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Summary

We review state of the art techniques of structural and functional imaging techniques to investigate localization-related epilepsies and describe the abnormalities of mesial temporal lobe epilepsy with hippocampal sclerosis observed with these imaging modalities. We illustrate the value of interictal and ictal PET studies for localizational purposes in epilepsies.

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L'importance du PET pour le diagnostic des épilepsies

Dans cet article nous revoyons les différentes techniques d'imagerie fonctionnelle appliquées aux épilepsies focales et décrivons les résultats observés avec ces techniques dans les épilepsies temporales avec sclérose hippocampique. Nous démontrons l'intérêt des études de PET ictal et interictal dans la localisation des foyers épileptiques.

Die Rolle des PET in der Epilepsiediagnostik

Nach einem Überblick über die modernen bildgebenden Techniken für das Aufspüren von strukturellen und funktionellen Abnormitäten bei Lokalisationsbezogenen Epilepsien beschreiben wir die Befunde, die mit diesen Techniken beim Syndrom der mesialen Temporallappenepilepsie gefunden werden. Mit Beispielen illustrieren wir den hohen Stellenwert von interiktalen und iktalen PET-Untersuchungen in der Lokalisationsdiagnostik von Epilepsien.

*** Acknowledgements:** Parts of this review have been published in previous articles and/or are taken from the cited references. In particular: The survey on structural and functional imaging techniques to investigate localization-related epilepsies was compiled by Thomas R. Henry, who chaired the Group of imaging experts (Sait Albayram, Fernando Cendes, Nadia Colombo, Graeme D. Jackson, Robert C. Knowlton, Susan S. Spencer, Hermann Stefan, Wim Van Paesschen) in the Istanbul Meeting. The conclusions of this meeting were recently published in *Epilepsia* (Wieser HG for the ILAE Commission on Neurosurgery, 2004)^[1]. The section on tumor-associated epilepsies: Imaging gliomas with PET is from the survey of Bénard et al. (2003)^[2]. Other sources are referenced and gratefully acknowledged, too. I am particularly grateful to Prof. Alfred Buck, M.D., M.S., Chief PET Research, Department of Nuclear Medicine, University Hospital Zurich and his team, and to Dr. Katharina Henke, PD Dr. Marketa Hajek and PD Dr. Nadia Khan, who conducted or collaborated in several PET studies.

1. Survey on structural and functional imaging techniques to investigate localization-related epilepsies (see Wieser HG for the ILAE Commission on Neurosurgery, 2004)^[1]

Currently, the imaging modalities that have been demonstrated to provide reliable information in **localization-related epilepsies** are:

- Interictal magnetic resonance imaging (MRI), to study abnormalities of brain structure,
- interictal proton magnetic resonance spectroscopy (proton-MRS), to study reductions of N-acetyl-aspartate (NAA) as a measure of neuronal integrity,
- ictal-interictal single-photon emission computed tomography (SPECT) with [Tc-99m]technetium-hexamethylpropyleneamine oxime (HMPAO) or with [Tc-99m]technetium-ethylene cysteine dimer (ECD), to study ictal perfusion changes,
- interictal positron emission tomography (PET) with 2-[F-18]fluoro-2-deoxyglucose (FDG), to study glucose metabolic dysfunction, and
- interictal PET with [C-11]flumazenil, to study altered densities of central benzodiazepine receptors (cBZRs).

Other imaging modalities have provided useful data in epilepsy research, but these modalities have not yet been studied adequately to support a role in defining

Localization-related epilepsies. Such imaging modalities include:

- Ictal functional MRI (to study ictal blood flow),
- postictal MRI with T2 or diffusion mapping (to study effects of single or repeated seizures on local water redistribution),
- interictal proton-MRS with gamma-aminobutyrate and homocarnosine spectra (to study inhibitory neurotransmitter concentrations),
- interictal proton-MRS with glutamate-glutamine spectra (to study excitatory neurotransmitter concentrations),
- interictal phosphorus-MRS with adenosine triphosphate and inorganic phosphorus spectra (to study pH and cellular energy metabolism),
- interictal SPECT with [¹²³I]iomazenil (to study cBZR density),
- interictal PET with (S)-[N-methyl-C-11]ketamine (to study N-methyl-D-aspartate receptor density),
- interictal PET with [C-11] alpha-methyl-L-tryptophan (to study serotonin synthesis), and
- interictal PET with [C-11]deuterium-L-deprenyl (to study glial density, by measuring monoamine oxidase-B concentration).

In order to homogenize and thereby simplify the discussion on the clinical value of these investigational procedures, we concentrate on the syndrome of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) and ask the question:

2. What are the abnormalities of MTLE-HS observed with these imaging modalities?

a) **Interictal MRI** is highly sensitive and specific in detecting hippocampal sclerosis (HS) in MTLE, and also in the detection of neoplasia, dysplasia, vascular malformations and other lesions that occur in MTLE. Qualitative MRI interpretation, and quantification of hippocampal volume (volumetry) and water density (T2 relaxometry), are useful in detecting HS. While MRI is the “gold standard” for in vivo detection of HS, qualitative and quantitative MRI may fail to detect mild HS that is subsequently found on histopathological examination. The hippocampal MRI abnormalities in MTLE-HS can be bilaterally symmetric, but are more often unilateral, or clearly asymmetric. Brain MRI also frequently shows abnormalities of volume (atrophy) and signal (T2 increase or T1 decrease) in structures outside of the hippocampus, usually ipsilateral to the sclerotic hippocampus.

In surgically treated MTLE-HS the usual hippocampal abnormalities are:

- Atrophy (detected with MRI in 90-95% of cases in which HS is found in resected tissue),
- loss of internal architecture (in 60-95%),
- T2 increase (in 80-85%), and
- T1 decrease (in 10-95%).

The commonly occurring extrahippocampal abnormalities in surgically treated MTLE-HS are:

- Atrophy-signal alterations of the ipsilateral amygdala, temporal neocortex, temporal lobe white matter, fornix, mammillary body, insula, thalamus, or basal frontal cortex.
- Atrophy-signal alterations of the contralateral hippocampus (less severe than ipsilateral hippocampal alterations), and
- dilatation of the ipsilateral or contralateral temporal horn of the lateral ventricle (often a ‘falsely lateralizing’ finding, in that temporal horn dilatation often is more severe on the side contralateral to the sclerotic hippocampus).
- Diffuse hemispheric atrophy can occur ipsilaterally in MTLE-HS, but is rare.

b) **Interictal proton-MRS** assesses neuronal integrity by NAA measurement, usually by comparing concentrations of this neuron-specific chemical with concentrations of choline or creatine. Unlike brain mapping with MRI, SPECT and PET techniques, the entire brain is not included in typical MRS measurements and often only a few, relatively large voxels are sampled with MRS. The relatively poor signal-to-noise ratio of proton-MRS mitigates against sampling of small volumes of brain tissue, and the relatively long time required to obtain spectra in each defined volume renders determination of spectra in many voxels impractical. For example, many proton MRS investigations use four voxels in a single thick image plane, typically as right and left mesial and lateral temporal lobe voxels when temporal lobe epilepsy (TLE) is to be imaged. Technical improvements may achieve increased signal-to-noise performance, possibly supporting a larger field of view and increased spatial resolution.

In surgically treated MTLE-HS the usual mesial temporal abnormalities are:

- Decreased NAA/Cho-Cr ratio, ipsilateral to the sclerotic hippocampus (detected with MRS in about 90% of cases in which HS is found in resected tissue), and
- decreased NAA/Cho-Cr ratio, contralateral to the sclerotic hippocampus (in 30-40%). Interestingly, upon successful resection of a sclerotic hippocampus, the contralateral mesial temporal NAA abnormality often resolves within several months after seizures cease.

c) **Ictal-interictal SPECT** maps cerebral perfusion during and shortly after single seizures, compared with the interictal state. Often, in unilateral MTLE-HS, interictal [^{99m}Tc]HMPAO or [^{99m}Tc]ECD retention is mildly or moderately decreased in the anterior temporal lobe ipsilaterally, but “false lateralization” of interictal temporal lobe hypoperfusion occurs in perhaps 10% of patients. When the radioligand is injected during a complex partial seizure, the temporal lobe of ictal onset usually shows a great increase in radioligand retention, and false lateralization is quite rare when using coregistered ictal versus interictal temporal lobe perfusion maps. Peri-ictal SPECT studies of TLE have shown a characteristic evolution in regional perfusion, as the region of ictal hyperperfusion declines to severe hypoperfusion for several minutes postictally, then within about 20 minutes perfusion rises back to a milder degree of interictal hypoperfusion. This phenomenon has been called the ‘postictal switch’, and can cause false lateralization when interictal scans are compared with early postictal scans which are mistakenly considered to represent an ictal scan. Ictal-interictal SPECT studies require considerable expertise in timing of the radioligand injection, which must be performed with continuous electroencephalography.

In surgically treated MTLE-HS the usual ictal alterations in regional perfusion are:

- Anterior temporal hyperperfusion, ipsilateral to HS, or bilateral but greater on the side of HS (detected with ictal-interictal SPECT in about 90% of cases in which HS is found in resected tissue).
- Extratemporal hyperperfusion ipsilateral to predominant anterior temporal hyperperfusion, often including the thalamus, basal ganglia and occipital cortex.
- Extratemporal decreases in perfusion, often including ipsilateral or bilateral frontal and parietal areas.

Thus, it appears likely that ictal SPECT maps areas of ictal onset and of most intense seizure propagation.

d) **Interictal FDG PET** maps interictal glucose metabolism, based on the deoxyglucose model. Glucose metabolism and cerebral blood flow appear to be uncoupled in the interictal state of TLE. False lateralization of temporal lobe hypometabolism on interictal FDG scans is rare in MTLE-HS, unlike the more frequent occurrence of falsely lateralized temporal lobe hypoperfusion on interictal SPECT. Research and clinical application of FDG PET in MTLE is greatly facilitated by coregistration to the subject's MRI and by quantitative analysis, as is also true for ictal-interictal SPECT and most functional imaging modalities.

In surgically treated MTLE-HS the usual interictal glucose metabolic alterations are ^[3-6]:

- Anterior temporal lobe hypometabolism, ipsilateral to HS, or bilateral but greater on the side of HS (detected with interictal FDG PET in 90-95% of cases in which HS is found in resected tissue), and
- extratemporal hypometabolism ipsilateral to predominant anterior temporal hypometabolism, usually including the thalamus, and often including basal ganglia, the insula, inferior frontal cortex, and lateral parietal cortex.

e) **Interictal FMZ PET** maps cBZR density, which thereby maps the density of the principal inhibitory site of mammalian cortex, the GABA_A receptor-chloride ionophore complex. Severe decrease of cBZR density in sclerotic hippocampi occurs with loss of principal neurons of CA1 and other mesial temporal subregions, but the severity of cBZR loss may be greater than the severity of neuronal loss in HS, based on autoradiographic studies of human surgical specimens. Extensive research has established compartmental models of FMZ distribution that permit absolute and relative quantitative measurements of cBZR density using FMZ PET. Mapping of cBZR density with FMZ PET may be more useful than is cBZR mapping with IMZ SPECT, because FMZ modeling can fully exclude interictal blood flow alterations from FMZ-based maps, but IMZ-based maps may include components of both cBZR and blood flow alteration.

In surgically treated MTLE-HS the usual interictal cBZR alterations are:

- Decreased cBZR density in anterior mesial temporal regions, ipsilateral to HS, detected with interictal FMZ PET in over 90% of cases in which HS is found in resected tissue, and
- extratemporal cBZR decreases ipsilateral to predominant anterior mesial temporal cBZR reductions, occasionally including the thalamus, and the insula.
- Thus, reductions in cBZRs are much more focal with the anterior mesial temporal lobe in MTLE-HS, than are ictal hyperperfusion and interictal glucose hypo-

metabolism. Nonetheless, other limbic system sites that are highly connected with the hippocampal-amygdalar-entorhinal complex, in some cases also show evidence of cBZR loss.

3. Examples of interictal and ictal PET studies in the context of presurgical evaluation

a) Interictal and ictal 18F-FDG PET for localizational purpose in epilepsies.

PET has an established role in the noninvasive localization of epileptic foci during presurgical evaluation. [18F]fluorodeoxyglucose (FDG) PET is able to lateralize and regionalize potentially epileptogenic regions in patients who have normal MR imaging and is also useful in the evaluation of various childhood epilepsy syndromes, including cryptogenic infantile spasms and early Rasmussen's syndrome [7]. Novel PET tracers that were developed to image neurotransmission related to opiate receptors [8], gamma-aminobutyric acid (GABA) [with [11C]flumazenil] and serotonin-mediated [with alpha-[11C]methyl-L-tryptophan (AMT)] function provide increased specificity for epileptogenic cortex and are particularly useful when FDG PET shows large abnormalities of glucose metabolism. Detailed comparisons of PET abnormalities with intracranial electroencephalographic findings also improve our understanding of the pathophysiology of human epilepsy [9-11]. In children with tuberous sclerosis, the PET tracer alpha[11C]methyl-L-tryptophan (AMT) has been shown to be selectively taken up by epileptogenic tubers, thus allowing differentiation from nonepileptogenic tubers in the interictal state [12].

Figures 1, 2 and 3 depict examples of interictal FDG PET scans and how they substantiate clinical diagnosis. Figure 4 is an example of an ictal FDG PET study in a patient with a prolonged status-like seizure discharge in the left temporo-occipital cortex. This patient had been operated on with so-called "palliative" selective amygdalohippocampectomy with moderate success.

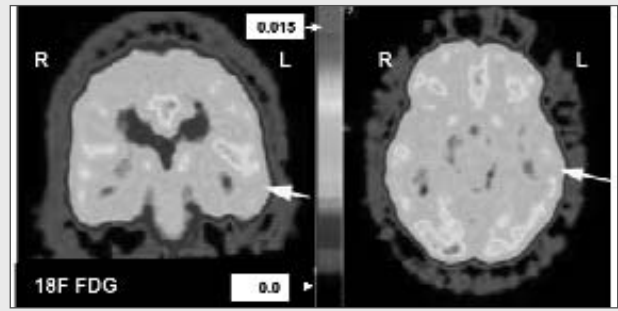


Figure 1. Interictal 18F-FDG-PET in a 38 years old patient suffering from psychomotor seizures with acoustic aura and frequent secondary generalization since 2 years. Note the circumscribed hypometabolic area in left middle temporal gyrus (arrows) and the hypermetabolic insula and slightly asymmetric putamen and thalamus with increased metabolism on the left. Scalp EEG showed a left mid-temporal sharp wave focus, but high resolution MRI was normal. Because of the auditory symptoms an "autosomal dominant partial epilepsy with auditory features" (ADPEAF) was considered but there is no epilepsy in the family of this patient. No genetic examination was done (ADPEAF is associated with a disponibility gene on chromosome 10q 24). Coronal and transversal views.

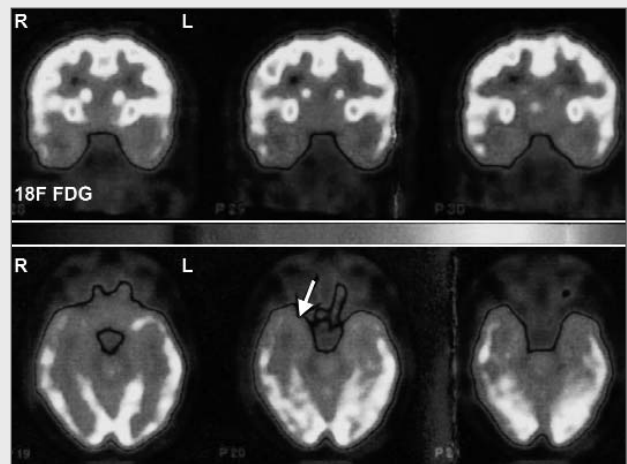


Figure 2. Interictal 18F-FDG-PET in a 32-years old male patient with severe bitemporal mesial hypometabolism, corresponding with bitemporal sharp-wave foci and bitemporal hippocampal sclerosis. Coronal and transversal views.

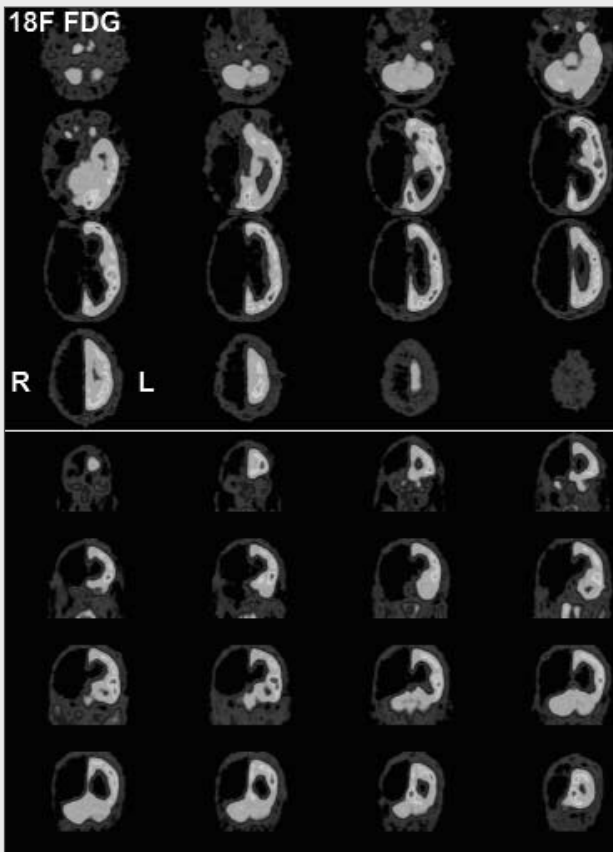


Figure 3. Interictal 18F-FDG-PET in a 30 year old female with Rasmussen's encephalitis and right hemispherectomy at age 23 years, following a limited right central resection at age 6 years.

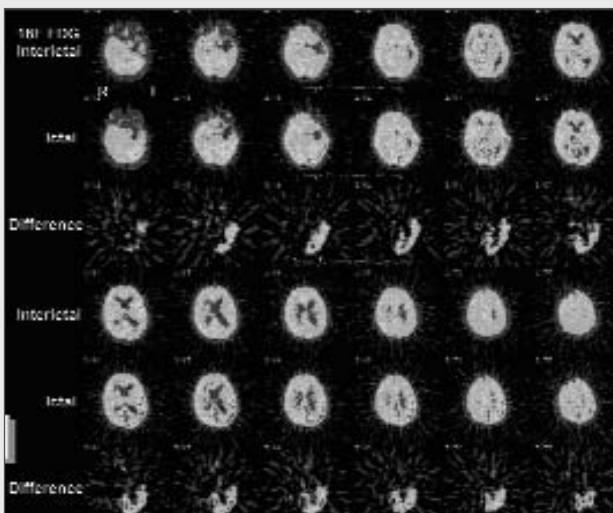


Figure 4. Ictal FDG PET study in a patient with a prolonged status-like seizure discharge in the left temporo-occipital cortex. This patient had been operated on with so-called "palliative" selective amygdalohippocampectomy with moderate success (see Interictal = Baseline). During the prolonged seizure discharge in the left temporo-occipital cortex (see Ictal and Difference between Interictal and Ictal) the patient presented with aphasic and visual symptoms, and was anxious with inadequate response to external stimuli.

b) Interictal 18F-FDG PET before and after selective amygdalohippocampectomy to study the postoperative changes of preoperatively present temporal hypometabolism

The results of this study were as follows [13]: Preoperatively patients with MTLE-HS had significantly reduced regional metabolic rates of glucose (rCMRglu) ipsilateral to the focus in the mesial temporal lobe. Postoperatively, the rCMRglu values were reduced in the operated mesial temporal structures, as expected. In the first postoperative PET study (at postoperative month 3) the ipsilateral lateral TL cortex showed significant reduced glucose utilization in comparison with the control group. One year after surgery, however, the rCMRglu values in the lateral TL cortex were no longer significantly changed compared with the control group. Indeed, patients with MTLE-HS and being seizure-free postoperatively showed increases of glucose utilization in all brain regions, including the contralateral hemisphere, except at the operation site and in the mesiobasal contralateral structures.

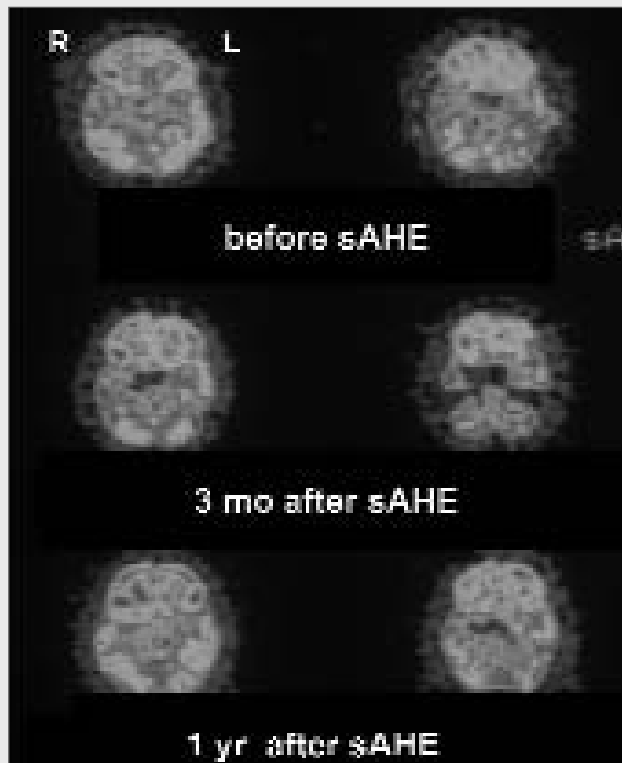


Figure 5. Interictal 18F-FDG-PET before, 3 months and 1 year after right selective amygdalohippocampectomy (sAHE) illustrating the late improvement of lateral temporal hypometabolism ipsilateral to the sAHE.

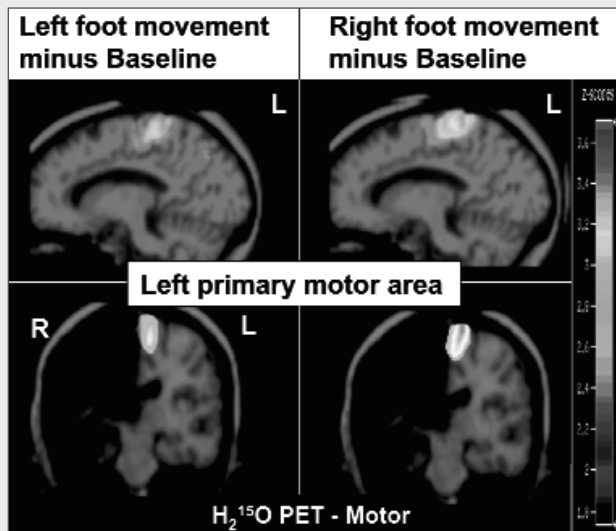


Figure 6. $H_2^{15}O$ PET study during sequential right and left foot movements and at rest in a patient with Rasmussen's encephalitis (same patient as in Figure 3). Fused with MR images significant blood flow increases in the left motor area are measured with $H_2^{15}O$ PET and result from the contrasts "left foot movement - baseline" and "right foot movement - baseline". Activation of left primary motor area is stronger during right than left foot movements. There is no activation in the diseased left hemisphere. The bar indicates the color-coded z-scores (sagittal view) (modified from Wieser et al.^[14]).

c) Studies of cortical motor function and memory using $H_2^{15}O$ PET

Figure 6 depicts a $H_2^{15}O$ PET study in a patient with Rasmussen's encephalitis in whom the question arose whether a hemispherectomy could be performed because of recurrence of seizures without additional motor deficits. This patient had had a right central resection at age 6 as a treatment for drug-resistant status epilepticus due to localized Rasmussen's encephalitis. She became seizure-free postoperatively, but suffered a left hemiplegia which improved to the extent that she could walk again without assistance. Because of the recurrence of seizures, an enlargement of the resection to a hemispherectomy was performed 17 years after the first operation without additional motor deficit. Prediction of this favorable postoperative outcome was possible because the PET findings suggested that a compensatory reinforcement of the ipsilateral uncrossed corticospinal and cortico-reticulospinal pathways had taken place, and that no additional motor deficits were to be expected after a right hemispherectomy.

Functional neuroimaging allows the non-invasive preoperative assessment of **memory** functions of the ipsilateral and contralateral mesial temporal lobe (MTL) in individual patients. Henke et al.^[15] examined memory-related activity within to-be-resected MTL structures in 12 candidates for sAHE with $H_2^{15}O$ PET be-

fore sAHE and studied the reallocation of memory functions to the contralateral MTL before and after surgery. Learning tasks were designed to activate predominantly the right or left MTL. Those patients who significantly activated to-be-resected ipsilateral MTL structures during the ipsilateral learning task (i.e. the left MTL during verbal learning or the right MTL during nonverbal learning) experienced a postoperative memory decline. Preoperative activation in the contralateral MTL during the ipsilateral learning task positively correlated with the postoperative outcome for ipsilateral memory. There was no significant postoperative reallocation of ipsilateral memory functions to the contralateral MTL.

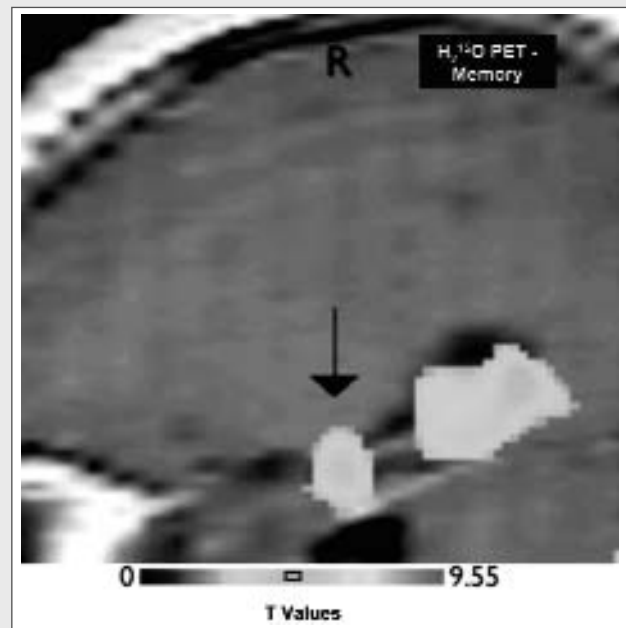


Figure 7. $H_2^{15}O$ PET memory study: Preoperative hippocampal activation in a patient with right MTL during the critical ipsilateral learning task versus the control task. The preoperative PET activations thresholded at 0.01 are superimposed on the individual postoperative clinical MR scans depicting the areas of resection. Activity increases during the ipsilateral learning task are located in the ipsilateral right hippocampal area (non-verbal learning vs. control). After sAHE the patient experienced a postoperative drop in memory performance. R, right side of brain. Arrow: hippocampal activations. Individual color scales represent T values; the top numbers correspond to the largest. (modified from Henke et al.^[15]; for technical details see this reference). Deep single word encoding (verbal learning), associative picture learning (non-verbal learning) and shallow single word encoding (a perceptual task for the control condition) was used. The instruction for verbal learning required patients to decide for each presented noun whether it was rather pleasant or unpleasant. The instruction for non-verbal learning required patients to decide for picture pairs consisting of a house and a person whether the person is an inhabitant or a visitor of the house. The control task required patients to count the vowels across a pair of nouns (for details see^{[16],[17]}).

In this study postoperative memory deficits were absent if the contralateral MTL had taken over memory functions of the pathological ipsilateral MTL. On the other hand, memory deficits occurred if the to-be-removed structures were still functionally active during ipsilateral memory tasks. Comparisons of the intraarterial amobarbital tests with functional neuroimaging of memory have yielded a high concordance between the two methods. Thus, functional neuroimaging may eventually replace the invasive amobarbital procedures for the prediction of memory outcome and for the counseling of patients.

4. Tumor-associated epilepsies: Imaging gliomas with PET (see [2])

Brain tumors can be visualized with PET. Several radioisotopes and radiopharmaceuticals have been used in clinical research studies. ^{15}O -water was used to measure tumor blood flow and $^{15}\text{O}_2$ to measure oxygen utilization. Nucleoside analogues such as ^{11}C -thymidine have been utilized with mixed success to detect cell division rates. Few reports have been published with this tracer for brain tumor imaging. Thymidine analogues are not transported well across the blood-brain barrier (BBB). Initial reports suggested the feasibility of imaging brain tumors with ^{11}C -thymidine. However, BBB disruptions appear to account for a significant proportion of the uptake when the label is attached to the methyl carbon. Other nucleoside analogues, such as [^{124}I]iododeoxyuridine-5-fluoro-2'-deoxyuridine have also been considered for PET imaging of brain tumors. Fluorothymidine has recently been proposed to measure tumor proliferation rate, but uses of this tracer for brain tumor imaging have not yet been published. Putrescine has also been labeled to evaluate polyamine metabolism.

Therapeutic agents such as carmustine have been labeled with positron emitters for imaging tumors as well as for performing in vivo pharmacokinetic studies. Another interesting area of research is the development of ^{18}F labeled compounds for imaging tumor hypoxia for correlation with the response to radiation therapy.

These radiopharmaceuticals, including radio-labeled choline analogues and amino acids (O- ^{11}C)-methyl-L-tyrosine and O- ^{18}F)-fluoromethyl-L-tyrosine as well as O-(2- ^{18}F)-fluoroethyl-L-tyrosine (FET) (see **figure 9**) and S-(2- ^{18}F)-fluoroethyl-L-methionine (18FEMET), ^{11}C -methyl-methionine (MET) and ^{11}C -leucine) present definite research interest, but no clear practical clinical utility has yet been defined for these tracers. They are used, together with ^{18}F FDG PET, to differentiate between tumor and inflammatory tissue, and to evaluate the grading of a tumor.

However, FDG remains the keystone of PET imaging in oncology. Malignant cells have highly elevated rates of glucose uptake and metabolism compared to non-

malignant cells. Tumor cells with high glycolytic rates have high levels of enzymes that control glycolysis such as hexokinase, phosphofructokinase and pyruvate dehydrogenase. Changes in glucose transport rate are not simply related to the accelerated growth rate but are transformation specific. Increased membrane glucose transport capability has been shown to occur with neoplastic transformation. There is a significant increase in the number of functional glucose transporters at the transformed cell's surface, and nearly all cellular oncogenes activate glucose transport. Six mammalian glucose transporters have been identified and overexpres-

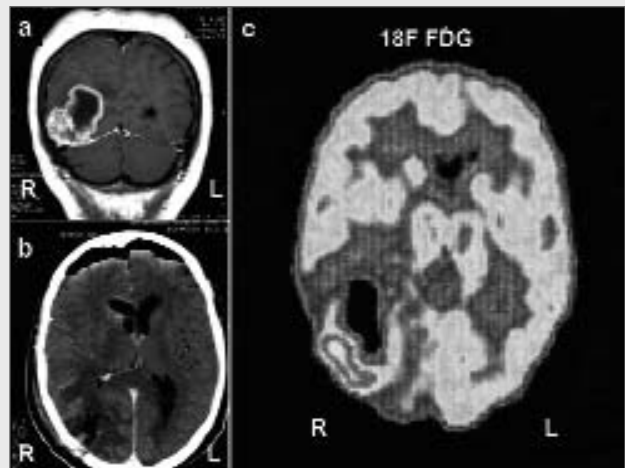


Figure 8. Preoperative MRI (a), postoperative CT (b) and preoperative ^{18}F FDG PET (c) in a 65-year-old female patient with a cystic tumor (histology: metastasis of mamma carcinoma) and symptomatic epilepsy with simple and complex partial seizures. The aura consisted of simple geometric figures and complex scenic pictures in the left visual half-field.

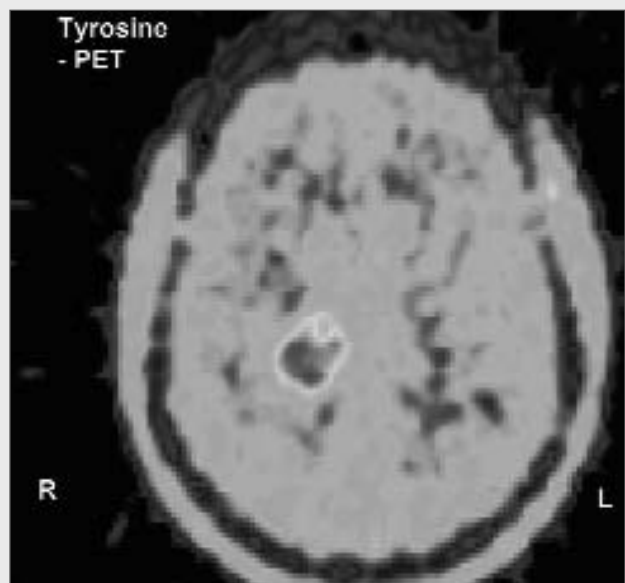


Figure 9. Tyrosine PET in a 35-year-old female patient who presented with asymmetric tonic seizures. MRI revealed an unclear lesion in the right thalamus and the tyrosine PET study suggested that it could be a higher graded tumor.

sion of both GLUT-1 and GLUT-3 mRNA has been demonstrated in brain tumors, with a higher ratio of GLUT-3 in more aggressive lesions. PET can capitalize on this increased capacity for glucose transport observed in malignant glial cells to image brain tumors with FDG (see figure 8).

While low-grade tumors reveal low levels of metabolism, those with high grade appear hypermetabolic compared to normal brain tissue, as illustrated in figure 9.

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