PET images (Fig. 4) is hypometabolism in the frontal and anterior temporal lobes bilaterally [26,27]. This pattern of anterior hypometabolism is consistent with the findings on histopathologic examination, and frontal and temporal lobe atrophy on CT and MR images [28]. The small number of studies reported in the literature may not allow determination of the accuracy of [¹⁸F]-FDG PET imaging in the diagnosis of Pick's disease. Furthermore, there are disorders, such as other frontal lobe dementias and schizophrenia, that also may have a pattern of frontal lobe hypometabolism, and these should be considered in the differential diagnosis. Clinical findings, however, are significantly different between these two disorders. At the present time, there are no clear therapeutic interventions for Pick's disease and PET imaging is

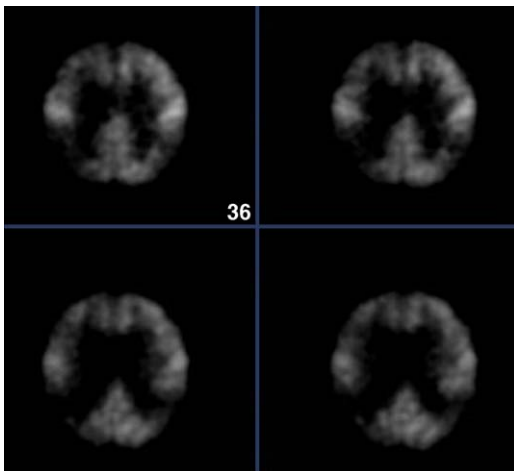


Fig. 3. FDG-PET scan of a patient with advanced Alzheimer's disease. The findings demonstrate significant bilateral temporoparietal hypometabolism in addition to frontal lobe hypometabolism. The sensorimotor areas, visual cortex, and cerebellum are relatively preserved.

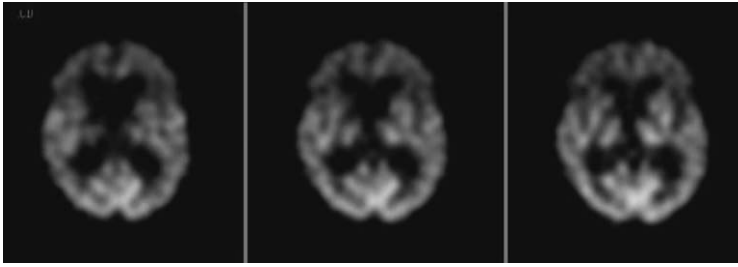


Fig. 4. FDG-PET scan of a patient with Pick's disease demonstrating moderately decreased metabolism in the frontal lobes including the anterior cingulate gyrus. The temporoparietal, occipital, and subcortical areas have relatively preserved metabolism.

less likely to have a role in the long-term management of such patients.

Brain tumors

Primary intracranial tumors comprise approximately 5% to 9% of all cancers and carry a median survival of approximately 1 year. Further, gliomas represent 50% of all intracranial tumors. PET can play an important role in the evaluation and management of patients with brain tumors, including the grading of tumors, determination of prognosis, and the differentiation of recurrent tumor from radiation necrosis [29,30].

Many of the studies of brain tumors with PET have been performed using FDG, although studies have been reported in which tracers, such as carbon-11-L-methionine ($[^{11}\text{C}]\text{-L-MET}$; reflecting neutral

amino acid transport), have been used [31,32]. Most FDG studies have concluded that high-grade tumors are hypermetabolic, whereas low-grade tumors are hypometabolic. In a study by DiChiro et al on 72 patients, the mean CMRglc, measured with FDG, for low-grade tumors was 4 ± 1.8 mg glucose/100 g/min, whereas high-grade tumors had a CMRglc of 7.4 ± 3.5 mg glucose/100 g/min. Other groups [33,34] have corroborated the finding of hypermetabolism in high-grade tumors and hypometabolism in low-grade tumors. One distinction from this typology is juvenile pilocytic astrocytomas, which typically have a high glucose metabolism despite their benign nature [35,36]. It should be noted that PET does not differentiate between primary lymphomas of the CNS, brain secondaries, or malignant gliomas, because all of these may be hypermetabolic [37]. In fact, a PET study of brain metastases from small cell lung cancer indicated increased rCMRglu, rCBF, and

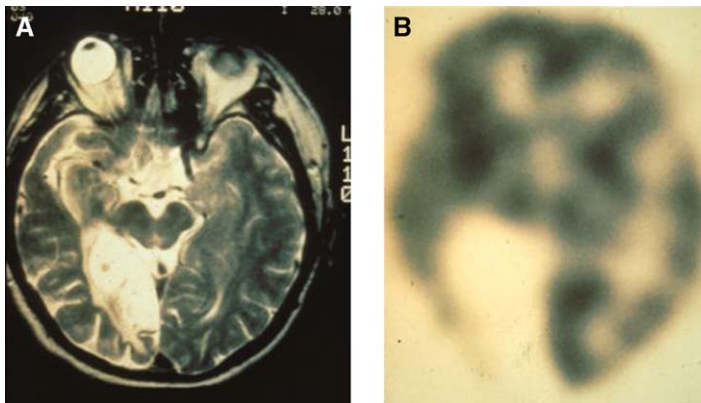


Fig. 5. (A) Patient with a history of right temporal lobe astrocytoma status post-radiation therapy presenting with worsening symptoms and an MR imaging abnormality that could not be categorized as either radiation necrosis or recurrent tumor. (B) FDG-PET scan demonstrates hypometabolism in the same region with no foci of increased activity where the MR imaging abnormality was noted. This finding indicates that there is radiation necrosis and no evidence of recurrent tumor.

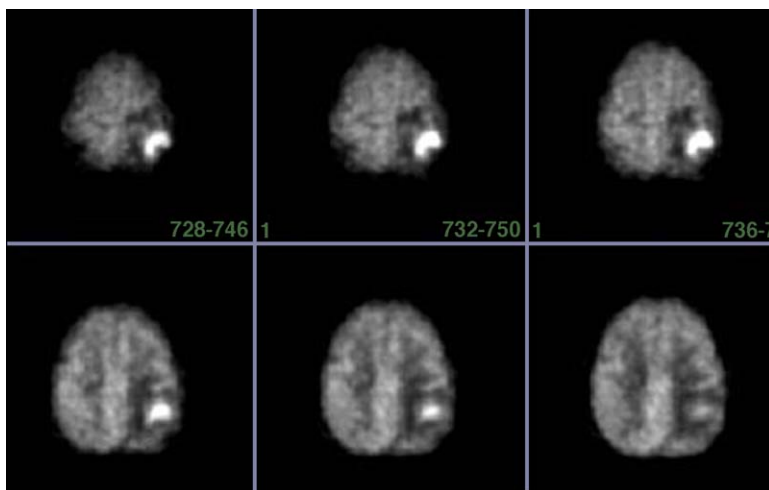


Fig. 6. FDG-PET scan of a patient with astrocytoma in the right parietal lobe status post-surgical resection and radiation therapy now with clinical concern for recurrence. The scan demonstrates a large area of intensely increased metabolism in the right parietal lobe consistent with recurrent tumor.

regional cerebral blood volume (rCBV) in tumor tissue even though there was a high degree of variability in these measures [38]. No correlation between survival and metabolic or hemodynamic parameters, however, could be demonstrated.

Although [^{18}F]-FDG-PET seems to be useful in grading brain tumors and determining their prognosis, PET also has another advantage over anatomic imaging. Unlike CT or MR imaging, PET can distinguish radiation necrosis from tumor recurrence [39,40]. The sensitivity for making this determination may be as high as 86% with a specificity as high as 56% [41]. Others, however, have questioned how useful this approach may be in distinguishing radiation necrosis from active tumor [42]. In general, areas of radiation necrosis are hypometabolic (Fig. 5), whereas tumor recurrence appears hypermetabolic on FDG-PET (Fig. 6). One study showed that radiation necrosis was associated with hypometabolism in the white matter only, whereas necrosis caused by chemotherapy was associated with gray matter changes in addition to white matter abnormalities. These investigators were also able to distinguish an area of tumor recurrence among necrotic changes. Further, they found no false-positive or false-negative results in this study.

Parkinson's disease

PD is caused by loss of the pigmented neurons in the substantia nigra and the locus coeruleus and is

characterized by the triad of bradykinesia, tremor, and rigidity. The loss of pigmented neurons is associated with decreased production of dopamine, decreased storage of dopamine, and nigrostriatal system dysfunction. It is believed that initially there is an up-regulation of dopamine receptors [43] followed by a down-regulation that occurs as the disease progresses. Eventually, PD can lead to dementia in 20% to 30% of the patients. PET offers the ability not only to study cerebral metabolism, but the dopamine transmitter receptor system, which may prove extremely useful in the diagnosis of PD and the determination of the pathophysiology of this disease [44,45].

Several groups have reported hypermetabolism in the basal ganglia in early, untreated PD [46,47]. Similarly, hemiparkinsonism is associated with hypermetabolism in the contralateral basal ganglia [48]. Another group [49] reported decreases in glucose metabolism in the basal ganglia contralateral to the side of the symptoms in patients with hemiparkinsonism-hemiatrophy syndrome. PD patients have been shown to have mild diffuse cortical hypometabolism compared with controls. Further, this hypometabolism correlates with the severity of bradykinesia, but is unrelated to the duration of the disease.

Regarding therapy, one study demonstrated that hypometabolism in the striatum and inferior thalamus in the side contralateral to the predominant parkinsonian signs was associated with L-dopa unresponsiveness, whereas hypermetabolism in the striatum and inferior thalamus contralateral to the predominant side were found in L-dopa-responsive patients [50].

Blesa et al [51] reported a reversal of pallidal hypermetabolism with levodopa therapy. Another study by Jenkins et al [52] indicated that PD patients had improved activation in the supplementary motor cortex during a motor function task when akinesia was reversed with apomorphine infusion (a dopamine agonist).

Dementia in PD seems to be associated with a uniform cerebral hypometabolism. Severe dementia in PD may be indistinguishable from AD on PET images, however, both showing significant bilateral parietal hypometabolism [53]. Peppard et al [54] showed that PD patients with dementia differed from PD patients without dementia in that the former had hypometabolic perirolandic and angular gyrus regions. PD patients with dementia, however, did not have significantly different CMRGluc values than AD patients [55]. Further, the parietal cortex:caudate-thalamus ratio negatively correlated with the severity and duration of the disease in PD patients and in AD patients. The results from these studies indicate that PD patients with dementia may suffer from an underlying Alzheimer-type process or may have a dementia specifically associated with the PD that affects the frontal lobes. The dopaminergic system may also play a role in the dementia symptoms of PD because reduced presynaptic dopamine activity in the caudate is associated with impairment in neuropsychologic tests measuring verbal fluency, working memory, attentional functioning, and somatosensory discrimination [56–58].

PET imaging in PD has also been performed with [^{18}F] fluorodopa to evaluate presynaptic dopaminergic

function, and has shown abnormalities in the nigrostriatal dopaminergic projection [59,60] and reduced basal ganglia activity, particularly in the posterior putamen (Fig. 7) [61]. Others have argued that the limited spatial resolution of PET with fluorodopa may result in substantial underestimation of the true rate of fluorodopa uptake and metabolism in vivo, and may also obscure regional heterogeneity in the neurochemical pathology of PD [62]. Garnett et al [63] showed that in hemiparkinsonism, there is a marked decrease in activity in the contralateral basal ganglia. There is also decreased activity, although to a lesser extent, in the ipsilateral basal ganglia.

Fluorodopa studies have been used to investigate clinical course and the effects of therapy in patients with PD. For example, in patients with mild PD, levodopa infusion decreased dopa influx in the putamen, whereas in patients with advanced PD, levodopa induced significant up-regulation of dopa influx [64]. This study might explain the less graded clinical response to levodopa in advanced PD and potentially explain the pathogenesis underlying motor fluctuations. More recent PET studies have demonstrated that although loss of putamen dopamine storage predisposes PD patients to motor complications, it cannot be the only factor determining when such motor symptoms arise clinically [65]. Additional PET studies suggest that loss of striatal dopamine storage capacity along with pulsatile exposure to exogenous L-dopa results in pathologically raised synaptic dopamine levels and deranged basal ganglia opioid transmission. This, rather than altered dopamine receptor binding, may be the cause of inap-

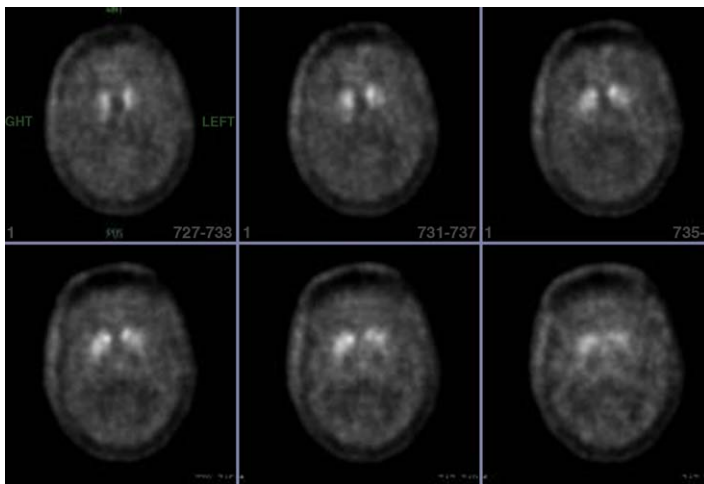


Fig. 7. [^{18}F]-fluorodopa scan of a patient with moderately severe Parkinson's disease shows uptake in the caudate but little uptake in the putamen. More severe cases may show little uptake throughout the striatum.

propriate overactivity of basal ganglia-frontal projections, resulting in breakthrough involuntary movements [66].

Imaging with postsynaptic dopamine receptor tracers has also provided important information regarding the disease pathogenesis and course. [¹¹C]-N-methylspiperone (a postsynaptic D2 receptor antagonist) has shown variable results in activity early in the disease and decreased tracer binding in advanced PD [67,68]. It should also be noted that PET imaging with [¹¹C]-N-methylspiperone in hemiparkinsonism patients has shown bilateral variability in striatal uptake [69]. [¹¹C]-raclopride has also been used to investigate D2 receptors in PD patients. An increase in [¹¹C]-raclopride activity (receptor up-regulation) has been observed in the striatum contralateral to hemiparkinsonian symptoms in early disease corroborating the notion of initial up-regulation of dopamine receptors followed by subsequent down-regulation as the disease progresses [70].

A number of new surgical techniques have been developed for the treatment of PD and their effect has been observed with PET. For example, pallidotomy has been associated with increased activation of premotor areas and reduced hyperactivity of the lentiform nucleus [71,72]. Pallidal and subthalamic stimulation also increase activation of premotor areas but decrease activation in the primary motor area [73,74]. Suppression of unilateral tremor with thalamic stimulation has been shown to be associated with a reduction in CBF. These findings corroborate the general notion that increased activity in the subthalamic-pallidal projection is directly implicated in the pathophysiology of PD, and that surgical techniques that block these output nuclei lead to partial restoration of cortical physiology. The changes associated with transplantation of fetal tissue for PD has demonstrated inconsistent findings, with some studies showing increased fluorodopa uptake and others no significant changes [75,76].

Cerebrovascular disease

Cerebrovascular disease is the third leading cause of death in the United States and affects approximately half a million people. Stroke is often associated with a poor outcome, however, in part because of the lack of understanding of the mechanisms that underlie stroke and the process by which recovery may take place. PET imaging has been of great benefit in advancing the understanding of the pathophysiology of cerebrovascular disorders. PET imaging allows for the detection of stroke earlier and

with higher sensitivity than anatomic imaging with either MR imaging or CT. Further, PET imaging has been useful in evaluating the extent of the functional damage, because areas not immediately affected by the infarct may show hypometabolism or decreased blood flow. Initial stroke severity has been shown to correlate with the initially affected volume as determined by PET, whereas neurologic deterioration during the first week after stroke correlates with the proportion of the initially affected volume that infarcted, and functional outcome correlates with the final infarct volume [77].

In patients who have suffered a stroke, there is a characteristic uncoupling between CBF and metabolism in the infarcted area [78,79]. Several studies using [¹⁵O]-H₂O have described “misery perfusion” in and near areas of infarct within the first hours to days after a stroke. This misery perfusion is described as a relative decrease in regional CBF compared with the regional glucose metabolism or oxygen metabolism. Further studies have shown that there is a marked increase in the regional oxygen extraction fraction (rOEF) in response to the diminished blood flow [80,81]. A recent study, however, showed no correlation between the degree of misery perfusion and angiographic findings in patients with carotid artery occlusion [82].

A recent study demonstrated that the oxygen consumption significantly decreased between the acute and chronic phases of stroke, but that acute-stage mesial-prefrontal metabolism was significantly correlated with neurologic recovery [83]. This study also showed that there was a delayed intrahemispheric remote hypometabolism that developed while the patient was clinically recovering and seems to be related to infarct size. Neurologic recovery was not a function of thalamic hypometabolism, but appeared to be influenced by mesial-prefrontal metabolism, possibly because this region is part of a network that has an important compensatory role in motor recovery.

Approximately 1 week after infarct “luxury perfusion” occurs, which is a relative increase of rCBF compared with cerebral metabolism [84]. Wise et al [85] found that rCBF increased compared with rCMRO₂ over several days postinfarct. Further, there was a subsequent decrease in the rOEF in the infarcted area 18 hours to 7 days after the infarct. This is believed to reflect mitochondrial dysfunction and energy failure of the damaged tissue. In addition to the infarcted area, there exists a penumbral zone, a hypometabolic and presumably ischemic area that surrounds the infarct core [86]. This area also has increased rOEF suggesting that this area has

decreased perfusion relative to the necessary oxygen requirements. If blood flow to this ischemic area is restored before irreversible damage occurs, then the tissue will likely recover and resume normal function [87].

Distant from the ischemic and the stroke sites, there are regions that also show alterations in metabolism despite being normal on anatomic imaging studies, such as CT or MR imaging [88,89]. It is not completely certain, however, what are the clinical consequences of these distant hypometabolic regions [83]. The most distinctive and characteristic example of such remote effects is crossed cerebellar diaschisis, first described by Baron et al [90]. Crossed cerebellar diaschisis (Fig. 8) refers to hypometabolism and hypoperfusion in the cerebellar cortex contralateral to the site of the infarct in the cortex and usually occurs during the first 2 months after infarction [91]. It is believed that this is caused by an interruption of the cerebro–ponto–cerebellar pathways as a result of the stroke. Interestingly, patients with persistent cerebellar diaschisis have a decrease in oxygen consumption that is less than the decrease in glucose use [92]. This

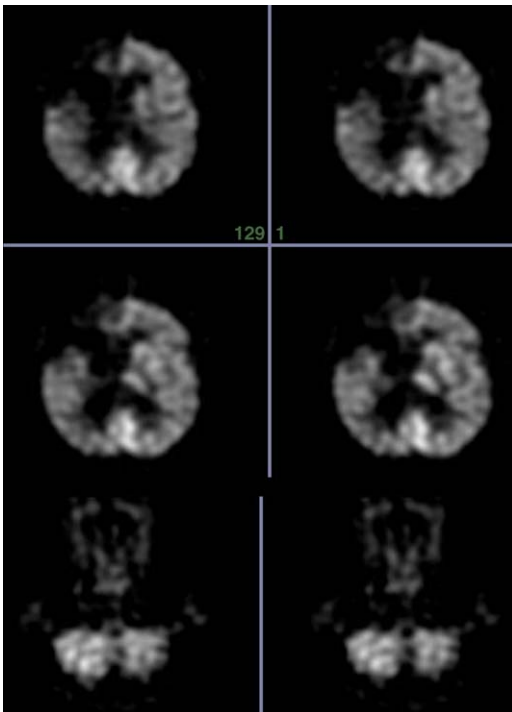


Fig. 8. FDG-PET scan of a patient after embolic stroke in the distribution of the right anterior cerebral artery. There is severely decreased metabolism in the right frontal lobe extending to the midline. There is also crossed cerebellar diaschisis with decreased metabolism in the left cerebellum.

uncoupling of oxygen consumption and glucose use may reflect a change in brain metabolism caused by deafferentation. Another study did demonstrate that the degree of neurologic improvement was worse in the patients with cerebellar diaschisis, which may be simply reflective of more severe and widespread ischemia resulting in the diaschisis [93]. There are also other areas that are hypometabolic after a cortical infarct [94]. These areas include the ipsilateral thalamus; the ipsilateral caudate nucleus; and the ipsilateral primary visual cortex (if the infarct is in the anterior visual pathways). A recent study also demonstrated a decline in oxygen metabolism in the unaffected hemisphere from the acute to the subacute stage, which suggests a delayed effect from transcallosal fiber degeneration [95].

PET studies have also been investigated the presence of chronic ischemia to determine the risk of stroke in these patients. Gibbs et al [96] found increased rCBV with normal rCBF and rCMRO₂ ipsilateral to occlusion of the internal carotid artery. The increase in rCBV is likely caused by the vasodilation that occurs in response to the decreased perfusion pressure. When the compensatory vasodilator response is at maximum, any further decrease in perfusion pressure may result in a decreased rCBF with the high likelihood of ischemia and eventually stroke. Because rCBF remains relatively constant until the maximum rCBV is attained, the rCBF:rCBV ratio (which correlates well with rOEF) decreases by autoregulation before ischemia develops. Similar findings were reported by Sette et al [97], in which patients with cerebrovascular disease had evidence of normal autoregulation and an increase in rOEF in response to decreased perfusion pressure.

PET studies have not been shown to be as successful in assessing risk of stroke or the potential outcome of surgical intervention in patients with carotid artery disease [98,99]. Count-based PET measurement of OEF without arterial sampling has been shown accurately to predict the risk of stroke in patients with carotid artery occlusion [100]. This is corroborated somewhat by another study that demonstrated a lower frequency of hemodynamic abnormalities in asymptomatic patients [101]. In an earlier study of patients with carotid artery disease being treated with antithrombotic medication, there was no difference in the incidence of stroke in patients with normal and those with abnormal hemodynamics. The same group found no correlation between the degree of carotid artery stenosis and the hemodynamic measures of the cerebral circulation in 19 patients with significant carotid artery occlusion. In patients before and after extracranial-intracranial bypass

surgery, however, decreases in rCBV and normalization of the rCBF:rCBV ratio were found after surgery [102]. Despite this finding, Powers et al [103] noted that 3 of 21 patients who underwent bypass surgery suffered ipsilateral stroke within 1 year. Further, none of the 23 patients who did not have surgery, but had PET findings similar to those in the surgical group, had a stroke. The conclusion from this study was that the PET results of the hemodynamic status of patients with carotid artery disease could not adequately predict which patients would benefit from bypass surgery.

There have been several studies correlating the functional recovery in patients with stroke to functional changes on PET scans [104]. Cerebral metabolic rates of glucose measured early after stroke have shown that receptive language disorders best correlate with metabolism in the left superior temporal cortex, and word fluency best correlates with metabolism in the left prefrontal cortex [105]. A PET study of patients with left inferior frontal gyrus strokes and resulting aphasia demonstrated a stronger-than-normal response in the homologous right inferior frontal gyrus [106]. Although the level of activation in the right inferior frontal gyrus did not correlate with verbal performance, increased activity in the perilesional area occurred in the two patients who gave the best performance in certain verbal tasks and who also showed the most complete recovery from aphasia. Similar results were described in several other studies of patients with aphasia secondary to stroke that demonstrated increased right temporal lobe activity as a mechanism to compensate for the impaired left hemispheric function [107,108]. The best degree of speech restoration, however, has been found in those patients with at least some preservation of activity in the left temporal lobe that can ultimately be incorporated into the functional language network [109,110]. Another study measuring CBF associated with passive elbow movement showed that hemiplegic stroke initially activated the bilateral inferior parietal cortex, contralateral sensorimotor cortex, and ipsilateral dorsolateral prefrontal cortex, supplementary motor area, and cingulate cortex, but later included activation of the ipsilateral premotor area [111]. These results suggested that recovery from hemiplegia is accompanied by changes of brain activation in sensory and motor systems.

PET studies have also been used to monitor the success of various treatment regimens. PET has been used to evaluate the effects of thrombolytic therapy in acute stroke and has found that critically hypoperfused tissue can be preserved by early reperfusion and that large infarcts can be prevented by early

reperfusion to misery perfused but viable tissue [112]. Imaging of benzodiazepine receptors by flumazenil PET has been found to distinguish between irreversibly damaged and viable penumbra tissue early after acute stroke [113]. In the future, functional imaging modalities that could eventually include tracers for neuronal integrity might be used to help in the selection of patients for thrombolytic therapy possibly permitting the extension of the critical time period for inclusion of patients to aggressive stroke management strategies [114]. Hakim et al [115] found that stroke patients treated with nimodipine had a greater increase in the rCBF in the ischemia core (7 days after the infarct) than did patients receiving placebo. There was also an increase in rCBF in the penumbral zone in the nimodipine group compared with the placebo group (but these results were not statistically significant). Another study using [¹⁸F]-FDG PET found that patients on nimodipine had greater increases in glucose metabolism in the affected areas compared with controls [116].

Head trauma

There have been a limited number of studies using PET in the evaluation of patients with head trauma. One of the problems with the use of PET in these cases is that PET cannot distinguish between structural damage and cerebral dysfunction because these may all result in areas of decreased metabolism [117]. It is helpful to compare PET with anatomic images, such as those obtained by MR imaging or CT, especially because cerebral dysfunction can extend beyond the boundary of anatomic lesions [118] and may even appear in remote locations from the trauma.

Lesions, such as cortical contusions, intracranial hematoma, and resultant encephalomalacia, have metabolic effects that are confined primarily to the site of injury. Subdural and epidural hematomas, however, often cause widespread hypometabolism and may even affect the contralateral hemisphere [119]. Another entity, diffuse axonal injury, has been found to cause diffuse cortical hypometabolism with particularly marked decrease in metabolism in the parietal occipital cortex (Fig. 9) [120]. Further, crossed cerebellar diaschisis, and ipsilateral cerebellar hypometabolism, has been found in head-injury patients with supratentorial lesions [121].

Alavi et al [118] found a good correlation between the severity of head trauma as measured by the Glasgow Coma Scale and the extent of whole brain hypometabolism. Another study demonstrated that persistent symptoms in minor head-injury patients

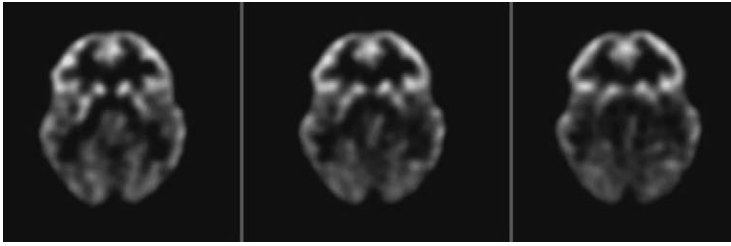


Fig. 9. FDG-PET scan of a patient with traumatic brain injury showing decreased metabolism in the parietal and occipital cortices consistent with diffuse axonal injury.

may be associated with corresponding deficits in both neuropsychologic testing and cerebral metabolism [122]. Another study demonstrated that regionally decreased glucose metabolism was observed in 88% of patients [123]. The prevalence of global cortical CMRglc reduction was higher in severely head-injured patients (86% versus 67% mild-moderate), although the absolute values were similar across the injury severity spectrum. As many as half of head-injury patients may also have increased glucose metabolism as early as 1 week after injury [124]. This hyperglycolysis may occur either regionally or globally and also suggests that the metabolic state of the traumatically injured brain should be defined differentially in terms of glucose and oxygen metabolism. PET imaging may not be as helpful in determining overall prognosis in head-injury patients, however, particularly children and adolescents, with respect to rehabilitation [125].

It has also been found that after head injury, even though a patient may be in a persistent vegetative state, their brain actually responds to the emotional attributes of sound or speech. This was determined using PET to measure CBF changes when a story was told by a patient's mother [126]. During auditory presentation, there was increased activity in the rostral anterior cingulate, right middle temporal, and right premotor cortices.

Epilepsy and other seizure disorders

Epilepsy affects 0.5% to 1% of the population, can cause focal or generalized seizures, and usually begins in childhood. In general, during an epileptic seizure cerebral metabolism and blood flow are markedly increased. The focus of partial seizures can be identified using [^{18}F]-FDG PET because these areas have increased metabolism during the seizure and decreased metabolism in the interictal period [127,128]. It has been shown that single hypometabolic regions can be identified in 55% to 80% of

patients with focal EEG abnormalities [129,130]. Performing ictal PET studies is somewhat impractical, however, because of the short half-life of the positron emitters and other logistical reasons. One of the most effective treatments for partial epilepsy, refractory to medical intervention, is surgical removal of the involved area. Using high-resolution PET images, accurate localization of seizure foci can be achieved to aid in selecting the appropriate surgical intervention [131]. It also seems that certain clinical features affect the metabolic and CBF findings [132]. The degree of asymmetry in the region of the seizure focus seems greater with increasing duration of the seizure disorder. Cerebral glucose metabolism seems to have a greater rate of increase in asymmetry than CBF. These results indicate an uncoupling of cerebral metabolism and blood flow that is progressive and results from the differential response of glucose metabolism and blood flow to chronic seizure activity. The type of seizure preceding the PET study may also affect the metabolic landscape such that hypometabolism is limited to the epileptogenic zone if the preceding seizure is focal limbic, whereas patients with widespread limbic seizures have hypometabolism that included one or several additional areas of the limbic cortex [133].

Another important aspect of seizure studies is how to distinguish those patients who will do well postoperatively from those who will be less likely to benefit from temporal lobectomy. Several PET studies did not find any correlation between the severity of abnormal temporal lobe activity and the frequency of postoperative seizures [134]. Other studies have shown that in those patients with hypometabolism only in the affected temporal lobe, there is a higher likelihood of a successful outcome [135–137]. It has also been shown that patients with a greater degree of hypometabolism in the temporal lobe (ie, a more distinct asymmetry) tended to have a better outcome than those with a lesser degree of asymmetry [138,139]. It may be that those patients without significant hypometabolism of the affected

temporal lobe (ie, minimal asymmetry between the temporal lobes) might have extratemporal or bitemporal seizure foci. These patients may be less amenable to surgical resection. This is corroborated by other studies that have shown that patients with hypometabolism detected in the opposite hemisphere to the epileptic focus on EEG may be more likely to have postoperative seizures [140] and those patients with extratemporal hypometabolism tend to have a higher likelihood of postoperative seizures [141]. The authors have recently reported that the FDG-PET finding of thalamic hypometabolism may be an important added measure in the evaluation of patients with temporal lobe epilepsy with regard to postoperative seizure outcome [142]. Compared with patients with no thalamic asymmetry, patients with ipsilateral thalamic hypometabolism had a slightly higher risk, and those with contralateral hypometabolism had a markedly increased risk, for having postoperative seizures.

The temporal lobe is the most common focus of partial epilepsy (Fig. 10). Studies show that the sensitivity of PET in detecting temporal lobe epilepsy foci is over 70% in patients with partial complex seizures using FDG [143–145]. One FDG-PET study showed ipsilateral hypometabolism of the seizure focus in the temporal pole, but relatively increased metabolism in the ipsilateral mesiobasal region [146]. Contralateral to the seizure focus, metabolism was increased in the lateral temporal cortex and mesiobasal regions. A study using statistical parametric mapping (SPM) compared hemispheric asymmetry on FDG-PET images in patients with mesial temporal lobe epilepsy with controls [147]. When the SPM

program was used to detect temporal interhemispheric asymmetry, hypometabolism was identified on the side chosen for resection in most cases (sensitivity, 71%; specificity, 100%) and was predictive of favorable postsurgical outcome in 90% of the patients.

The other major site of seizure focus in partial epilepsy is the frontal lobe. Because many of these seizures begin in the medial or inferior aspects of the frontal lobe, scalp EEG readings do not provide adequate localization of foci [148]. Franck et al [149] used [^{18}F]-FDG PET to study 13 patients with presumed frontal lobe epilepsy and found PET to be the best modality for localizing seizure foci in this location. Additionally, the authors suggested that PET might help in determining the site of surgical excision or suggest a contraindication to surgical intervention in patients with multiple or bilateral foci. One study of 180 surgical specimens from patients with frontal lobe epilepsy found a high correlation between hypometabolic regions on PET images and structural, histopathologic changes in the surgical specimens, again demonstrating the value of PET in detecting seizure foci [150].

Performing ictal PET studies is somewhat impractical because of the relatively short half-life of positron-emitting isotopes, such as fluorine-18, and other logistical reasons [151]. Several ictal PET studies have been reported in the literature, however, which have been successful in detecting seizure foci in patients with partial seizures as hypermetabolic areas [152]. Complex partial seizures are associated with bilaterally increased CBF in a number of cortical areas, particularly the temporal and frontal lobes

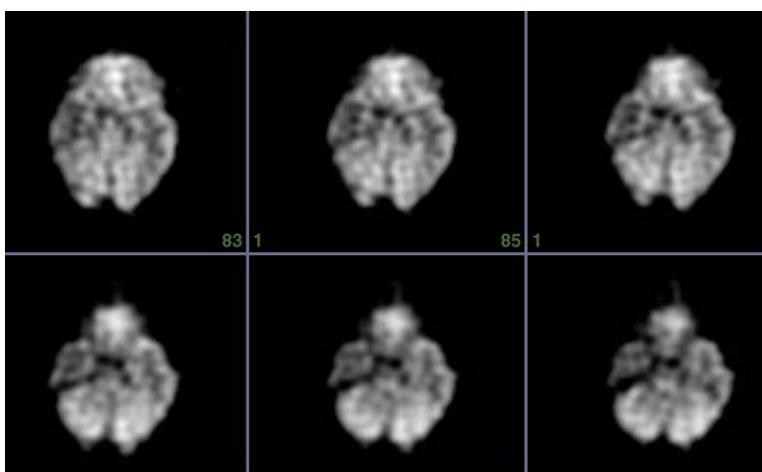


Fig. 10. Interictal FDG-PET scan of a patient with temporal lobe seizures refractory to medical treatment. The scan demonstrates moderate hypometabolism in the right temporal lobe consistent with a seizure focus.

[153]. In addition, these patients also had increased blood flow to the subcortical nuclei, which are activated during ictus.

Summary

PET will continue to play a critical role in both clinical and research applications with regard to CNS disorders. PET is useful in the initial diagnosis of patients presenting with CNS symptoms and can help clinicians determine the best course of therapy. PET studies can also be useful for studying the response to therapy. From the research perspective, the various neurotransmitter and other molecular tracers currently available or in development will provide substantial information about pathophysiologic process in the brain. As such applications become more widely tested, their introduction into the clinical arena will further advance the use of PET imaging in the evaluation and management of CNS disorders.

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