Neurologic applications were at the forefront of PET imaging when the technique was developed in the mid-1970s. Although oncologic indications have become prominent in terms of number of studies performed worldwide, neurology remains a major field in which functional imaging provides unique information, both for clinical and research purposes. The evaluation of glucose metabolism using FDG remains the most frequent exploration, but in recent years, alternative radiotracers have been developed, including fluorinated amino acid analogues for primary brain tumor imaging and fluorinated compounds for assessing the amyloid deposits in patients with suspected Alzheimer disease. As the brain is enclosed in the skull, which presents fixed landmarks, it is relatively easy to coregister images obtained with various cross-sectional imaging methods, either functional or anatomical, with a relatively high accuracy and robustness. Nevertheless, PET in neurology has fully benefited from the advent of hybrid imaging. Attenuation and scatter correction is now much faster and equally accurate, using CT as compared with the traditional transmission scan using an external radioactive source. The perfect coregistration with the CT data, which is now systematically performed, also provides its own set of valuable information, for instance regarding cerebral atrophy. However, hybrid imaging in neurology comes with pitfalls and limitations, in addition to those that are well known, for example, blood glucose levels or psychotropic drugs that greatly affect the physiological FDG uptake. Movements of the patient’s head, either during the PET acquisition or between the PET and the CT acquisitions will generate artifacts that may be very subtle yet lead to erroneous interpretation of the study. Similarly, quantitative analysis, such as voxel-based analyses, may prove very helpful in improving the diagnostic accuracy and the reproducibility of the reading, but a wide variety of artifacts may also be introduced, and should therefore be identified and corrected.

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Introduction: Advantage of Hybrid Imaging in Isotopic Functional Imaging

Isotopic functional imaging is a unique technique for providing clinical and research information on brain activity related to different metabolic processes. Regional glucose metabolism studied with FDG-PET is the most frequent information that can be used for clinical diagnosis to track activity in the entire brain, in both cortical and subcortical structures. Moreover, precise measurements of the nigrostriatal dopaminergic pathway integrity, using [18F]-DOPA for example; regional evaluation of amino acid uptake, for example, with [18F]-fluoroethyltyrosine (FET); or measurement of local deposits of amyloid protein with different tracers provide important research and clinical functional and physiopathologic information.

PET is resting on the detection of electromagnetic waves produced when an emitted positron and an electron annihilate. Attenuation of electromagnetic waves during their cerebral travel leads to major inaccuracies in measuring the proper distribution of activity into the brain. Currently, CT is most frequently used as a “transmission scanner” to provide proper calculation of attenuation.
Moreover, measures of specific metabolic processes are not sufficiently useful for clinicians if the location of the particular activity and the structure of the given brain region are not known. Accordingly, a decrease of glucose uptake in a given region provides very important PET functional information, but without precision about the underlying tissue abnormality, a precise differential diagnosis is very difficult to achieve. In epilepsy or in dementia studies, the medial temporal lobe comprises several substructures with different functions, and the repartition of the activity between the structures is of main importance. CT coupled with PET is able to provide a global view of the hippocampal structures, whereas subregions can be further delineated on MRI acquisitions if required. In cerebral oncology, increased regional amino acid uptake may be a marker of tumoral processes, but the location in a previously resected brain area is key information for further therapeutic decision.

**Pitfalls and Limitations:**

**Methodological Aspects Common to All Indications and Tracers**

**Artifacts of Movements**

One of the limitations of PET/CT, and most neuroimaging acquisitions, is the necessity to keep a patient in a constant position during the acquisition. However, even minor movements can lead to significant artifacts, as illustrated in the following figures. Additional methodological issues, such as poor image registration or incorrect attenuation correction, can also affect the quality of the images.

**Figure 1** FDG-PET study performed in a patient who had minor but repeated movements during the acquisition (transaxial slices). Resolution is degraded, and the images are blurred.

**Figure 2** Significant movement between the CT and the PET acquisitions, in the transaxial plane. The left side of the brain appears as hypometabolic, owing to erroneous attenuation correction. Note that the skin also appears as hypoactive on the left side of the scalp.
position. If the patient moves during the acquisition, the activity will be blurred over brain structures, resolution will be degraded, and result’s interpretation will be difficult or even impossible. The most recent PET devices have increased count rates capabilities, which allow shortening the duration of the acquisition and thus improving the patient tolerance and reducing the likelihood of experiencing significant movements. However, an FDG brain study is typically completed within 10-20 minutes. Different possibilities to constrain head position can be used, and they depend mostly on the environment, the type of patients, and the opportunities of the clinical services. An example of such a blurred FDG-PET study is shown in Figure 1.

**Artifacts Associated With Attenuation Correction**

Attenuation correction of the photons emitted by the brain may be achieved through three methods: first, a transmission scan is performed using a rotating external source of Ge68/68Ge and 

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**Figure 3** Significant movement between the CT and the PET acquisitions, in the sagittal plane. In this case, the parietal cortex appears as hypometabolic, and the artifact is best identified by looking at the sagittal slices.

**Figure 4** Minor movement between the CT and the PET acquisitions, in the transaxial plane. In this case, there is only a very slight, yet artifactual, decrease in uptake by the cortex in the left hemisphere, and the skin.
generates a μ-map that is accurate in that the energy from both the emission and transmission photons are identical. However, the quality of this μ-map is limited, even with a lengthy acquisition. A transmission scan using a source of Cs137 is faster, but then the energies from the emission and transmission photons are different. A second possibility is to simply draw elliptic volumes of interest and segmenting the data within these volumes of interest, applying unique attenuation coefficients. The image quality is visually correct, but quantitation is obviously approximate. The third possibility is to use PET/CT, where a CT scan is typically performed before the emission scan is started, and the CT-generated μ-map presents excellent signal-to-noise ratios and spatial resolution. Even though the conversion of the μ-values measured with low-energy x-rays to 511 keV of positrons follows a nonlinear pattern, it has been shown that an approximation by a bilinear model works in an appropriate fashion.\textsuperscript{8} In routine clinical practice where the attenuation correction is achieved using the CT data, there are two distinct issues that may significantly degrade the quality of the metabolic study: Firstly, movements between PET and CT acquisitions will offset the μ-map and generate attenuation-corrected images that do not reflect the actual distribution of the tracer. The image quality is grossly degraded, and this pitfall is easily recognized when the movement between PET and CT is marked, but minor movements may lead to subtle changes in the images and affect its interpretation (Figs. 2-4). Visual inspection of both data sets is mandatory, as manual correction of the misregistration easily corrects the issue. Automated registration algorithms have also been developed to avoid this problem.\textsuperscript{9} Secondly the presence of metallic material, such as reconstructive skull plates, may lead to over-correcting the emission data and artifactual areas of increased uptake in the PET images.\textsuperscript{10} In this case, calculated attenuation correction using the ellipse method improves the image quality even though the quantitative assessment remains biased. Smaller metallic objects such as electroencephalogram electrodes may generate local foci of increased activity at their location outside of the brain, without altering the diagnosis when it is made visually. It may become an issue, however, when comparing quantitative analyses of FDG brain studies performed with and without electroencephalogram electrodes.\textsuperscript{11}

The effect of misregistered μ-map and emission data becomes even more important when performing dynamic studies or when using high-resolution PET scanners such as the high resolution research tomograph that displays a 2-mm isotropic spatial resolution. In these cases, motion correction has to be applied. Various methods exist but are not discussed here because they belong to highly specialized centers.\textsuperscript{8,12}

Positioning of the Patient

Depending on the patient’s morphology, positioning may be a real difficulty for patients with limited neck mobility. Consequently, the image quality may be decreased if the head is not positioned in the centre of the field of view, where the

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**Figure 5** Low-dose, unenhanced CT of the brain (90 kV, 50 mA s). The study does not provide any reliable anatomical information.

**Figure 6** FDG-PET study showing diffusely decreased cortical uptake. The unenhanced CT of the brain (120 kV, 80 mA s) shows a major atrophy and dilation of the lateral ventricle with an Evans index of 0.40.
resolution is optimal. Most PET images are read visually by the medical specialist, and an important change in orientation may give difficulties for appropriately identifying brain regional activity. The superimposition of a structural image improves the readability and increases the accuracy of reorientation of the whole brain volume.

**CT Scanning Parameters**

There is a compromise to be reached between low-dose CT scan with minimal radiation exposure and thin-slice CT scan, with higher dose providing more pertinent information on brain structure for interpretation of functional images. When CT is performed solely for attenuation correction, the current should be set to the lowest level, but the images cannot be relied upon to provide any meaningful diagnostic information (Fig. 5). On the contrary, even without intravenous contrast enhancement, a thin-slice CT acquired with the appropriate settings may provide valuable information regarding cortical atrophy and ischemic sequelae, as shown in Figs. 6 and 7. It should be noted that the x-ray tube voltage does not affect the accuracy of the attenuation correction and the validity of the quantitative metabolic measurements.13

**Tracer-Specific Aspects**

**FDG**

PET-FDG is currently the most useful neuroimaging acquisition for the purpose of a global evaluation of brain activity in

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**Figure 7** FDG-PET study showing a photogenic area in the right cerebellar hemisphere. The unenhanced CT of the brain (120 kV; 80 mA s) shows a corresponding hypodense lesion consistent with an ischemic sequel.

**Figure 8** Markedly decreased quality of the FDG-PET study performed in a diabetic patient. The blood glucose level was 261 mg/dL at the time of injection.
neurologic patients. The images provide a tridimensional information on both cortical and subcortical structures allowing to consider brain activity in functional networks. Most interestingly, the combination of PET and CT does allow emphasizing a regional impairment of brain activity in a region with a normal structure. This is for example the case for dysconnection and dysfunction of cortical regions secondary to deep brain lesions. The absence of structural abnormality on CT does not provide a certainty for the absence of lesion, and a MRI investigation may be necessary. However, in brain trauma, for example, a regional impairment of metabolic activity may be easier to detect and interpret than axonal abnormalities observed by diffusion tensor imaging-MRI. A clear pitfall will be caused by head movements if one wishes to superimpose structural and functional imaging for localization purpose. In structures with small volume, it may be very misleading to have a misalignment in images overlapping. Corrections are possible, but they are time consuming and are rarely implemented in routine.

An informative FDG-PET acquisition heavily depends on the conditions of the study. Blood glucose level is a major parameter influencing the image quality (Fig. 8). Hyperglycemia is associated with competition between plasma glucose and FDG. High intracellular glucose and circulating insulin levels increase FDG uptake by the muscle and further reduce the uptake in the brain. Blood glucose levels superior to 150-200 mg/dL usually contraindicate a functional FDG brain study. In diabetic patients, it is recommended to perform the study in a euglycemic situation during stable therapeutic management. The FDG study of the brain is affected both qualitatively and quantitatively by hyperglycemia. It has been recently suggested that diabetes and poor glycemic control decrease the FDG uptake in cortical areas associated with Alzheimer disease (AD), that is, posterior cingulate gyrus and angular gyrus, whereas the accumulation of amyloid-related tracer C11-PiB is not affected. Decreased count rates, for instance owing to a partially paravenous injection, result in similarly poor image quality (Fig. 9). Conversely, as hyperglycemia has different effects on the normal brain and primary cerebral tumors, it increases the tumor to background activity ratio, and glucose loading has in fact been proposed to improve the detection rate of gliomas.

Psychotropic drugs should be known, and avoided, when they decrease the global brain activity. Accordingly, sedation should be avoided as much as possible because global and regional brain modification of activity may complicate the readability of regional modifications related to brain pathology. When absolutely needed, especially in children, sedation may be performed without significantly altering the results, but it should be achieved as late as possible after FDG injection. Benzodiazepines such as diazepam tend to significantly decrease the overall glucose utilization of the brain while preserving the regional impairment associated with AD. Sensory input should be reduced as much as possible because FDG-PET is a functional study and sensory stimuli will increase regional activity related to the given (visual, motor, or auditory) stimulation and complicate the readability of the entire brain image.

Radiolabeled Amino Acids
Radiolabeled amino acids such [11C]methionine or [18F]-FET have been shown to be useful for both diagnosing primary brain tumors and assessing their recurrence. When a tumor has been resected, the nonspecific structural modifications over time may be clarified by using labeled amino acid PET to search for tumor recurrence. At distance from surgery and radiation therapy, FET-PET/CT is capable of discriminating postradiation changes from tumor recurrence, based upon the intensity of uptake. Here, the superimposition of
A functional and structural image is clearly required for a proper interpretation of the type of regional abnormality, especially considering that in the early stage following an invasive procedure, that is, surgery or biopsy, nonspecific uptake may observed, as shown in Fig. 10.

**[18F]-DOPA**

For PET, [18F]-DOPA remains the best marker of presynaptic nigrostriatal dopaminergic loss of integrity. The combination with CT is particularly important to rule out local or remote structural lesions that can interrupt the nigrostriatal pathway or determine a modification of the striatal anatomy, which could in turn disturb the tracer distribution and mimic the neurodegenerative loss of dopaminergic axonal terminals in the neostriatum. A significant pitfall is the necessary use of carbidopa, which should be given orally at least one hour before injecting the tracer. It does not cross the blood-brain barrier and blocks the peripheral uptake of [18F]DOPA, hence improving the tracer availability in the striatum. In addition, even though the activity ratio between the striatum and the cerebellum is a strong indicator of the integrity of the pathway, further analyses, that is, pharmacokinetic modeling, are required when FDOPA-PET is to be given a physiological interpretation.

**Amyloid Tracers**

There has been a major interest in the last years for tracers of brain amyloid pathology, which is a hallmark of AD. Currently three fluorinated tracers have received Food and
Drug Administration approval as diagnostic agents: florbetapir, florbetaben, and flutemetamol. There are intense researches to better understand the sensitivity and the specificity of the findings, and the significance of different amounts of amyloid deposits. Although the interpretation criteria have been defined, uncertainty remains regarding the cutoff values. Efforts are being made to translate the research findings into the clinical practice, but all three tracers might not performed equally, and none has reached a perfect sensitivity and specificity for clinical use. Interestingly, current recommendations favor a combined use of "etiopathologic" information provided by PET amyloid and neurodegenerative information such as hippocampal atrophy on CT scanner or impaired metabolic activity on PET-FDG images for reaching high likelihood of AD diagnosis.

Visual vs Quantitative Analysis

Voxel-Based Analyses

Few voxel-based analysis programs are freely available for quantifying individual abnormalities of brain activity compared with reference populations. The best known was developed at the Hammersmith Hospital in London and is referred to as Statistical Parametric Mapping. This program (and others) provides results that depend on the entire procedure of normalization and on the reference population. The results are expressed as statistical probability of regional abnormality. This may be an interesting additional way of assessment of regional brain activity, confirming or complementing visual analysis, and reducing the interobserver variability. CT is also required because different normalization procedure may be more or less independent of brain atrophy. This is shown in Figure 11. Obviously, the quality of the normal database has a major effect on the reliability of the Statistical Parametric Mapping analysis, as shown in Figure 12. Currently available programs provide univariate analyses, but vector machine learning programs may also provide multivariate classification of a given PET scan according to reference populations.

Voxel-Based Morphometry

There is a huge literature on the interest of voxel-based morphometry (VBM) to provide information on regional distribution of atrophy related to neurodegenerative diseases. Such an atrophy needs to be compared with images obtain in normal controls to assess the degree of abnormality of the atrophy. There is certainly a major interest in PET/CT for combining evaluation of hippocampal atrophy on CT with distribution of metabolic abnormalities in hippocampal areas, because FDG-PET metabolic activity in medial temporal regions is particularly difficult to assess visually, owing to a wide interindividual variability and to complex regional interconnections. In cortical regions, FDG-PET is clearly influenced by regional atrophy, but a thin cortical area may show normal metabolic activity or impaired glucose uptake differentiating normal from dysfunctional area. Provided the CT is acquired as a high-quality study, it can be used as a base for VBM as efficiently as MRI.

CMRglu

In a limited number of cases, quantitative values of glucose uptake (cerebral metabolic rates of glucose) or quantitative...

Figure 11  SPM analysis of the PET study illustrated in Figure 6: The areas appearing as cortical hypometabolism in the SPM analysis are generated by the spatial mismatch between the actual PET study and the template used in the SPM treatment. SPM, Statistical Parametric Mapping.
Figure 12. FDG-PET/CT study obtained in a 76-year-old woman. The visual analysis shows a normal distribution of the tracer (A), confirmed by SPM analysis using a database of normal volunteers aged 65 years and older (B). When using a database of normal subjects younger than 40 years is used, a frontal hypometabolism is artificially generated (C). SPM, Statistical Parametric Mapping.
assessment of any other metabolic process may be of interest. The gold standard relies on arterial blood samples and is used for research purposes. There are strategies for imaging aortic or carotid artery activity over time, for example, using CT for delineation of vascular structures, and providing an arterial time-activity curve. However, the activity is a global one, and there is still a need for information concerning plasma and metabolites activity. The many pitfalls associated with absolute quantitation of glucose cerebral consumption are not discussed here, as they concern a very limited number of highly specialized centers. A review may be found in Alavi et al. 35

Conclusions
There is frequently a true necessity to combine functional and structural information to interpret brain pathology. MRI is widely available, and it is currently providing multiparametric images combining functional and structural data. Structural MR images may have an amazing spatial resolution; however, some structural information (such as diffusion tensor imaging) is much more difficult to interpret in everyday clinical setting. Moreover, the use of the MR functional images in individual clinical cases remains infrequent. Isotopic functional images frequently provide a precise image of brain metabolic activity with relatively accurate interpretation in individual cases. The combination of PET and CT is an interesting compromise to obtain, in a relatively short time, good information on the brain activity, with sufficient spatial and structural information for providing useful clinical data.

References
15. Society of Nuclear Medicine Procedure Guideline for FDG PET Brain Imaging. Available at: http://www.snm.org/guidelines; 2009