

Positron Emission Tomography in Clinical Neurology

Karl Herholz, MD, and W.-D. Heiss, MD

Department of Neurology, University Cologne, and
Max-Planck Institute for Neurological Research, Köln, Germany

Positron emission tomography (PET) imaging in clinical neurology serves several purposes: differential diagnosis, especially in the early stage of neurologic disorders, description of pathophysiologic changes that are responsible for manifestation and course of a disease, and evaluation and follow-up of treatment effects. Many of these applications are possible with the most widely available PET tracer, 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG). Additional tracers are used clinically to detect the disturbance of specific neurotransmitter and receptor systems, blood flow, oxygen metabolism, and amino acid uptake. Main diagnostic issues addressed in this review are early diagnosis of Alzheimer's disease and other dementias, differential diagnosis of movement disorders, diagnosis of recurrent brain tumors, identification of viable tissue in ischemic stroke, and localization of epileptogenic foci. Techniques for presurgical localization of eloquent cortex and monitoring of therapy are presented. © 2004 Elsevier Inc. All rights reserved.

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Introduction

Clinical examination is more powerful in neurology than in many other medical specialties with respect to its ability to precisely localize a lesion, probably because focal lesions in the highly structured nervous system lead to well-described combinations of symptoms, the classical syndromes that are often specific for lesion location. Residual uncertainty about lesion location can often be removed by magnetic resonance imaging (MRI) or computed tomography (CT), and these imaging techniques, together with patient history, may also provide some clues with regard to lesion etiology. Yet, there are many aspects of neurologic diseases, in particular the molecular mechanisms that underlie their clinical manifestation, that cannot adequately be studied *in vivo* by clinical means and structural imaging. There is also much need for individual optimization of therapy, which cannot be covered by standard criteria and procedures, and whose impact needs to be studied by adequately designed studies. Early diagnosis based on functional and thus reversible changes is always an important issue, especially in neu-

rology given the brain's very limited potential for structural recovery, and its importance will grow as new therapeutic possibilities to prevent irreversible damage are being developed. In this brief review, we wish to indicate the main areas in neurology where diagnostic use of positron emission tomography (PET) is already established in the literature, and where it could grow depending on future clinical studies.

Dementia

Alzheimer's Disease

Alzheimer's dementia is the most frequent dementing disease, and it is associated with very characteristic reductions of cerebral glucose metabolism in association areas. Meanwhile, more than 20 years have passed since the first descriptions of the typical Alzheimer's disease (AD) findings in 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG)-PET. It has been noted from the beginning that the temporal-parietal association cortex is most affected, with the angular gyrus usually being located the center of the metabolic impairment, and frontolateral association cortex is also involved frequently (see ref. ¹ for review). These changes are different from those of normal aging, which leads to predominantly *mesial* frontal metabolic decline, and may cause some apparent dorsal parietal (rather than temporal-parietal) and

Address correspondence to: Karl Herholz, Neurologische Universitätsklinik und Max-Planck-Institut für neurologische Forschung, Josef-Stelzmann-Str. 9 50931, Köln Germany. E-mail: karl.herholz@pet.mpin-koeln.mpg.de

frontotemporal (perisylvian) metabolic reduction due to partial volume effects caused by atrophy.^{2,3} There may be a distinct hemispheric asymmetry, which usually corresponds to the predominant cognitive deficits (language impairment in the dominant and visuospatial disorientation in the subdominant hemisphere). In contrast to other dementia types, glucose metabolism in the basal ganglia, primary motor and visual cortex, and cerebellum is usually well preserved. Voxel-based comparisons with normal reference samples clearly showed that the posterior cingulate gyrus and the precuneus are also impaired early on.⁴ This is usually not directly obvious by mere inspection of FDG–PET scans because metabolism in that area is above the cortical average in normal brain,⁵ and with beginning impairment it returns to the level of the surrounding cortex but does not stick out as a hypometabolic lesion. Thus, if a visual interpreter fails to take into account the normal level of metabolism of the posterior cingulate gyrus, this important diagnostic sign can be missed. On the background of sufficient numbers of FDG–PET scans in normal controls it is increasingly feasible to base the interpretation of patient studies not merely on visual interpretation of the tracer distribution, but on quantitative mapping with reference to an appropriate normal sample.^{2,6–9}

Use of FDG–PET to diagnose AD entirely rests on the typical distribution of these functional changes in the brain, but impairment of local FDG uptake is not specific for AD pathology. Correspondingly, high sensitivity in the order of 90% to 95% has been documented in several studies, but specificity for discrimination from other neurodegenerative disorders is lower and in the order of 65% to 75%.¹⁰

The current main issue for diagnosis of AD with PET is early diagnosis when patients present with a mild cognitive deficit (MCI), but before clinical dementia arises. This may be of particular importance for subjects with a high premorbid cognitive level, who can experience a substantial decline of cognitive function before reaching the lower normal limit of standard neuropsychologic tests. There are many indications that this will be possible with FDG–PET. Data are accumulating that presence of the AD metabolic pattern in MCI predicts conversion to clinical dementia of Alzheimer type, and therefore indicates “incipient AD.” In a longitudinal study of ApoE4-positive nondemented subjects with memory complaints, FDG–PET findings predicted cognitive decline after two years of follow-up.¹¹ Impairment of cortical glucose metabolism has also been observed in asymptomatic subjects at high risk for AD.^{12–15} We studied patients with MCIs, mostly limited to the memory domain, with MMSE scores of 24 or higher and not yet fulfilling the criteria of probable AD. They were therefore diagnosed as “possible AD,” and most of these patients would have fulfilled the criteria of MCI

(that were not yet used by us at that time). We found that 60 to 70% of those patients who already had moderate or severe metabolic impairment of association cortices in FDG–PET declined on MMSE by three points or more within two years (mostly leading to clinical dementia), whereas only 10% to 20% of patients without such metabolic impairment had that decline.¹⁶ More recently, the predictive value of temporoparietal metabolic impairment for conversion to AD has been confirmed in MCI.^{17–20} Currently, impairment of the posterior cingulate is regarded as the most sensitive indicator,⁴ but there are also indications that the other association areas are also impaired early on.²

A main limitation for uncritical use of FDG–PET for diagnosis of AD is that patients with Parkinson’s disease (PD) may show a very similar metabolic impairment,^{21,22} even in the absence of major cognitive deficits.²³ These changes may even be reversible with successful electrical stimulation of the subthalamic nucleus.²⁴ Yet, with appropriate clinical information, the “pseudo-AD” metabolic pattern should not be a major problem because it is seen only in patients with long-standing PD who also have the clinical motor symptoms of PD. In principle, any relevant functional impairment of cortical association areas irrespective of its underlying etiology could mimic AD in FDG–PET and with respect to clinical symptoms. To exclude nondegenerative lesions as causes of focal FDG reductions that could mimic AD, it is always wise to compare the PET images with structural images that are part of any comprehensive diagnostic workup.

Patients with late-onset AD may show less difference between typically affected and nonaffected brain regions, which could potentially lead to reduced diagnostic accuracy with FDG–PET.^{25,26} This could reflect the fact that at higher age, multifactor damage to the brain is likely to accumulate. Actually, in neuropathologic studies the proportion of unclassifiable dementia is increasing in the oldest ages. Thus, in very old multimorbid patients, FDG–PET is probably of little diagnostic use, which is in accord with general clinical wisdom, and does not represent a major limitation.

Changes of cerebral blood flow are similar to those of glucose metabolism in AD, and they can also be imaged with SPECT using Tc-99m-HMPAO or other blood flow tracers. Yet, in the few direct comparisons of FDG–PET with single photon emission computed tomography (SPECT) that have been performed,^{27–29} FDG–PET was always shown to be more accurate. Because the highest benefit of function imaging for diagnosis of dementia probably will be obtained in cases that do not yet present with the typical symptoms of AD but may have more subtle symptoms that would be classified clinically as MCI,^{18,30,31} high accuracy is certainly needed.

Degeneration of cholinergic neurons is a histochemical hallmark of AD,^{32,33} whereas the cholinergic system

is mostly intact in vascular dementia³⁴ and in frontotemporal dementia. These neurons express acetylcholine esterase (AChE) as an enzyme for degradation of acetylcholine. In recent years, the piperidine analogs C-11-labeled *N*-methyl-4-piperidyl-acetate³⁵ and *N*-methyl-4-piperidyl-propionate³⁶ have been developed for *in vivo* imaging of cerebral AChE with PET. Reduced cortical AChE activity in AD has been observed in several studies with these tracers.^{37–40} Thus, imaging of cholinergic neurotransmission could become an important tool for differentiation between different types of dementia.

Since many dementia researchers consider amyloid deposition as the most important and specific pathophysiologic event in AD, newly developed tracers that label amyloid plaques and neurofibrillary tangles are likely to play an increasingly important role.^{41–44} Recently developed tracers include 2-(1-(6-[(2-[¹⁸F] fluoroethyl) (methyl)amino]-2-naphthyl) ethylidene) malonitrile (FDDNP) that is lipophilic enough to enter the brain and binds to amyloid beta(1–40) fibrils and tau aggregates *in vivo* in humans.⁴⁵ Binding of FDDNP competes with chemically related antiphlogistic drugs naproxen and ibuprofen.⁴⁶ Another approach is based on histologic dyes that are known to bind to amyloid, such as thioflavin and congo red.^{47–50} Very promising data have been presented for the thioflavin-based compounds,⁵¹ especially for [*N*-methyl-¹¹C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole.⁵² The real-time biodistribution kinetics have been studied in transgenic mouse models of AD using multiphoton microscopy. Pittsburgh Compound-B entered the brain quickly and labeled amyloid deposits within minutes. The nonspecific binding was cleared rapidly, whereas specific labeling was prolonged.⁵³ Human data have also been presented, demonstrating accumulation in temporal cortex in AD.⁵⁴ Recent data in transgenic mice suggest that a relatively simple stilbene derivative, *N*-[¹¹C]methylamino-4'-hydroxystilbene, may also be useful as a PET imaging agent for mapping amyloid beta plaques.⁵⁵

Dementia with Lewy Bodies

Patients with dementia with lewy bodies (DLB) often clinically have fluctuating levels of attention and consciousness, optical hallucinations, and may develop the motor features of Parkinson's disease.^{56,57} Reduced FDG uptake is found very similar to AD, but also in the primary visual cortex, which is usually spared in AD.^{58–60} The impairment of glucose metabolism in the visual cortex may well be the correlate of the impairment of visual processing and visual hallucinations. Yet, the diagnostic reliability of the finding is not yet clear, and could potentially be confounded by reduced occipital FDG uptake secondary to severe vision impairment, for

example, caused by ocular diseases. Another characteristic finding is the reduction of 6-[¹⁸F]fluoro-L-DOPA (FDOPA) uptake in the putamen that was described in DLB^{61,62} but is absent in AD.⁶³

Frontotemporal Dementia

Frontotemporal dementia (FTD) is characterized clinically by leading changes in personality and behavior, such as apathy or disinhibition, whereas memory impairment may be absent or less prominent.⁶⁴ There are no unique histopathologic characteristics of FTD, which is the main manifestation of so-called Pick complex⁶⁵ which also includes primary progressive aphasia and semantic dementia. In principle, FTD is identified easily on FDG–PET scans by a distinct frontal or frontotemporal metabolic impairment.^{66,67} Apparently, mesial frontal metabolic impairment is most common, and can be found in nearly every case of FTD.⁶⁸ Very frequently, there is also prominent focal atrophy of the frontal and temporal lobe in one hemisphere, corresponding to a metabolic deficit that is also very asymmetric, is centered in the anterior pole of the temporal lobe and extends to other association areas. It seems that FTD can also be differentiated from corticobasal degeneration with predominant parietal metabolic reduction,⁶⁹ although histopathologic features may overlap.⁷⁰ Frontal metabolic impairment is also part of many other diseases and conditions, including progressive supranuclear palsy (in combination with midbrain impairment),⁷¹ spinocerebellar atrophy,⁷² and cocaine abuse.⁷³ Moderate frontal dysfunction and hypometabolism is also observed in many psychiatric disorders, and therefore cannot be regarded as a specific diagnostic feature.

Vascular Dementia

Diagnosis of vascular dementia (VD) is easily made in the case of multiple cortical infarcts (multiinfarct dementia), but may be a difficult issue in cases with severe microvascular changes but without major cortical infarcts. There is not yet a consensus about clinical criteria, and correspondence between existing criteria (e.g., ICD-10, DSM-IV, NINDS-AIREN, CAMDEX) is poor.^{74,75} Several studies suggested that a diffuse global reduction of cerebral glucose metabolism is a typical finding in VD, and that the degree of that reduction in association cortex is similar to that seen in AD.^{76,77} Thus, the contrast between metabolic impairment in association areas and preserved metabolism in primary areas (basal ganglia and cerebellum) that is typical for AD but not for VD, seems to provide some distinction with FDG–PET between these two types of dementia.⁷⁶

Creutzfeldt-Jakob Disease

Clinically, this disease is characterized by rapidly progressive dementia, often accompanied by insomnia, myoclonus, and other extrapyramidal disorders. In all cases reported so far, cerebral glucose metabolism was severely reduced in a multifocal fashion.^{78–82}

Movement Disorders

PD and Multiple System Atrophy

PD is a clinical diagnosis, and standard diagnostic procedures including CT and MRI mainly serve to exclude other diseases that may lead to Parkinsonism. Functional imaging with PET has the potential to demonstrate the disturbance of dopamine synthesis that is the hallmark of idiopathic Parkinson's disease (IPD), and thus allows confirmation of diagnosis.⁸³ This is of particular interest if clinical features are somewhat atypical, for example, with respect to an unusually early age of onset.

If symptoms are mild and clinically uncertain, a positive PET finding may serve to exclude psychogenic movement disorders, which may otherwise be difficult to discriminate from early IPD. It may also be difficult to differentiate clinically between monosymptomatic resting tremor, which probably is a subtype of IPD, and essential tremor, which is a different disease with better prognosis. As with all neurodegenerative disorders, clinical importance of that distinction is likely to increase as soon as specific drugs become available that could prevent progression.⁸⁴

If symptoms are severe and accompanied by features that are atypical in IPD, such as incontinence or cognitive impairment early during progression, pyramidal signs, ataxia, or lack of response to L-DOPA, distinction of IPD from multiple system atrophy and related disorders is required. Established clinical criteria for IPD have been demonstrated to be rather restrictive, and a recent comparison with neuropathologic diagnoses concluded IPD can present with a broader clinical picture of disease than previously thought acceptable.⁸⁵ Degeneration of dopaminergic neurons with reduction of their respective PET markers has been described in all diseases that cause parkinsonism, but the relative involvement of the rostral and caudal parts of the striatum (i.e., caudate vs. anterior and posterior putamen) provides some distinction between disease.

The most widely used PET tracer is PD FDOPA. In patients with IPD, striatal tracer uptake and retention is reduced, most strongly on the side opposite to the major motor signs.^{86,87} The posterior parts of the putamen are affected most and the heads of the caudate nuclei least, which corresponds to preferential degeneration of dopaminergic neurons in the caudal and mediolateral part

of the substantia nigra pars compacta.⁸⁸ This typical differential intrastriatal distribution of reduced uptake is often referred to as the “rostrocaudal gradient.”⁸⁹ The FDOPA uptake deficit in putamen is related to indices of motor function in IPD, such as clinical Hoehn and Yahr grades⁹⁰ and finger tapping.⁹¹ FDOPA uptake in the putamen is also reduced in monosymptomatic resting tremor, which seems to be the purest form of tremor-dominant PD.^{92,93} In contrast, dopaminergic neurons and dopamine transporters are intact in clinically similar essential tremor.⁹⁴ Essential tremor is clinically similar to tremor-dominant PD, but does not respond to L-DOPA, and usually does not progress to severe disability.

Distinction between IPD and other disorders with parkinsonian symptoms is more difficult based on FDOPA studies alone because many of these disorder are associated with some degree of impairment of FDOPA uptake.⁹⁵ The distinction is much better if indicators of postsynaptic receptors and neuronal function, such as C-11-raclopride or FDG, are included. Reduction of dopamine receptor binding and CMRglc in the putamen is not a feature of mild to moderate IPD, but is seen in multiple system atrophy and in diseases that lesion the basal ganglia.^{96–101} Thus, FDG–PET has a clear potential to improve the clinical distinction between these different diseases with Parkinson symptoms.^{95,102}

Most of the initial studies with FDOPA employed kinetic analysis of uptake curves with arterial blood samples including correction for plasma metabolites. It was shown that simplified models using occipital cortex as a reference tissue region do not provide accurate estimates of aromatic L-amino acid decarboxylase activity. Nevertheless, discriminant analyses indicated that simple estimates like the striatum-to-occipital ratio or the graphically derived unidirectional transport rate constant K_i with tissue reference^{103,104} separate normals from PD patients at least as accurately as estimates of striatal diethyldithiocarbamate activity based on plasma input function.^{105,106}

In most patients with IPD, glucose metabolism as measured with FDG is rather normal. There may be a tendency towards elevation in the putamen⁹⁰ and reduction in the mesial frontal cortex,¹⁰⁷ but these minor alterations rarely reach significance.¹⁰⁸ High putamen CMRglc is usually complementary to low FDOPA,¹⁰⁷ also with respect to the frequently observed hemispheric asymmetry. Parkinson tremor is associated with increased CMRglc in a metabolic network comprising the thalamus, pons, and premotor cortical regions.¹⁰⁹ The cerebellum also shows a tendency towards higher metabolism than normal that seems to be more closely related to akinesia and rigidity rather than to tremor.⁹³

With advancing IPD, hypometabolism in the frontal and temporo–parieto–occipital association cortices may

develop, very similar to that seen in AD. It is more frequently seen in patients who already developed autonomic failure.¹¹⁰ In contrast to AD, the reduction of CMRglc in association cortex is not generally associated with dementia or other cognitive impairment.^{21,111–114} Hemispheric asymmetry corresponds with asymmetry of putaminal FDOPA uptake and associated motor symptoms.¹¹⁵ Metabolic deficits tend to be more severe and more focused in temporoparietal cortex in demented patients.¹¹⁶ There is relatively little correlation with cognitive functions in nondemented patients.^{117,118} It has only been demonstrated that parietal-occipital hypometabolism is associated with mild impairment of memory and associative visual processing.¹¹⁹ Impaired CMRglc in temporo-parieto-occipital association the cortex in IPD may be related to the occurrence of hallucinations and psychosis.

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), also known as Steele-Richardson-Olszewski syndrome, is a mostly sporadic neurodegenerative disease with vertical gaze paresis (due to a supranuclear disorder in the midbrain that lends the name to the disease), a Parkinsonian movement and gait disorder with frequent and severe falls, apathy, and cognitive impairment. Neuropathologically it is characterized by pathologic tau deposits, similar to FTD, but mainly located in the midbrain.

CMRglc in PSP is reduced in the prefrontal association cortex, most strongly in its mesial part, including the anterior cingulate and orbitofrontal cortex, and in the midbrain.^{69,71,120–126} CMRglc may also be reduced in the striatum and thalamus. The abnormality in the midbrain is difficult to recognize on visual evaluation of FDG-PET images because the normal midbrain already has lower metabolism than the cortex and basal ganglia. Therefore, quantitative image analysis is recommended for detection of this diagnostic feature that distinguishes PSP from other disorders with frontal and striatal metabolic impairment.¹²⁷

Reduction of FDOPA uptake is relatively mild, and may be absent in early PSP, suggesting that parkinsonism in PSP may relate to dysfunction distal to the dopaminergic neurons.^{95,128–130} Dopamine reuptake sites are also reduced but, compared to IPD, reduction is relatively mild, and there is no anterior-posterior gradient of striatal impairment.^{131,132} Reduction of the caudate dopaminergic innervation similar to the putamen was also noted with biochemical methods in PSP, and may contribute to frontal cortex dysfunction and apathy.¹³³ There is also a reduction of D2 receptor binding capacity¹³⁴ that is even more pronounced in the caudate (24%) than in the putamen (9%).¹³⁵ Opioid receptor binding is reduced in most patients in the caudate and

putamen, whereas such reduction are less frequently seen in striatonigral degeneration and are absent in IPD.¹³⁶

Chorea

Chorea Huntington [Huntington's disease (HD)] is an autosomal dominant disorder with complete penetration, which leads to severe hyperkinesias, disability, dementia, and death, is associated with a severe and early reduction of CMRglc beginning in the caudate nucleus and also rapidly affecting the putamen. In later stages, when dementia develops, hypometabolism also extends to the thalamus and cortex.^{137–146} Yet, functional cortical activation, studied by a visuospatial task with fMRI, remains intact despite impairment of resting cortical CMRglc.¹⁴⁷ Thalamic hypometabolism was also noted as an early feature in the rigid juvenile form of HD,¹⁴⁸ and it correlates with dystonia in adults.¹⁴⁵ Significantly reduced caudate CMRglc was observed in asymptomatic gene carriers,^{149–153} preceding the development of atrophy. Yet, some researchers noted already subtle clinical abnormalities in at-risk subjects with reduced caudate CMRglc,¹⁵⁴ and with the development of reliable methods to detect the pathogenic trinucleotide expansion in the Huntington gene on chromosome 4, the interest in the use of PET for presymptomatic diagnosis has waned.

HD is associated with a striatal reduction of D1 and D2 receptors and of the dopamine transporter.^{155–160} PET results support the notion that the HD disease process is a function of trinucleotide length and age, and that the development of clinical signs and symptoms is associated with coronary angiography (CAG) repeat lengths greater than 35.5.¹⁶¹ Both striatal D1 and D2 dopamine receptors are lost in parallel from both the caudate and putamen in presymptomatic HD. Thus, dopamine receptor binding provides a sensitive means of detecting subclinical striatal dysfunction.¹⁶² In contrast, the FDOPA uptake remains largely normal.¹⁴⁰ D2 receptor and glucose metabolism binding in the caudate nucleus appears to be correlated with some cognitive tests.^{163,164}

Other choreatic diseases may be associated with striatal hypermetabolism instead of hypometabolism. This was seen as a reversible finding in Sydenham's chorea¹⁶⁵ and in chorea associated with primary antiphospholipid syndrome,¹⁶⁶ but not in some cases with chorea due to systemic lupus erythematosus.¹⁶⁷ Yet, hypoperfusion and hypometabolism in the striatum and other cerebral regions, more moderate but otherwise similar to HD, were observed in chorea-acanthocytosis.^{168,169} Benign hereditary chorea is associated with normal or moderately reduced striatal glucose consumption.^{170,171}

Ataxia

Classification of neurodegenerative ataxia was often revised in the past decades. With the recent rapid progress in molecular genetics, the hereditary ataxias are now usually classified according to the underlying mutations. Currently, more than 20 different types of autosomal dominant spinocerebellar ataxias have been identified. Some types include only few families of restricted geographic origin, others (e.g., type 1, 3, and 6) are more common and few cases have been studied with PET. Within genetic types, there may be substantial phenotypic variation. Since FDG–PET is closely linked to neuronal function, one would expect that it is probably more closely related to the symptoms (phenotype) than to the genotype. Often, widespread glucose hypometabolism similar to multiple system atrophy was also found, but findings may differ considerably between families and subjects.^{72,172–174} There may also be a reduction of FDOPA uptake in the putamen.^{175,176} Widespread cerebral reduction of glucose metabolism is also present in other ataxias due to systemic and metabolic disorders, including paraneoplastic syndromes¹⁷⁷ and alcoholism.¹⁷⁸

Brain Tumors

Brain tumors are major structural brain lesions, and therefore diagnosis usually relies primarily on the structural imaging modalities CT and MRI. Yet, an optimum clinical therapy cannot ignore functional aspects within brain tumors, such as proliferation rate and invasiveness, and those of surrounding and remote brain, such as the location of eloquent brain areas (responsible for language and motor function with irreversible impairment when damaged) and changes of functional brain organization induced by tumors. The interaction and balance between tumor and brain function is particularly delicate in gliomas, the most frequent type of primary malignant brain tumor, because of their invasive growth, and the lack of curative measures for most of them. Thus, all therapeutic interventions must preserve or improve brain function, rather than sacrificing it for some tumor treatment of limited efficacy. On the other hand, tumor treatment should be as aggressive and effective as possible to save years of life. This delicate balance requires detailed information not only on tumor location and extent but also on the functional status of the tumor and surrounding brain that can be provided by PET and has to be evaluated carefully in each individual patient. Thus, there is a definitive role for PET for treatment planning, and it is also obvious that PET cannot be evaluated in isolation for that purpose but must be coregistered with structural imaging. Another major clinical issue is management of recurrent

of residual tumor because it is often hard to differentiate from unspecific changes secondary to therapy, and because efficacy of treatment is often unknown. With improvement of diagnosis and monitoring of therapy, PET can substantially improve that situation.

FDG and Tumor Grading

PET contributes to grading of the malignancy of brain tumors, and thereby selecting the most appropriate type of therapy. FDG uptake is related to histologic tumor grade^{179,180} and to survival in primary and recurrent gliomas.^{181,182} FDG uptake in low-grade gliomas (mostly of grade 2 in adults) is usually close to that of normal white matter, whereas most grade 3 gliomas have FDG uptake similar to or even exceeding that of normal gray matter. Untreated glioblastomas, as the most malignant gliomas (grade 4), usually also show high uptake, which may be inhomogeneous due to microscopic and macroscopic necroses that are typical for this tumor type. After treatment and at a late stage areas with low metabolism may prevail. Cutoff levels of 1.5 for tumor-to-white matter FDG uptake ratio and 0.6 for tumor-to-cortex ratio are useful in the differentiation of low-grade from high-grade gliomas.¹⁸³ The sensitivity and specificity to detect high grade gliomas by these thresholds have been determined as 94% and 77%, respectively.

High and very high FDG uptake is also seen in malignant lymphoma,^{184,185} and may be used to differentiate it from toxoplasmosis in patients with acquired immunodeficiency syndrome (AIDS).¹⁸⁶ Results are mixed for metastases, which may show high FDG uptake, but sensitivity of MRI is much better and malignancy is already clinically evident.¹⁸⁷ Pilocytic astrocytomas are a rare type of astrocytoma, mainly occurring in childhood with histologic grade 1. Thus, they are the most benign gliomas, and they can be cured if complete resection is possible. Yet, they may exhibit radiologic signs of malignancy without being malignant, and also have variable glucose metabolism without clear relation to prognosis.^{188,189}

Meningiomas are generally grade 1 tumors, but FDG uptake is variable, and can provide an index of tumor aggressivity and probability of recurrence.¹⁹⁰ Similar observations have been made in a small series of cranial neuromas.¹⁹¹ High FDG uptake has also been observed in benign pituitary adenomas, including microadenomas.^{192,193} Prolactinomas¹⁹⁴ and granular cell tumors of pituitary and hypothalamus¹⁹⁵ may appear hypometabolic with FDG.

The main limitation of FDG for clinical studies of brain tumors is the high glucose consumption of normal gray matter (approximately 45 $\mu\text{mol}/100\text{ g}/\text{min}$) that may be in the same range as malignant tumors. Thus, even malignant tumors may be missed if surrounded by intact gray matter. Metabolism of gliomas should be

compared to normal white matter, which has much lower glucose consumption, and even most low-grade gliomas have slightly higher FDG uptake. Yet, they may be difficult to delineate and, compared to high gray matter FDG uptake, they will appear as inactive. Thus, evaluation of glucose consumption in brain tumors can only be done reliably if the location of the tumor is accurately known, best by digital image coregistration with MRI. It should also be kept in mind that high FDG uptake is not specific for brain tumors, but may also be seen in florid inflammatory lesions (e.g., sarcoidosis, acute demyelinating myelitis), focal epilepsy, and recent ischemic infarcts with nonoxidative glycolysis.

Amino Acid Tracers

Most brain tumors show an increased uptake of amino acids that is probably due to increased carrier-mediated transport at the blood–brain barrier (BBB). Thus, increased uptake is also seen in most low-grade gliomas in the absence of BBB damage, which is a substantial advantage over CT, MRI, and FDG–PET.^{196–198} For many years, ¹¹C-methionine (MET) has been used most widely for brain tumor imaging, but other ¹¹C-labeled amino acids and F-18-labeled compounds F-18-fluoro-tyrosine, O-(2-[F-18]fluoroethyl)-L-tyrosine, FDOPA, and 3-O-Methyl-6-[(18)F]fluoro-L-DOPA also have given very similar results. In contrast-enhancing gliomas, the spatial extent of increased MET uptake is larger than that of contrast enhancement,^{199,200} and may include not only solid tumor but also surrounding tumor infiltration zone. There is a close correlation with tumor vessel density.²⁰¹

In gliomas, amino acid uptake is higher in high-grade tumors than in low-grade tumors,^{196,202–204} and it is also associated with prognosis.²⁰⁵ It has been demonstrated that the most metabolically active tumor part on PET (FDG or amino acid) indicates the most informative location for taking a biopsy,^{206–208} which otherwise could be misleading if the most malignant part of the tumor was missed. There are also differences of uptake depending on tumor type: oligodendrogliomas tend to have higher uptake than astrocytomas of same histologic grade, despite being clinically somewhat less aggressive.^{196,204,209} MET uptake is increased in other malignant brain tumors, including lymphoma,^{210,211} metastases, and meningiosis.²¹² Yet, benign meningiomas and hemangioblastomas also have high amino acid uptake (above 2.5-fold of normal tissue), and moderately increased uptake is also seen in neuromas (typically one- to two-fold).²¹³ Thus, tumor grading with amino acid PET is possible only if the histologic tumor type is known.

A relation between amino acid uptake and survival was observed in gliomas,²¹⁴ even within groups of same

histologic grade²⁰⁵ and in childhood brain tumors.²¹⁵ In a large series of 89 low-grade gliomas, methionine uptake was a significant survival factor among patients with astrocytomas and with oligodendrogliomas.²¹⁶ The results suggested that MET uptake should be evaluated with respect to guidance of therapy because tumor resection was a favorable prognostic factor in patients with high methionine uptake but not in patients with low uptake.

Amino acid PET may also offer some help for differentiation between tumor and chronic nontumor lesions. At a threshold of 1.47-fold uptake of C-11-methionine in tumors compared to the contralateral brain, this distinction was accurate in 79% in a large clinical series,²⁰⁴ and a similar accuracy has been observed in a surgical series.²¹⁷ Yet, one must keep in mind that about 20% of low-grade gliomas remain below this threshold, and some acute ischemic infarcts, hematomas, and florid inflammatory lesions (e.g., abscesses) may show high uptake above that threshold.^{218–221} High amino acid uptake clearly is not specific for tumors.

Amino acids also accumulate in the normal pituitary. This high normal uptake is difficult to distinguish from pituitary tumors, which show increased uptake.^{222,223}

In principle, labeled nucleosides as indicators of proliferation apparently should deliver the information that comes closest to histologic grading. In initial brain tumor studies, 2-[C-11]thymidine showed slightly increased uptake compared to the normal brain (tumor-to-cortex ratio > or = 1.2), but no correlation was found between thymidine uptake and tumor grade. There is high background due to labeled metabolites, in particular C-11-CO², and validation is not complete and hampered by complex metabolism.²²⁴ More recently, 3'-[¹⁸F]fluoro-3'-deoxythymidine (FLT) has been introduced²²⁵ with much higher tumor-to-brain ratios (in the range of 3 to 10).²²⁶ There is much less confounding metabolism, and validation of FLT as a proliferation marker is already available for nonbrain tumors.²²⁷

Recurrent Tumors

Detection of recurrent tumor is an important issue because growth of recurrent tumor will lead to increase of symptoms and ultimate death of the patient. FDG–PET has been used successfully for that purpose in high-grade tumors^{228–230} and for detection of malignant progression in low-grade gliomas.²³¹ Differentiation from necrosis is a difficult issue in gliomas (of grade 2 to grade 4) because there are nearly always residual tumor cells, even in absence of solid tumor, and there is very often necrosis, either spontaneous during tumor progression or due to therapy. Very often, several of these different states coexist at the same time in different

parts of a lesion,²³² and therefore the question “recurrent tumor or necrosis” is an oversimplification.^{233,234} On the background of these general problems, FDG–PET has been used successfully to differentiate between recurrent tumor and necrosis,^{235–237} but there is a considerable degree of overlap.²³⁸

Although few data are available for MET compared to FDG, there seems to be a distinct advantage in terms of sensitivity (up to 85%) and specificity (up to 93%),^{196,204,239–241} that has also been demonstrated in an experimental study.²⁴² MET uptake is substantially lower or absent in necrotic brain areas, but mildly increased uptake (up to 1.5-fold of contralateral brain) may be present, which is probably due to passive diffusion of the tracer across the damaged BBB in necrosis. Compared to coregistered contrast-enhanced MRI, foci of highest methionine uptake are often found not in coincidence but in vicinity to contrast-enhancing lesions. Case reports have shown that this may indicate an active tumor with high MET uptake in the vicinity of necrosis with contrast enhancement.²⁴³

Monitoring of Therapy

Monitoring of treatment efficacy in brain tumors, and in particular in gliomas, is an important and closely related issue. Many tumors do not respond, and responses are often incomplete. Continuation of ineffective chemotherapy has many side effects, including possible cumulative bone marrow toxicity, and could be avoided by early detection of inefficacy. Similarly, dose escalation in radiotherapy beyond standard tumor doses involves an increased risk of side effects, and may only be warranted if viable tumor tissue is still present after standard therapy. That approach has successfully been implemented in a pilot study with FDG–PET.²⁴⁴ In an experimental study, a reduction of glucose consumption, but not of protein synthesis, was seen after seven days of effective chemotherapy in correlation with reduced DNA synthesis.²⁴⁵ This finding corresponds with clinical studies in brain tumors²⁴⁶ and in extracerebral tumors. Yet, effective chemotherapy and irradiation may lead initially to a transient increase of FDG uptake,^{247–249} and thus the timing of these studies is crucial. Reduction of FDG uptake has also been observed after radiotherapy,²⁵⁰ but in an experimental study FDG tumor uptake remained high six days after irradiation, even in the case of complete remission.²⁴² In the same study a significant decrease of thymidine and MET uptake was seen, suggesting that these tracers are better suited for monitoring than FDG. Clinically, a reduction of MET uptake was observed after interstitial irradiation (brachytherapy)²⁵¹ and after successful chemotherapy of oligodendroglioma.²⁵² In another study there was a correlation between high pretreatment

uptake of MET and reduction in MET uptake in response to radiotherapy.²⁵³ An interesting observation was reported in lymphoma, where MET uptake persisted (corresponding to the usual poor clinical outcome) after radiation therapy, whereas contrast enhancement rapidly disappeared.²¹¹ MET–PET has an obvious potential to monitor the efficacy of therapy of glioma that should be studied in larger prospective series.

Activation Studies

Brain tumors close to eloquent brain areas present particular difficulties for surgical treatment. Intraoperative location of critical motor and language function can be achieved by electrophysiologic methods, but in the case of language surgery must be performed in local anesthesia that is cumbersome. Exact presurgical location is therefore an important clinical goal. Infiltrative glioma growth poses a particular challenge for tailoring of resections, because infiltrated tissue may still be functional.²⁵⁴ Because even total resection of most gliomas cannot prevent tumor recurrence, emphasis must be put on preservation of function. Compared to commonly used fMRI, PET provides a more physiologically specific and robust signal, and is therefore a viable alternative to fMRI.^{255–258} O-15-water is the most frequently used CBF tracer for this purpose, typically allowing up to 12 CBF measurements. Motor and language tasks can also be performed during the first 30 minutes after injection of FDG to record functional changes of local CMRGlC. FDG activation studies are performed either in a separate session from the resting reference study, and there have also been suggestions for double-injection protocols to combine activation and resting condition in one session.²⁵⁹ Coregistration and fusion image display with 3-D MRI is necessary for accurate anatomic localization,^{260–262} and integration into intraoperative neuronavigation is possible.²⁶³

Location of functionally activated areas may be altered in brain tumor patients due to several effects. First, there may be a mass effect that displaces motor cortex, where the functional activation can be found at the anatomically expected location. Thus, it is important to have coregistered MRI scans and image fusion for direct comparison, although accurate anatomical localization may still be difficult if the sulci cannot longer be identified due to the mass effect and edema. Direct effects of the tumor on motor or language cortex usually lead to reduced activation, often associated with impaired function. Yet, there have also been few instances of false positive activations, in particular, in the vicinity of hyperperfused lesions.^{264,265} Functional activations may occur at atypical anatomic locations, apparently representing reorganization of functional networks.^{266,267} The potential for reorganization is greater during early

development in childhood than later in life.²⁶⁸ The implications of these changes seen in activation studies for location of critical brain functions require further study. Not all areas that are activated during functional tasks are essential for task performance in the sense that a lesion would severely impair function, but may also include areas that are secondarily activated during task performance.

The main clinical issue usually is localization of motor cortex (arm and leg). Useful activation tasks are repetitive finger tapping and foot movements that lead to reliable activations centered in the respective areas of contralateral motor cortex in healthy subjects.^{269,270} There are also regular activations of the supplementary motor cortex and of the cerebellum, more on the ipsilateral side.^{271,272} In patients with brain tumors, displacement of functionally activated areas dorsoventral dimension of the precentral gyrus that exceed those explained by anatomic displacement due to mass effect have been observed.²⁷³ A comparison of PET findings with intraoperative electric stimulation and transcranial brain stimulation found overlapping results were obtained in 31 of 49 studies, and neighboring location of motor areas in 14.²⁵⁵

The capacity to understand and to speak language is strictly lateralized in most subjects to the dominant hemisphere. With few exceptions, this is the left hemisphere in right-handers, whereas in left-handers language may be represented in either hemisphere or even bilaterally.²⁷⁴ In addition to language dominance, details of the anatomic localization of sensory and motor language areas (Wernicke's and Broca's), which may vary unpredictably even in normal individuals,²⁷⁵⁻²⁷⁷ are also of interest for surgical planning in patients with tumors in the inferior frontal and temporoparietal association areas. Wada testing has been used as a gold standard for determination of language dominance, and PET activation studies have been validated against that gold standard in several studies.^{256,278-280} The more difficult question of whether the extent of language activation areas can provide guidance for tailoring resections has also been addressed.^{257,281,282} Correspondence with intraoperative electrical stimulation was highly significant, although activated areas tended to include some sites where there was no language disturbance with electrical stimulation, and there were also a few sites with electrical language disturbance but no significant preoperative activation effect. Thus, language activation studies are helpful for planning of surgery, but currently cannot completely replace intraoperative monitoring.

A considerable variety of language activation paradigms have been tried for localization of language function.²⁸³⁻²⁸⁶ Automated speech tasks are not very useful to localize language areas.²⁸⁷ Passive listening activates temporal language areas in the superior temporal

cortex, but that is not always significant in individual subjects. More active semantic or language production tasks (e.g., the generation of semantically related verbs in response to presentation of nouns) provide more clearly lateralized activations, in particular, in the inferior frontal cortex of the dominant hemisphere,²⁸⁸ and in most instances also in the superior temporal cortex, anterior cingulate cortex, and an adjacent supplementary language area, and in the cerebellum (predominantly contralateral to the dominant cerebral hemisphere). An essential advantage of PET on the clinical application of language activation studies is that active speaking during language production tasks does not induce technical artifacts (as it is common with fMRI), and therefore, direct monitoring of task performance is possible even in functionally impaired subjects.

Similar to motor function, there is considerable reorganization of language in patients with brain tumors in the dominant hemisphere.²⁶⁶ This includes increased activation of secondary language sites and a shift to the right side, which may be present already in subjects with lesions but without aphasia. Lesion-induced plasticity is larger in childhood than in adults,^{289,290} and even in adults the rightward shift of language activation tends to be stronger as a consequence of early compared to late lesions.²⁹¹ It is not yet clear whether such apparent plasticity is sufficient to support language function to an extent that would allow surgical resections of primary language areas that are partially damaged due to tumor infiltration.

Cerebrovascular Disease

Acute cerebrovascular disease, the cause of the clinical syndrome of stroke, is the most common neurologic disorder, with an annual incidence of 150 to 200 per 100,000 in Western industrialized countries. There are three main etiologic categories: ischemic stroke (70% to 80%), spontaneous intracerebral hematoma (10% to 20%), and subarachnoid hemorrhage (5% to 10%). The most direct functional measurements of oxygen supply and consumption, which is the most critical parameter in acute ischemic stroke, have been made with ¹⁵O-PET. Functional effects on normal brain tissue have mostly been studied by measurement of CBF or CMRglc.

Ischemic Stroke

The cause of ischemic stroke is a severe and usually sudden decrease of CBF below a level of about 15 mL/100 g/min (a decline by about two out of three from its normal average level of about 50 mL/100 g/min in the human brain). It is mostly due to atherothrombotic or embolic occlusion of a supplying artery. Severity and

duration of that insult are the major determinants of tissue fate, whether infarction develops or whether there is recovery.²⁹² In most cases there is a central core of dense ischemia, where residual flow is very low and the time to infarction consequently short, which is surrounded by an area of graded and less severe flow disturbance where function is impaired but morphology preserved for an ill-defined period. This area—the penumbra—has the potential for functional recovery provided that local blood flow can be reestablished at a sufficient level and within a certain time window.²⁹³ This is clinically possible by intravenous or intraarterial thrombolysis,²⁹⁴ but at the risk of intracranial bleeding if the complete infarct is already too large. Therefore, functional imaging currently has the main goal to identify exactly the state and extent of penumbra and complete infarct to better select and improve therapeutic options.

Several studies have indicated that necrosis is present in tissue whose cerebral metabolic rate for oxygen (CMRO²) is below 65 $\mu\text{mol}/100\text{ g}/\text{min}$ ($= 1.5\text{ mL}/100\text{ g}/\text{min}$) or whose CBF is below 12 $\text{mL}/100\text{ g}/\text{min}$.^{295,296} Voxels exhibiting initial flow rates between 10 and 22 $\text{mL}/100\text{ g}/\text{min}$ were found in the area of the final cortical–subcortical infarcts.²⁹⁷ On the other hand, voxels with the same penumbral criteria escaped infarction and the minimum CBF of salvageable tissue was found to be 7 $\text{mL}/100\text{ g}/\text{min}$.²⁹⁸ That means that these thresholds are variable, depending on the time of measurement after the attack, and brain regions with CBF between 12 and 22 $\text{mL}/100\text{ g}/\text{min}$ may be considered as the penumbra zone.²⁹⁹

Metabolically, acute ischemic stroke is characterized by a mismatch of relatively preserved oxygen metabolism but severely reduced CBF. This condition, which is often called misery perfusion, implies that the blood flow is insufficient to meet the energy metabolic demand for oxygen and substrate of still viable tissue.^{296,300–302} In that situation oxygen metabolism is maintained by an increased oxygen extraction fraction (OEF). It is indicative of the precarious condition of the tissue, but it also holds promise for a full recovery. Yet, in most patients a slow continuous decline of CMRO² is seen in the borderzone of an ischemic infarct.^{298,302} A few studies suggested that it could be prevented by therapeutic intervention.^{300,303}

Ligands to central benzodiazepine receptors, such as ¹¹C-flumazenil (FMZ), can be used as markers of neuronal integrity since they bind to the widely distributed GABA receptors of intact cortical neurons.³⁰⁴ The validity of this concept has been demonstrated in cat MCA occlusion by comparing the FMZ binding to quantitative assessment of flow and energy metabolism.³⁰⁵ It has also been applied to patients with acute ischemic stroke, demonstrating a high correlation with development of eventual infarction.^{306,307}

After an acute ischemic event arterial vessels may be damaged, and eventual reperfusion may then lead to postischemic hyperperfusion.^{308–310} This hyperperfusion may develop in viable tissue, where it is often mild and does not prevent good outcome,^{311,312} but it may also occur within ischemic infarcts, where it is called “luxury perfusion.”³¹³ This phenomenon is a major reason for the inability of sole CBF measurements to predict tissue outcome reliably.

CMRglc is mostly reduced in acute ischemic infarcts,^{314–316} but to a lesser degree than CMRO². In a few cases—less than 10% of patients with acute and subacute infarcts—CMRglc is increased in some parts of the infarct to levels above that found in normal gray matter. This phenomenon is believed to indicate nonoxidative glycolysis, which may lead to intracellular accumulation of lactate.³¹⁷ Intracellular pH in most infarcts shows an alkaline shift that may be correlated with the occurrence of perfusion in excess of metabolic demand. It could also enhance the glycolysis rate or could represent mainly the pH_i of phagocytic cells that use aerobic glycolysis to synthesize hydrogen peroxide.^{318,319}

Hemorrhage

In patients with intracerebral hemorrhage, PET can reveal the effects of the space-occupying lesion on CBF and metabolism, and thereby provide information on the functional state of the surrounding tissue and on the prospects of recovery. The hematomas present themselves as defects of a normal tracer uptake.³²⁰ Large hematomas may lead to increased OEF in the periphery, probably due to their mass effect that demands evacuation.^{321–323} Yet, in another study, only reduction of OEF was seen in the periphery of intracerebral hematomas.³²⁴ The inflammatory issue reaction during resorption of an intracerebral hematoma may lead to moderate focal increases of ¹¹C-methionine uptake.^{218,325}

Subarachnoid hemorrhage may lead to severe cerebral vasospasm, which may lead to ischemic infarcts. Good estimates of this risk are required for optimum timing of angiography and surgery (clipping of the aneurysm). In patients with postoperative vasospasm generalized impairment of oxygen metabolism with a reduced tissue oxygen supply, even in the apparently normal cortex, and additional impairment of regional perfusion in the territory of vasospasm were observed.³²⁶ The generalized reduction of CMRO² is thought to be due to the initial aneurysm rupture.^{327,328}

Remote Effects (Diaschisis)

Alterations of metabolism and blood flow in acute stroke are not limited to the infarct or hemorrhage and its

immediate surroundings, but there are also remote reductions that are probably largely due to neuronal inactivation (diaschisis).³²⁹ The most obvious case is crossed contralateral cerebellar diaschisis, which is probably due to inactivation of cortico–ponto–cerebellar pathways.^{330–338} It occurs within hours of supratentorial ischemic insults,^{339,340} is most frequently seen after basal ganglia, frontal, and parietal lesions,³⁴¹ may persist over a long time with eventual cerebellar atrophy, but usually lacks major correlates in neurologic functional impairment.^{342,343} Contralateral cerebellar diaschisis associated with hemiataxia was demonstrated in few patients with thalamic lesions, and it was presumed to result from retrograde deactivation of the cerebellar hemisphere via the dentate–rubro–thalamic pathway.³⁴⁴ The reverse, supratentorial diaschisis after cerebellar infarct has been seen only rarely.³⁴⁵ A study with ¹¹C-flumazenil suggested that reorganization of GABA-mediated mechanisms and glucose metabolism in cerebellum following cortical injury differs with size of lesion and age at the time of injury.³⁴⁶

Cortical diaschisis is particularly prominent with thalamic infarcts, which often lead to pronounced thalamocortical diaschisis with corresponding cognitive deficits.^{347–351} One may distinguish between intrahemispheric diaschisis,³⁵² where noninfarcted gray matter structures in the same hemisphere are functionally impaired, and transhemispheric or transcortical diaschisis with impairment of the contralateral hemisphere.^{353,354} Intrahemispheric diaschisis is a very frequent finding that has been noted already in the very early studies, often can be related to functional deficits, and probably plays an important role in functional recovery.^{314,355–359} It is most obvious with striatal infarcts, but in these cases that often represent incomplete infarcts due to temporary occlusion of the middle cerebral artery there may also be a substantial contribution of diffuse ischemic cortical damage. Even small lacunar striatocapsular infarcts can be recognized with PET by their functional effects.³⁶⁰

Chronic Hemodynamic Impairment

Chronic perfusion disturbance due to arterial vascular disease is a precarious condition necessitating vascular surgery in selected cases. Patients with a history of transient ischemic attacks, but with normal clinical and CT examination, usually have CBF values greater than 22 mL/100 g/min.³⁶¹ The distinct focal reductions in CBF and CMRglc found in many patients after transient ischemic attacks often correspond to the location of the clinical deficits.³²⁰ They are thought to be the result of small areas of embolic infarction not detected by morphologic imaging or as areas of selective neuronal loss without gross infarction.

Occlusion or high-grade stenoses of major arteries may reduce hemodynamic reserve capacity.³⁶² In its mildest stage, CBF is maintained within normal range by peripheral vasodilatation, which is reflected by an increased cerebral blood volume (CBV). Thus, the ratio CBF/CBV is decreased and its inverse, which is closely related to the mean transit time of intravascular indicators as used with dynamic CT and MRI, is increased. When the perfusion reserve is exhausted (i.e., at maximal vasodilatation), any decrease in arterial input pressure produces a proportional decrease in both CBF and the CBF/CBV ratio. In this condition of hemodynamic decompensation, the brain must draw on the oxygen carriage reserve to prevent energy failure and loss of function, as evidenced by an increase in the OEF from the normal 40% to 50% up to 85%.^{361,362} Patients with low CBF/CBV and submaximal elevations of OEF represent 10% to 15% of the patients with cervical occlusive disease;³⁶² they exhibit the most advanced atherosclerotic lesions, and they carry a high risk of recurrent stroke.³⁶³ However, the relation between CBF/CBV ratios and OEF is rather variable, and both are needed to provide complete information on the severity of hemodynamic impairment and risk of stroke.^{364–366}

Brain Function and Recovery After Stroke

Despite very limited structural recovery, the brain has a large potential for functional recovery by reorganization.³⁶⁷ The potential for rehabilitation may be limited by several global factors, such as age and microvascular angiopathy, that affect basically the whole brain. These may be very strong factors that are evident from many clinical studies, and they are also reflected in reduced glucose metabolism already at a resting state.³⁶⁸ The potential for recovery depends is large for lesions acquired during early life, when even hemispherectomy is often followed by good recovery of motor and language function.³⁶⁹ Reorganization may be mediated by compensatory functional changes in corresponding cortical areas of the nonaffected hemisphere, including the ipsilateral corticospinal pathway. Functional imaging studies suggest that metabolic recovery and functional plasticity in remaining subcortical structures of the injured hemisphere may also play an important role.^{369,370} After childhood has passed, the potential for recovery is reduced. Yet, it remains unclear whether there is a continuing influence of age beyond the limitations imposed by age-related multimorbidity on functional recovery after stroke.³⁷¹

Aphasia is a severely incapacitating symptom of stroke, and is a main cause of disability. Most studies have been performed in right-handed individuals with language dominance in the left hemisphere. The left temporoparietal region, in particular the angular gyrus,

supramarginal gyrus, and lateral and transverse superior temporal gyrus, are most frequently and consistently impaired, and the degree of impairment is related to aphasia severity.^{372,373} In contrast, metabolic impairment of subcortical structures is related to mainly language fluency and other behavioral aspects, but not to aphasia severity.³⁷⁴ In patients with aphasia due to purely subcortical strokes one regularly finds deactivation of temporoparietal cortex that probably is responsible for the aphasic symptoms.³⁷⁵ Metabolic disturbance in the left temporoparietal cortex is related to outcome of aphasia.³⁷⁶ Investigations in the subacute state after stroke showed a highly significant correlation with language performance assessed at follow-up after two years. The receptive language disorder correlated with CMRglc in the left temporal cortex and word fluency correlated with CMRglc in the left prefrontal cortex.³⁷⁷ In activation studies recovery was also associated with the ability to activate the left superior temporal gyrus.^{378–380} These results indicate that the functional disturbance as measured by CMRglc in speech-relevant brain regions of the dominant hemisphere early after stroke is predictive of the eventual outcome of aphasia. Facilitation of this activation has been demonstrated after treatment with piracetam.³⁸¹ The results also suggest that even limited salvage of peri-infarct tissue with acute stroke treatments will have an important impact on the rehabilitation of cognitive functions.

The wider language network is not confined to the dominant hemisphere. The role of the right hemisphere after ischemic infarcts of language areas in the left hemisphere has been addressed in several studies. Generally, more right hemispheric activations were seen in the subacute phase of an infarct with language activation than in normals with the same tasks.^{382,383} Language recovery in the first months after aphasia onset was associated with regression of functional depression (diaschisis) in structurally unaffected regions, in particular in the right hemisphere.³⁵⁷ Training-induced improvement in verbal comprehension in some aphasia patients was associated with activation of the posterior part of the right superior temporal gyrus and of the left precuneus.³⁸⁴ Thus, there is ample evidence that the brain recruits right-hemispheric regions for speech processing, when the left-hemispheric centers are impaired. Yet, outcome studies revealed that this strategy is significantly less effective than the repair of the original speech-relevant network in adults.³⁸⁵ Effectiveness of right hemispheric compensation appears to be larger in childhood.^{289,291}

Capsular infarcts or hematomas are a common reason for lesions to motor fibers with contralateral hemiparesis, but with intact motor cortex. Patients with such lesions usually show activation of sensorimotor and premotor cortex to the same extent as normal subjects.³⁸⁶

Even the imagination of such movements may lead to substantial activation of motor cortex. Tactile exploration of shapes with the paretic hand after subcortical infarction led to large activations in contralateral motor and sensory hand cortex.³⁸⁷ These activations were also similar to those observed in normal subjects with the same task. In a study of six patients with capsular or pontine infarcts, passive movements of the paretic arm also led to activation of contralateral sensorimotor cortex.³⁸⁸ With infarcts of motor cortex, the extent and intensity of activation obviously depends the site and extent of the lesion.

Frequently, activations of ancillary motor areas, such as ipsilesional premotor cortex activation, are observed.^{386,389} Secondary motor and frontoparietal non-motor cortices were more activated in patients with lesion onset before age 4 than after age 10, suggesting a greater potential for reorganization during early development than later in life.²⁶⁸ Learning new movements also increases CBF in SMA and premotor cortex in normal subjects.³⁹⁰ Learning-associated activations often also included sensorimotor and parietal cortex, basal ganglia, and cerebellum. Large interindividual variability has been noted,³⁹¹ which may be due to different learning strategies.³⁹² Thus, activation of ancillary motor areas after stroke could reflect a learning effect that could contribute to rehabilitation.

In normals and for the unaffected hand in stroke patients, only little activation of the ipsilateral motor cortex is seen during finger movement. It is a consistent finding in several studies that ipsilateral activation of motor cortex is stronger for movements of the paretic fingers after recovery from stroke.^{387,393–396} These data can be interpreted as evidence for stronger activity of the small noncrossing part of the corticospinal tract after lesion to the crossing fibers or neurons.

It is not clear whether increased activity in the ipsilateral motor cortex contributes to functional recovery in adults.^{389,397,398} Nonrecovered hemiplegic patients showed stronger activations ipsilateral and contralateral during passive movements than normal controls.³⁸⁸ In a small series, ipsilateral activation was only seen in the most severely impaired subject.³⁹⁹ In a study of resting CMRO₂, there was even a slight decline in the unaffected hemisphere during early recovery phase after stroke.⁴⁰⁰ It was not related to neurologic recovery, and was interpreted as a possible consequence of transcallosal fiber degeneration.

The thalamus is an important relay station for sensory afferences to the cortex, and it is also involved in the extrapyramidal motor system. A reduction of ipsilateral thalamic CMRglc at rest is often seen after hemispheric stroke,³⁴¹ and is associated with poor motor recovery.⁴⁰¹ By multiple regression and discriminant analysis Azari et al.⁴⁰² found a close relation of CMRglc between bilateral

SMA, ipsilateral thalamus, and contralateral cerebellum in recovered patients, suggesting a stronger functional association of these structures than in normals or nonrecovered patients. In a related study, activation of a similar network including the bilateral occipital and bifrontal cortex and cerebellum, contralesional cingulate, hippocampus, and thalamus was statistically associated with recovery of motor function.³⁵⁸

Epilepsy

Current clinical indications for PET in epilepsy are primarily seen in patients with focal epilepsy, which is refractory to medical treatment and considered for surgical therapy. Search of focal abnormalities in suspected focal epilepsy by PET is indicated if less expensive methods failed⁴⁰³ and for localization of eloquent cortex in critical regions.^{404,405}

The main findings with FDG–PET in epileptic foci have been described already in 1980.⁴⁰⁶ In the interictal state, there is a reduction of local glucose metabolism (CMRglc) and an associated reduction of local CBF. Glucose metabolism (and CBF) is focally increased during focal seizures, and globally increased during generalized absence seizures.⁴⁰⁷ These basic findings have been replicated because then many times and were compared to clinical, electrophysiologic, and other imaging findings.

Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most frequent type of focal epilepsy that is refractory to medical treatment. The main finding with FDG–PET is interictal focal hypometabolism in the mesial temporal lobe, usually extending into the temporopolar and temporolateral neocortex. Initial studies of TLE suggested that focal interictal hypometabolism is related to the severity of the pathologic lesion⁴⁰⁸ and with duration of epilepsy.⁴⁰⁹ If, in accordance with the EEG findings, it is a reliable indicator of the side of abnormality, and thus provides important information for planning of surgery.^{410,411} Yet, the size of the hypometabolic zone is generally much larger than the area of pathologic involvement.^{408,412} It usually extends into the temporolateral cortex,⁴¹³ whereas the pathologic lesions (most frequently mesial temporal sclerosis, but also heterotopias or low-grade tumors) mainly are located in the mesial temporal cortex, preferentially in the hippocampus. Patients with temporolateral impairment only and absence of temporomesial hypometabolism, however, mostly have their seizure origin in the lateral temporal lobe.⁴¹⁴

The degree of left temporal hypometabolism has been correlated with impairment of verbal memory.⁴¹⁵ A

pathophysiologic correlate of temporomesial reduction of CMRglc may be a reduced glucose-oxidation rate of the CA3 pyramidal subfields.⁴¹⁶ A coupled reduction of glucose metabolism and glutamate cycling was also demonstrated in epileptic lesions with FDG–PET and proton MRS,⁴¹⁷ and could also play a role in the pathophysiology of focal epilepsy. Yet, reductions in FDG are not correlated with those of *N*-acetyl-aspartate in MRS.⁴¹⁸ Pharmacologic activation of GABA-A receptors may partially reverse glucose hypometabolism.⁴¹⁹ An alteration of BBB GLUT1 glucose transporter activity in epileptogenic cortex could also contribute to reduced FDG uptake.⁴²⁰ The frequency of interictal spikes in EEG does not generally show a relation to focal CMRglc changes, although there has been a case report of an increase of CMRglc and CBF that was associated with interictal spiking.⁴²¹ Most studies found that the degree of focal hypometabolism does not parallel the severity of hippocampal atrophy⁴²² and hippocampal neuronal loss.⁴²³ Severe neocortical metabolic impairment may be due to microscopic cortical dysplasia.⁴²⁴

Hypometabolism may extend also to the insular cortex, whereby the anterior part of the insular cortex may be involved in emotional symptoms and the posterior insular cortex may be involved in somesthetic symptoms.⁴²⁵ Ictal dystonic posturing in TLE is associated with hypometabolism in the striatal region.⁴²⁶ Generally, the area of reduced CMRglc is regarded as a functional deficit zone rather than the epileptogenic zone.^{427–429} A correlative study with hippocampal cell density indicated that hippocampal cell loss results in decreased efferent synaptic activity to the thalamus and basal ganglia, causing decreased neuronal activity in these remote structures with consequent hypometabolism.⁴³⁰ Use of functional activation has been suggested to differentiate between areas with local synaptic dysfunction that are potentially epileptogenic and remote hypometabolism due to deafferentation.^{431–433}

Extratemporal cortical hypometabolism outside the seizure focus, in particular hypometabolism in the contralateral cerebral cortex, may be associated with a poorer postoperative seizure outcome in TLE, and may represent underlying pathology that is potentially epileptogenic.⁴³⁴ Bilateral temporal hypometabolism is typically present in approximately 10% of patients with TLE. It is associated with a higher percentage of generalized seizures and worse prognosis for seizure remission after surgery.^{435,436} Bilateral thalamic hypometabolism, and in particular thalamic metabolic asymmetry in the reverse direction to that of the temporal lobe asymmetry, is also associated with poor outcome.⁴³⁷ Remote reduction of CMRglc in TLE in the ipsilateral inferior frontal cortex and bilateral thalamus was reversible after resection of the epileptogenic lesion.^{438, 439}

In many instances potentially epileptogenic lesions are associated with discrete macroscopic morphologic

changes, and the high sensitivity of modern MRI techniques to detect these replaced functional imaging in presurgical workup to some extent.^{440–442} Still, FDG–PET appears to be more sensitive than MRI.^{443–446} In a recent series of 113 TLE patients who had surgically and pathologically proven lesions and a good surgical outcome, sensitivity was found to be 89%, and the specificity was 91%.⁴¹⁴

Neocortical Focal Epilepsy

FDG–PET may also be useful to detect abnormalities in patients with neocortical (mainly frontal, rather than temporomesial) partial seizures.^{447–450} Yet, sensitivity appears to be lower (approximately 50% to 75%) than in TLE.^{444,451–453} Sensitivity may be improved by standardized quantitative evaluation.⁴⁵⁴ Hypometabolic regions are often associated with structural imaging abnormalities. As in TLE, regional hypometabolism often includes but is not specific for epileptogenic regions.⁴⁵⁵ Thus, the clinical relevance of FDG–PET appears to be primarily in directing placement of intracranial electrodes for presurgical evaluation of refractory neocortical seizures.

GABA-A and Benzodiazepine Receptors

There is reduced binding of FMZ to the GABA-A receptor complex in epileptogenic foci⁴⁵⁶ that probably is caused by a decrease in the affinity of the tracer for the receptor rather than reduced receptor density in these foci.⁴⁵⁷ Foci of reduced FMZ binding may be found with high sensitivity of up to 94% in TLE.^{410,453} This finding is even more consistent after correction for partial volume effects.⁴⁵⁸ Reduced FMZ binding can be present also in the absence of abnormalities on MRI.^{459–462} The reduction of FMZ binding is much more focally restricted than reductions of FDG uptake.^{463–465} The area of focal reduction of FMZ binding probably indicates the epileptogenic zone that needs to be resected to become seizure free.^{448,466} In neocortical focal epilepsy, extensive cortical abnormalities on FMZ–PET are associated with frequent seizures,⁴⁶⁷ and predict poor outcome in epilepsy surgery, whereas resection of focally restricted FMZ abnormalities in the lobe of seizure onset is associated with excellent outcome even in the absence of a structural lesion.⁴⁶⁸ Epilepsy associated with dysembryoplastic neuroepithelial tumors or cavernomas may be related to reduced benzodiazepine receptor density in the vicinity of these lesions.^{464,469,470}

Malformations of Cortical Development

Increased FMZ binding was observed in ectopic neurons of band heterotopia and in cortex adjacent to cortical

dysplasias. A high incidence of focally increased FMZ binding in gray or white matter was observed in neocortical epilepsy with normal MRI, indicating that a substantial number these subjects migrational disturbances may be a cause of epilepsy that are not readily detected by MRI.⁴⁷¹ Mostly, reduced FMZ binding was seen in subependymal nodular heterotopia, focal cortical dysplasia, and polymicrogyria,⁴⁷² and dysembryoplastic neuroepithelial tumors.⁴⁷⁰

Active glucose consumption suggesting synaptic activity has been detected in band heterotopia^{473,474} and in heterotopic nodules and displaced gray matter.^{475,476} Measurements of CBF using ¹⁵O-water-PET during activation tasks also indicated that regions of malformations of cortical development may participate in normal cognitive functions,⁴⁷⁷ and widespread cortical atypical organization was seen.⁴⁷⁸

A study of focal cortical dysplasia and dysembryoplastic neuroepithelial tumor demonstrated that focal cortical dysplasia has intrinsic epileptogenicity, whereas neuroepithelial tumor is surrounded by epileptogenic cortical areas that need to be considered for resection.⁴⁷⁹ Focal cortical dysplasia may also show slightly increased uptake of ¹¹C-methionine⁴⁸⁰ that is less than that typically seen in gliomas. Cavernomas are also often associated with focal epileptic symptoms. Abnormal FDG uptake in adjacent areas probably is related to functional impairment, whereas focal reductions of FMZ uptake may indicate an epileptogenic cortex.⁴⁶⁴ Thus, if confirmed, FMZ–PET could guide surgical interventions in such cases.

Childhood Epileptic Syndromes

There are several complex encephalopathies that are characterized by developmental delay and epileptic seizures. In patients with infantile spasms and West syndrome, PET studies with FDG suggest that the spasms are the result of secondary generalization of epilepsy from cortical foci.⁴⁸¹ Multiple PET tracers are being used to detect epileptogenic brain regions and also to investigate developmental abnormalities of serotonergic and GABAergic neurotransmitter systems in this syndrome.⁴⁸² Patients with the Lennox-Gastaut syndrome have shown a variety of cerebral metabolic patterns: normal, focal, and diffuse (unilateral and bilateral) hypometabolism.^{483,484} Diffuse cortical dysfunction is common in the epileptic encephalopathies, and may reflect the underlying cause of the condition or arise as a consequence of uncontrolled seizures. Altered thalamic glucose metabolism is further evidence of subcortical involvement in these conditions.⁴⁸⁵

As in the other epileptic disorders, hypometabolism most likely reflects impaired synaptic function but often

also includes the epileptogenic cortex.⁴⁸⁶ Correspondingly, hypometabolism was most prominent in temporal lobes in the Landau-Kleffner syndrome,⁴⁸⁷ an acquired aphasia that begins in childhood and is thought to arise from an epileptic disorder within the auditory speech cortex. Yet, in few cases also focally increased CMRglc in the left superior temporal cortex was noted.⁴⁸⁸ This may have been a consequence of epileptic discharges during the study. In scans performed during slow-wave sleep there was also a marked bilateral increase in glucose metabolism in these areas.⁴⁸⁹ Even after cessation of epileptic fits in adulthood, some impairment of verbal short-term memory may persist, which was reported to correspond to reduced activation of the superior temporal cortex.⁴⁹⁰ Similar findings to the Landau-Kleffner syndrome were observed in the syndrome of continuous spike-and-wave discharges during slow sleep with abnormalities in association cortices that is probably related to a disturbance of neuronal maturation.⁴⁹¹

Hemispherectomy is being used to treat severe focal epileptic syndromes in childhood. Functional changes of that treatment have been studied with PET. The results suggest that compensatory allocation for movement of the weak hand primarily involves the premotor, inferior frontal, and insular cortices, and the supplementary motor area in the retained hemisphere, as well as the bilateral cerebellum. Receptive language and prosodic functions primarily activated the left perisylvian cortices. However, language and motor activations were also seen in cortical and subcortical remains on the hemispherectomized side, suggesting incomplete disconnection by functional hemispherectomy.⁴⁹²

Perspectives

In the field of dementia, PET is likely to play an increasing role for early diagnosis of AD to initiate neuroprotective therapy that delays progression to severe dementia with its associated burden and costs to patients, caregivers, and society. That goal can already be achieved by imaging glucose consumption with widely available FDG. For distinction of other dementing diseases from AD, the demonstration of impairment of specific neurotransmitter systems and use of specific molecular markers, for example, for amyloid plaques, may become the most specific diagnostic procedures. Further development and clinical use of increasingly sophisticated tracers to study all aspects of dopaminergic neurotransmission and related transmitter systems is likely to continue to play a major role in improving the diagnosis and our understanding of the molecular pathophysiology and genetic predisposition in movement disorders. Physicians planning treatment of brain tumors will increasingly use PET imaging to determine the best balance between radical tumor removal and preservation

of important brain function. Specific molecular tracers to measure tumor proliferation will be used to improve and monitor therapy. PET will also help to find new means to facilitate brain plasticity after major brain injury, in particular after ischemic stroke, by demonstrating not only blood flow and metabolic changes but also specific changes in transmitter systems and their potential for reactivation. PET will continue to improve our abilities to find focal and molecular alterations that underlie the many forms of epilepsy, not only in adults but increasingly also in childhood. In all neurologic disorders, the transfer of new molecular insights obtained in transgenic and experimental animals into the clinical arena by direct noninvasive investigation of these mechanisms in human disease with PET is expected to substantially contribute to improvement of neurological therapy in the next years.

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