The Clinical Role of Fusion Imaging Using PET, CT, and MR Imaging

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KEYWORDS

• Multimodality imaging • Image fusion
• PET/CT • PET/MRI • Quantification

Medical imaging has evolved rapidly during the last 2 decades, and we are now observing radical changes in the way medicine is practiced as a logical consequence of this growth. Nowadays, clinical diagnosis is rarely done without imaging, which makes molecular imaging an essential component of the clinical decision-making tree. Contemporary molecular imaging technologies now represent the leading component of any health care institution and have a pivotal role in the daily clinical management of patients.[1]

X-ray projection imaging, ultrasonography, CT, and MR imaging differentiate disease from normal tissue by revealing structural differences or differences in regional perfusion of the administered contrast media. The interpretation of the images can be complicated when normal perfusion patterns are disrupted by prior surgery or radiotherapy, which can lead to tissue damage or necrosis where contrast patterns can mimic those associated with neoplasia. This effect presents a significant challenge when imaging techniques are used to define the anatomic extent of disease, such as for planning highly conformal radiation treatment or highly targeted therapeutic regimens.[2]

In comparison with anatomic imaging techniques, functional imaging methods including planar scintigraphy, single-photon emission computed tomography (SPECT), positron emission tomography (PET), and MR spectroscopy assess regional differences in the biochemical status of tissues. In nuclear medicine, including SPECT and PET, this assessment is done by administering a biologically active molecule or pharmaceutical to the patient which is radiolabeled and accumulated in response to its biochemical attributes. The realization that the information provided by anatomic (CT and MR) and molecular (SPECT and PET) imaging modalities is complementarity spurred the development of various strategies for multimodality image registration and fusion. Correlative or fusion functional-anatomic imaging is now well established and its clinical value widely recognized.

Several investigators proposed and in most cases developed techniques to improve the correlation between the anatomic and physiologic information obtained using these anatomic and functional imaging studies. These methods include software-based image registration in which two or more sets of images from two or more different studies are fused following their separate acquisition on stand-alone imaging systems. Commonly, image registration techniques produce a single ''fused'' or ''combined'' image in which the functional SPECT or PET image is displayed in color over a gray-scale CT or MR image of the same anatomic region. Alternatively, hardware-based, dual-modality imaging systems including SPECT/CT, PET/CT, and, in the future, PET/MR imaging, more successfully achieve this

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goal, which underlies their wider clinical acceptance by the medical imaging community.

This article discusses recent advances in clinical multimodality imaging and the role of correlative fusion imaging in the clinical setting. Future opportunities and challenges facing the adoption of multimodality imaging are also addressed.

SOFTWARE-BASED IMAGE REGISTRATION AND FUSION

Software image fusion can be challenging to perform on a routine basis in the clinical setting because it requires exceptional digital communication in medicine (DICOM) connectivity, compatibility between the scanning protocols used by various imaging modalities, and outstanding collaboration between various clinical departments. These challenges may be overcome by the use of combined PET/CT systems described in the following section, although software-based coregistration offers greater flexibility and might in some cases offer some complementary advantages to hardware-based approaches.[3,4]

Achieving a high degree of accuracy for a spatial transformation between image sets can be complicated. Physical factors such as noise, limited spatial resolution, attenuation, scatter, and partial volume effect (PVE) and biologic factors such as persistent activity in the blood pool and nonspecific uptake may decrease the contrast and blur the images; therefore, it can be difficult to locate consistent landmarks. The coregistration problem in the brain is different from the situation in whole-body imaging. Furthermore, diagnostic CT images are usually taken using breath-holding techniques, whereas PET data are acquired during a relatively long time period with the resultant reconstructed image set being an average of all phases of respiration.[5] PET/CT investigations involving imaging of the thorax, abdomen, or pelvis, where organ motion exists, result in inconsistent image sets. This inconsistency can cause complications, for example, if the body boundaries of the CT data and the PET can be registered but the internal structures still differ significantly. Various PET/CT scanning protocols performed for a short period but with a similar breathing pattern have been designed to avoid the breath-holding problem.[6] The CT data acquired allow for both attenuation correction and registration of PET/CT data for accurate localization of metabolic abnormalities. Despite their difficulties, many semi- or fully automated registration methods have been developed and used with various degrees of success in research and clinical settings. An in-depth overview of software-based registration techniques and algorithms is beyond the scope of this review. For a detailed survey of the algorithms developed so far, the reader is referred to recent comprehensive reviews.[7–10]

Two main strategies have emerged in the literature to perform so-called ''rigid registration,'' such as brain PET-MR imaging registration of images of the same patient. The first strategy is based on the identification of similar structures in both images and subsequent minimization of a ''distance measure'' between them. The second strategy uses a voxel-per-voxel similarity measure of the full three-dimensional data set as a matching criterion (where *voxel* stands for a *volume element*, ie, a three-dimensional image point). The criterion that drives the registration algorithm is known as the ''similarity measure.'' The most popular similarity measures find their origin in information theoretic approaches. These approaches include minimization of histogram dispersion,[11] maximization of mutual information,[12] or maximization of the correlation ratio.[13] The most widely used criterion is mutual information, an intensity-based similarity measure, and many variants to this approach (eg, normalized mutual information) have subsequently been proposed in the literature. Nonrigid registration approaches are usually required to correlate images of the thorax and abdomen. These approaches are usually combined with linear registration techniques to correct for changes in body configuration, differences in breathing patterns, or internal organ motion and associated displacements. Within the context of the assessment of response to treatment in which intrapatient registration of pre- and post-treatment whole-body PET images may be required to automate the analysis of lesion size and uptake,[14,15] nonrigid registration with position-dependent rigidity approaches have been suggested. These techniques assign a high degree of rigidity to some regions (eg, lesions, brain) that will remain unchanged following the registration process.[16]

HARDWARE-BASED MULTIMODALITY IMAGING

Combined PET/CT Instrumentation

The historical development of multimodality imaging is marked by various significant technical and scientific accomplishments driven by an unprecedented collaboration between multidisciplinary groups of investigators. Even though the introduction of commercial PET/CT units in a clinical setting is a recent feature, the prospective benefits of correlative multimodality imaging have been well established since the early years of medical imaging. Many pioneering radiologic scientists and physicians recognized that the

capabilities of a radionuclide imaging system could be improved by adding an external source to allow acquisition of transmission data for anatomic correlation of the emission image.[2] Interestingly, the derived theoretical concepts that were occasionally patented[17,18] never materialized in practice until the late Dr. Bruce Hasegawa and colleagues at the University of California, San Francisco[19,20] pioneered in the 1990s the development of dedicated SPECT/CT. Dr. Hasegawa is the person to credit for the conception and design of the first combined SPECT/CT unit, which now stands as a wonderful tribute to his memory.[21] Later, Dr. Townsend and coworkers at the University of Pittsburgh[22,23] pioneered in 1998 the development of combined PET/CT imaging systems, which have the capability to record both PET emission and x-ray transmission data for correlated functional/structural imaging. More compact and cost-effective designs of dual-modality systems have been explored more recently. One such approach uses a rail-with-sliding-bed design in which a sliding CT bed is placed on a track in the floor and linked to a flexible SPECT camera.[24] A variety of rail-based, docking, and click-over concepts for correlating functional and anatomic images are also being considered with the goal of offering a more economic approach to multimodality imaging for institutions with limited resources.[25]

Among the many advantages offered by PET/CT is a reduction in the overall scanning time, allowing one to increase patient throughput by approximately 30%[26] owing to the use of fast CT-based attenuation correction when compared with lengthy procedures involving the use of external transmission rod sources. **Fig. 1** illustrates the timeline for various stand-alone PET and combined PET/CT scanning protocols following tracer injection and the typical 1-hour waiting time for ^{18}F-fluorodeoxyglucose (FDG). The patient is prepared for imaging by administering the radiopharmaceutical, typically 370 to 555 MBq (10 to 15 mCi) of ^{18}F-FDG in adults. A pre-injection transmission scan is usually performed on stand-alone PET scanners before tracer injection to reduce spillover of emission data into the transmission energy window, although post-injection transmission scanning

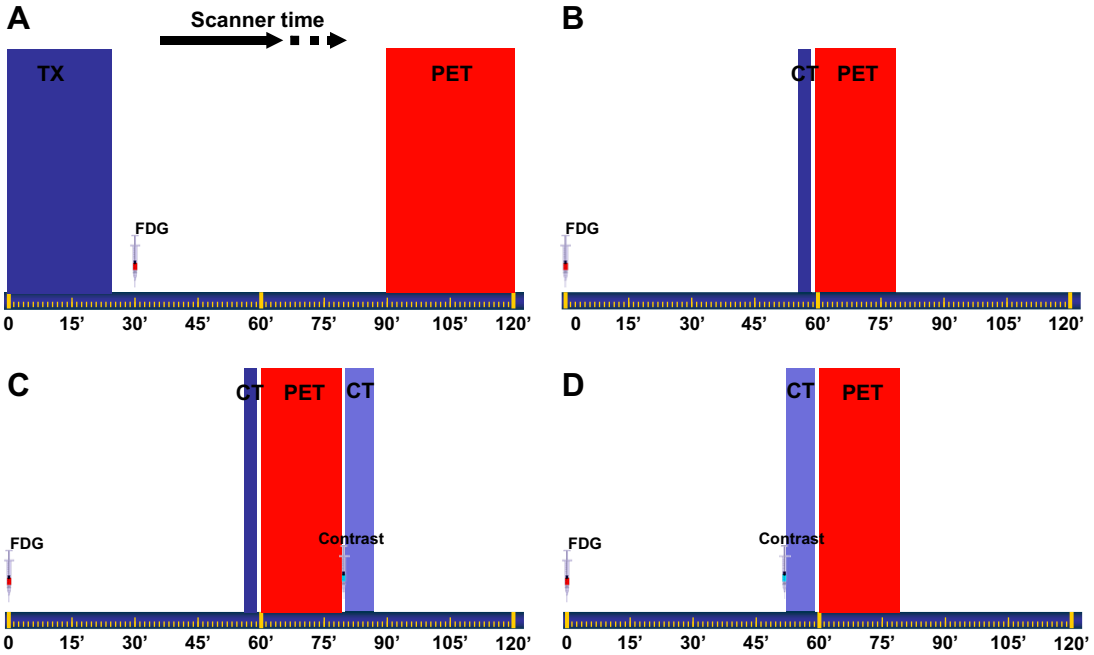

Fig. 1. Timeline for various stand-alone PET and PET/CT scanning protocols following tracer injection and typical 1 hour waiting time for ^{18}F-FDG. (*A*) The pre-injection transmission scan required on conventional stand-alone PET scanners (approximately 3 minutes per bed position on full-ring systems) is usually acquired before tracer injection. On contemporary combined PET/CT scanners equipped with fast detectors, the acquisition time is practically half the time required on conventional detectors. A low-dose CT for attenuation correction (*B*) or a study combined with a diagnostic quality contrast-enhanced CT (*C*) is usually performed depending on the clinical indication. The latter can also be used for attenuation correction but might result in artifacts in some cases by overcorrecting for attenuation in regions containing contrast medium (*D*). PET/CT allows one to reduce the overall scanning time, thus increasing patient throughput.

protocols have been successfully used in the clinic with the use of contemporary PET scanners.[27] When using combined PET/CT units, the patient is asked to remove all metal objects that could introduce artifacts in the CT scan and is then positioned on the table of the dual-modality imaging system. The patient undergoes an "overview" or "scout" scan during which x-ray projection data are obtained from the patient to identify the axial extent of the CT and PET study. The patient then undergoes a low-dose spiral CT acquisition followed by the PET study starting approximately 1 hour after FDG administration. The CT and PET data are reconstructed and registered, with the CT data used for attenuation correction of the reconstructed PET images. Depending on institutions and agreements between clinical departments and clinical requirements,[28–30] the images might be interpreted in tandem by a radiologist and nuclear medicine physician who can view the CT scan, the PET images, and the fused PET/CT data, followed by preparation of the associated clinical report. Some clinical indications commonly require administration with contrast media to acquire a relatively high-dose diagnostic quality CT scan.[31] The latter scan can be performed either before or following the PET study. In the former case, the contrast-enhanced CT is also used to correct the PET data for photon attenuation, and the low-dose CT scan is no longer needed. Care should be taken to avoid hot-spot artifacts in the attenuation-corrected PET images that might be caused by overcorrection of radiodense oral and intravenous contrast agents. As a rule of thumb, examination of the uncorrected images is recommended to distinguish technical artifacts from physiologic/pathologic hypermetabolism. Alternatively, post-processing correction methods have been proposed in the literature.[32,33]

Combined PET/MR Imaging Instrumentation

The interest in PET scanning within strong magnetic fields was first motivated by the need to reduce the distance positrons travel before annihilation (positron range) through magnetic confinement of the emitted positrons.[34–36] Indeed, Monte Carlo simulation studies predicted improvements in spatial resolution for high-energy positron emitters ranging between 18.5% (2.73 mm instead of 3.35 mm) for ^{68}Ga and 26.8% (2.68 mm instead of 3.66 mm) for ^{82}Rb for a magnetic field strength of 7 T.[36] These improvements are in agreement with the results obtained using another Monte Carlo code in which a 27% improvement in spatial resolution for a PET scanner incorporating a 10 T magnetic field was reported.[37]

The history of combined PET/MR imaging dates back to the mid-1990s even before the advent of PET/CT.[35,37,38] Early attempts to design MR-compatible PET units relied on slight modification of PET detector blocks of a preclinical PET scanner to keep the photomultiplier tubes (PMTs) at a reasonable distance from the strong magnetic field of a clinical MR imaging unit.[39–43] The detectors were coupled to long optical fibers (4–5 m), leading the weak scintillation light outside the fringe magnetic field to position-sensitive PMTs. Despite the limitations of this design, similar approaches were adopted by other investigators.[44–47] Other related design concepts based on conventional PMT-based PET detectors rely on more complex magnet designs, including a split magnet[48] or field-cycled MR imaging.[49]

Other investigators have developed PET/MR imaging systems configured with suitable solid-state detectors that can be operated within a magnetic field for PET imaging. These systems include avalanche photodiodes (APDs)[50] and Geiger-mode avalanche photodiodes (G-APDs).[51,52] APD-based readout has already been implemented on a commercial preclinical PET system, the LabPET scanner,[53] 10 years after the development of the first prototype based on this technology.[54] Various MR-compatible preclinical PET prototypes have been designed using both APD-based[55–60] and G-APD based[61,62] technologies. Other promising technologies that might be used for the design of future generation PET/MR imaging systems include amorphous selenium avalanche photodetectors, which have an excellent quantum efficiency, a large avalanche gain, and a rapid response time.[63,64]

Most of these systems have been tested within a high field (up to 9.7 T) and have produced PET and MR images that appear to be free of distortion, consolidating the hypothesis that there is no significant interference between the two systems, and that each modality is virtually invisible to the other.

The promising results obtained on preclinical systems have encouraged one of the major industrial players (Siemens Medical Solutions, Knoxville, TN) to develop the first clinical PET/MR imaging prototype (BrainPET), dedicated for simultaneous brain imaging, in collaboration with the University of Tuebingen in Germany.[65] **Fig. 2** illustrates the conceptual design and a photograph of the integrated MR/PET scanner, showing isocentric layering of the MR head coil, PET detector ring, and MR magnet tunnel together with concurrently acquired clinical MR, PET, and fused MR/PET images. The system is being assessed in a clinical setting by

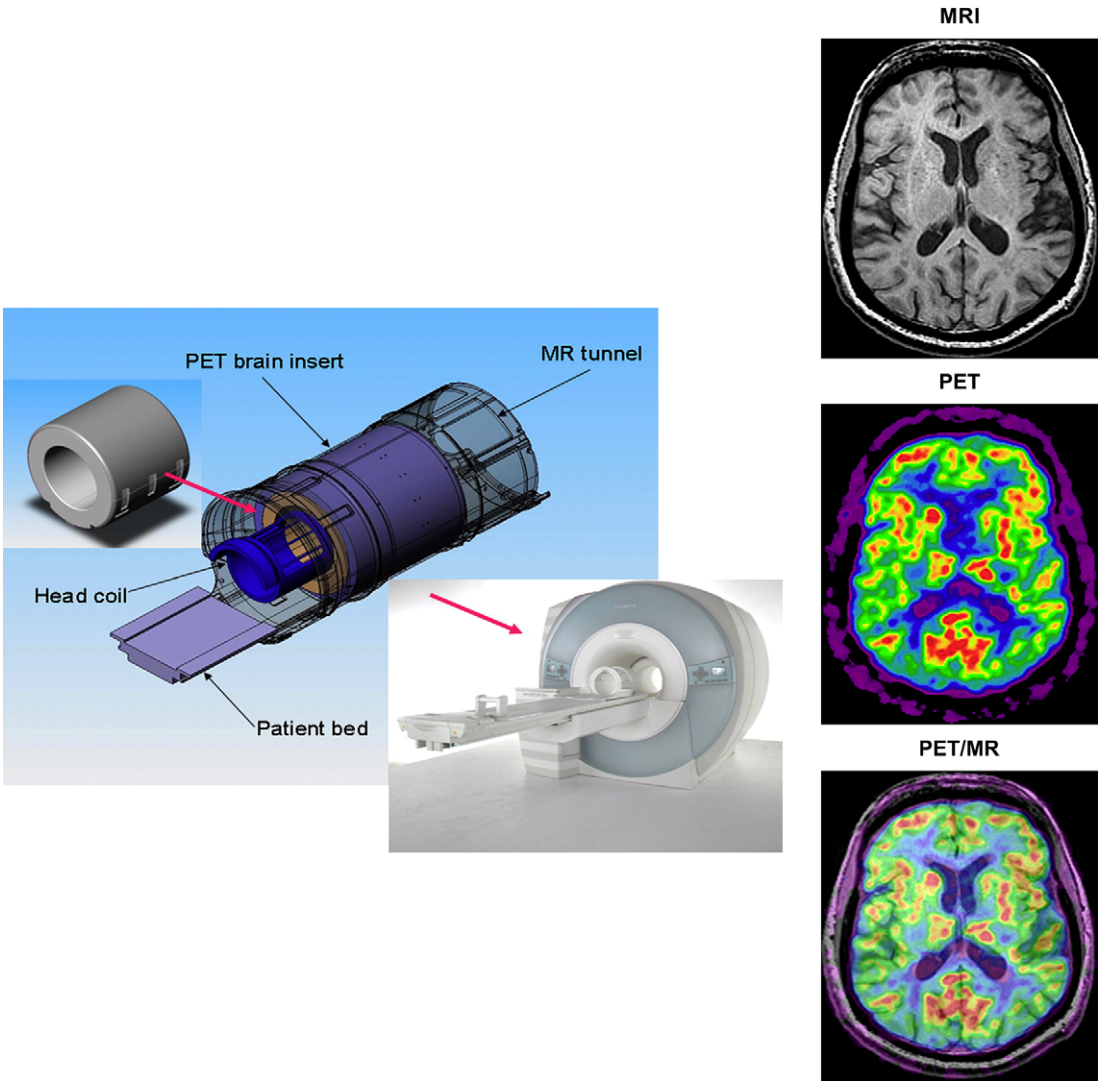

Fig. 2. Drawing and photograph of integrated PET/MR imaging design showing isocentric layering of MR head coil, PET detector ring, and MR magnet tunnel (*left*). Simultaneously acquired MR images, PET, and fused combined PET/MR images of 66-year-old man after intravenous injection of 370 MBq of FDG are shown. Tracer distribution was recorded for 20 minutes at steady state after 120 minutes. (*Adapted from* Schlemmer HP, Pichler BJ, Schmand M, et al. Simultaneous MR/PET imaging of the human brain: feasibility study. Radiology 2008; 248:1030; with permission.)

exploiting the full potential of anatomic MR imaging in terms of high soft-tissue contrast sensitivity in addition to the many other possibilities offered by this modality, including blood oxygenation level dependant (BOLD) imaging, functional MR imaging, diffusion-weighted imaging, perfusion-weighted imaging, and diffusion tensor imaging.[66] The prospective applications of a hypothetical whole-body PET/MR imaging system are being explored in the literature.[67–70] Such a system would allow one to exploit, in addition to the previously discussed applications, the power of MR spectroscopy to measure the regional biochemical content and to assess the metabolic status or the presence of neoplasia and other diseases in specific tissue areas.[71]

CLINICAL ROLE OF CORRELATIVE FUSION IMAGING

The clinical role of correlative imaging encompasses a wide variety of applications. It is now performed routinely with commercially available radiopharmaceuticals to answer important clinical questions in oncology,[72] cardiology,[73] neurology, and psychiatry.[74,75] As discussed previously,

much of the early image registration effort was restricted to intrasubject brain applications, where the confinement of compact brain tissues within the skull renders a rigid-body model a satisfactory approximation.[76,77] Correlative fusion imaging techniques were introduced in the clinic, mostly for neuroimaging applications, well before the advent of hardware-based, dual-modality imaging. Multimodality imaging had a pivotal role in the assessment of central nervous system disorders such as seizures, Alzheimer's and Parkinson's disease, head injury, and inoperable brain tumors.[78–80]

Brain SPECT imaging using ^{99m}Tc-labeled perfusion ligands shows a sharp increase during an epileptic seizure (ictal scan) at the position of the epileptogenic focus, whereas most epileptic foci show a diminished perfusion on the interictal scan. By means of ictal/interictal subtraction studies, with subsequent coregistration onto MR imaging (*S*ubtraction *I*ctal *S*PECT *C*oregistered to *M*R imaging [SISCOM]), a predictive value up to 97% for the correct localization of an epileptic focus has been reported,[81] which is higher than any other competing modality. **Fig. 3** shows an example of a ^{99m}Tc-labelled ethylene cysteine dimer (ECD) perfusion SPECT and FDG-PET studies of the same patient coregistered to an anatomic T1-weighted MR imaging study for the evaluation of epilepsy. The two ^{99m}Tc-ECD scans were performed during seizure (ictal) and when the patient was seizure free (interictal) the following day. Both SPECT studies and a three-dimensional, T1-weighted MR imaging study were coregistered using the normalized mutual information criterion, which is similar to mutual information but usually more robust and efficient in finding the correct fitting transform.[82] The differences between the ictal and interictal SPECT studies were overlaid on transaxial slices of the MR imaging study to permit accurate localization of the focus of the epilepsy. A coregistered FDG-PET study superimposed on the MR imaging study is also shown. This type of image registration and fusion technique has been a standard component of many clinical practices for the last 2 decades and is used routinely in the authors' institution. Corresponding techniques for other regions of the body have not achieved the same widespread clinical use.

Another example from the neuro-oncology field shows a patient with a glioblastoma (WHO IV) in the left temporal and frontal areas (**Fig. 4**). A similar registration approach as for **Fig. 3** was used for coregistration of an ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) brain PET scan and gadolinium-enhanced, T2-weighted MR imaging. This study showed that PET frequently detected tumors that were not visible on MR imaging. Moreover, substantial differences in terms of gross tumor volume delineation were reported when compared with MR imaging–guided treatment planning.[83]

A plethora of novel tracers are used routinely for assessing tumor metabolism and other biologic and physiologic parameters associated with many diseases.[84,85] These tracers have clearly demonstrated the enormous potential of PET/CT as an emerging modality in the field of molecular imaging. Multiple studies have demonstrated unequivocally the role of PET/CT, especially for oncologic applications.[72,86] Nevertheless, the limited role of PET/CT in some clinical indications, including central nervous system disorders, orthopedic infections, and inflammatory disorders, and in the evaluation and follow-up of metastatic disease has been advocated as a serious concern against the decision of vendors to stop manufacturing less expensive stand-alone PET systems for clinical use, which are more affordable for economically depressed nations.[87,88]

Molecular imaging in its broad definition represents methodologies and probes that allow visualization of events at the cellular and molecular levels.[89] The intended targets for this purpose include cells surface receptors, transporters, intracellular enzymes, or messenger RNA. The source of the signal detected by these techniques could originate directly from the molecule or its surrogates. In both clinical and research studies involving control subjects or volunteers, an accurate estimate of the tracer biodistribution and its pharmacokinetics is frequently a goal to understand the biochemical behavior of the probe and its suitability for the task at hand. This assessment also allows radiation dosimetry estimates to be performed to assess potential radiation risks associated with novel tracers before their administration to patients. **Fig. 5** shows typical biodistributions of ^{18}F-choline and ^{11}C-acetate probes in a subject. The CT scan can be used for attenuation correction of the PET data and for anatomic localization of tracer uptake and organ/tissue volumetric estimation, which is also required for dosimetry calculations. FDG-PET has limited impact in many malignancies presenting with low FDG avidity (eg, prostate cancer, hepatic metastases, and associated lymph nodes), where more specific tracers should be used. **Fig. 6** shows a clinical PET/CT study illustrating the limitations of ^{18}F-FDG for the detection of hepatic metastases and lymph node involvement which are clearly visible on the ^{18}F-FDopa study. In addition, the high sensitivity and specificity of FDG-PET for lymph node involvement and the capacity to better discriminate between

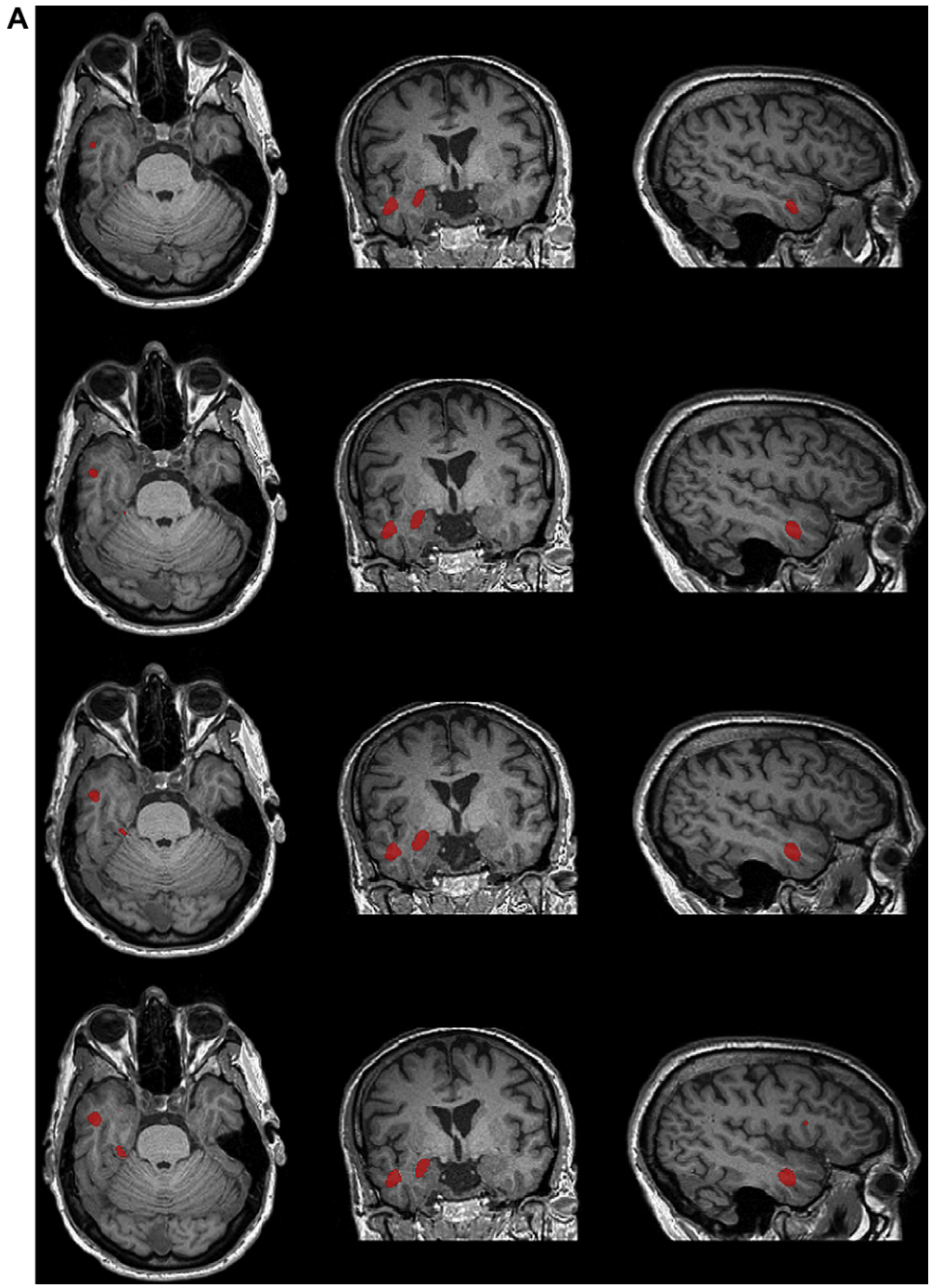

Fig. 3. Representative slices of a patient showing an example of SPECT/PET and MR imaging registration and fusion for the evaluation of epilepsy. Two ^{99m}Tc-ECD scans performed during seizure (ictal) and when the patient was seizure free (interictal) the following day are shown. Both SPECT studies and a three-dimensional, T1-weighted MR imaging study were coregistered using the normalized mutual information criterion. (*A*) The differences between the ictal and interictal SPECT studies are overlaid on transaxial slices of the MR imaging study to permit accurate localization of the focus of the epilepsy. (*B*) A coregistered FDG-PET study superimposed on the MR imaging study is also shown.

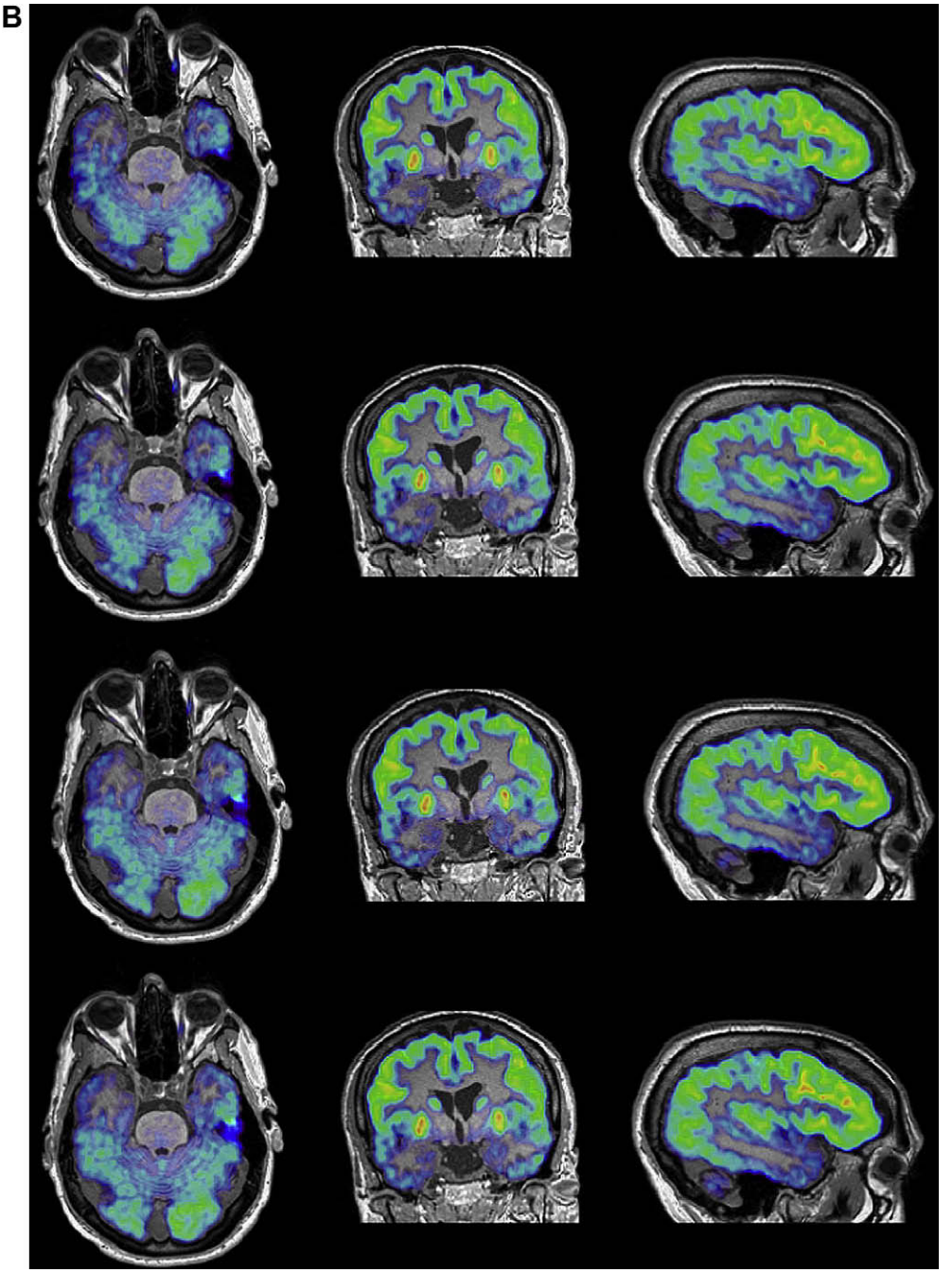

Fig. 3. (*continued*)

tumor extent and atelectasis may substantially alter the delineation of target volumes in radiotherapy.[86,90–94] **Fig. 7** shows an example where PET allowed excluding associated atelectasis that was impossible to differentiate using CT alone.[94]

ADVANCES IN ANATOMICALLY GUIDED QUANTIFICATION OF PET DATA

The primary motivation for multimodality imaging has been image fusion of functional and anatomic data to facilitate anatomic localization of functional

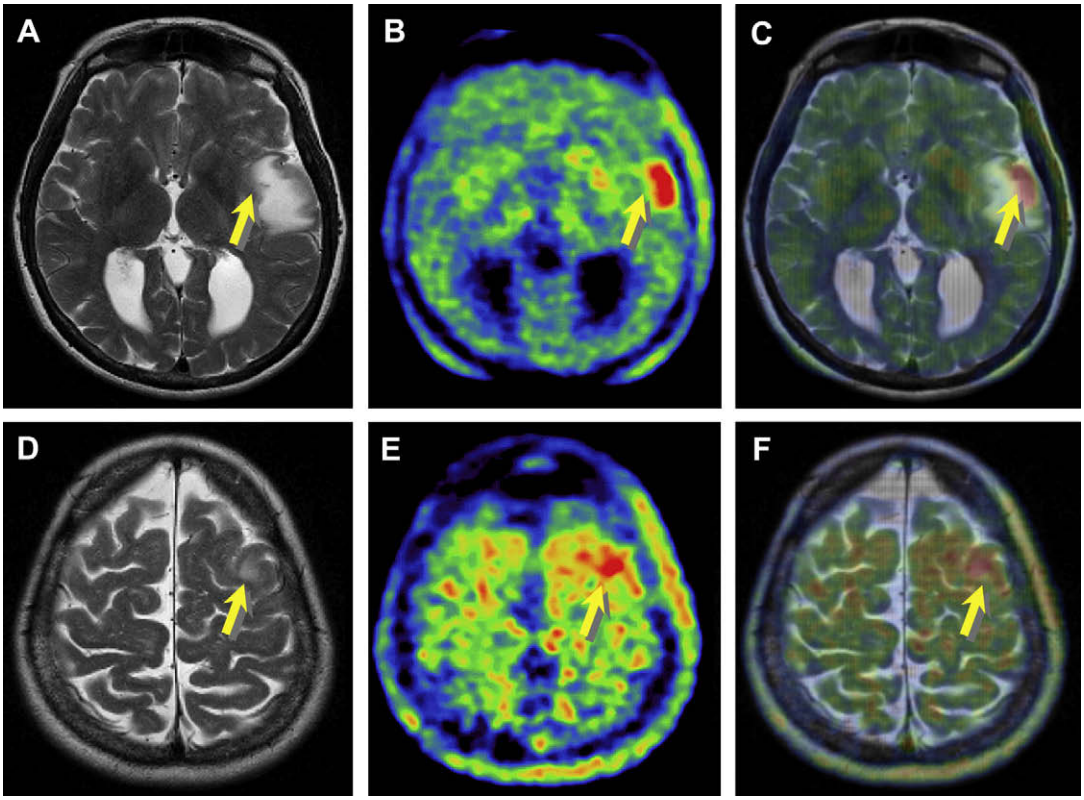

Fig. 4. Example of a patient with a glioblastoma (WHO IV) (*arrows*) in the left temporal and frontal areas. The images shown on the top row (temporal area) correspond to gadolinium-enhanced, T2-weighted MR imaging (*A*), coregistered ^{18}F-FET (*B*), and fused PET/MR imaging (*C*) of the first study. The same images are shown in the bottom row for the frontal area (*D*, *E*, and *F*). The ^{18}F-FET PET study revealed an additional lesion missed on MR imaging. In addition, the T2-weighted MR image and the ^{18}F-FET PET show substantially different gross tumor volume extension for radiotherapy treatment planning.

abnormalities and to assist region-of-interest (ROI) definition for quantitative analysis. The anatomic information also can be useful for many other tasks, including attenuation compensation, transmission-based scatter modeling, motion detection, and correction, introducing a priori anatomic information into reconstruction of the PET emission data and partial volume correction.[95]

Anatomically Guided PET Attenuation and Scatter Compensation

The use of CT-based[96,97] and, more recently, MR imaging–guided[98,99] attenuation compensation has received a great deal of attention in the scientific literature. As discussed earlier, the former has many advantages when compared with conventional transmission-based scanning, which is now considered obsolete following the advent of hybrid systems.[100] Nevertheless, CT-based attenuation correction has many drawbacks that need to be addressed through research, including polychromaticity of x-ray photons and the beam-hardening effect, misregistration between CT and PET images resulting from respiratory motion, truncation artifacts, the presence of oral and intravenous contrast medium, metallic implants, x-ray scatter in CT images, and other CT artifacts from any source.[97] MR imaging–guided attenuation correction is in its infancy and remains challenging for whole-body imaging.[98,99] This very active research topic will certainly impact the future of hybrid PET/MR imaging technology.

Traditionally, approximate scatter compensation techniques in PET have been applied in which the scatter component is estimated from measurements using additional energy windows placed adjacent to the photopeak window used to acquire the primary PET emission data. The expanding diagnostic and therapeutic applications of quantitative PET imaging have motivated the development of scatter correction techniques, which

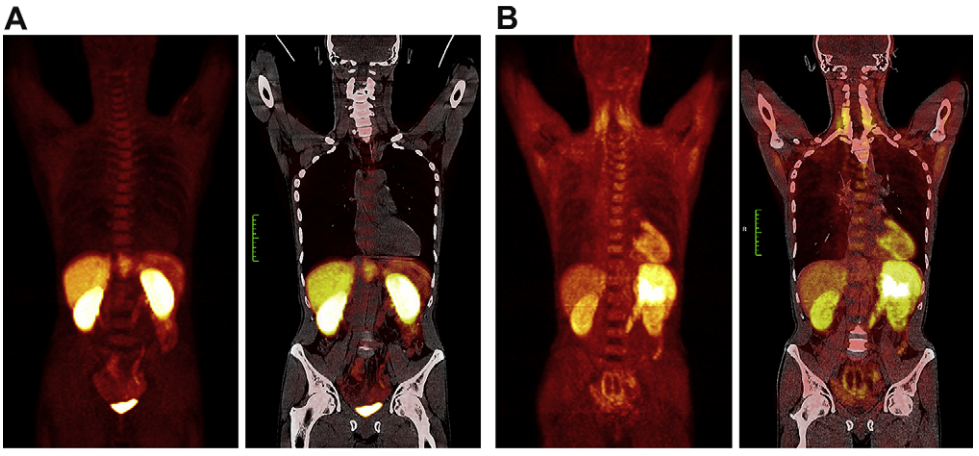

Fig. 5. Role of PET/CT in novel tracer biodistribution studies showing typical biodistributions for ^{18}F-fluorocholine (*A*) and ^{11}C-acetate (*B*) in the same subject. The CT scan is used for attenuation correction of the PET data and for anatomic localization of tracer uptake and organ/tissue volumetric estimation which is required for dosimetry calculations.

incorporate patient-specific attenuation maps derived from either transmission scans or CT imaging and the physics of interaction and detection of emitted photons to estimate the scatter magnitude and distribution accurately.[101] Transmission-based scatter correction methods use an attenuation map to define the inhomogeneous properties of the scattering object and derive a distribution of scattered events using line integrals calculated as part of the attenuation correction method. Algorithms belonging to this class of model-based methods have been successfully applied in a clinical setting.[102–105] Although computationally intensive, more refined algorithms that use a patient-specific attenuation map, an estimate of the emission image, and Monte Carlo–based radiation transport calculations to estimate the magnitude and spatial distribution of Compton scattered events that would be detected have also been considered.[106–108]

Anatomically Guided PET Image Reconstruction

An undesirable property of the statistical iterative reconstruction techniques including the popular maximum likelihood–expectation maximization (ML-EM) algorithm is that large numbers of iterations increase the noise content of the reconstructed PET images.[109] The noise characteristics can be controlled by incorporating a prior distribution to describe the statistical properties of the unknown image and thus produce a posteriori probability distributions from the image conditioned upon the data. Bayesian reconstruction methods form a powerful extension of the ML-EM algorithm. Maximization of the a posteriori (MAP) probability over the set of possible images results in the MAP estimate.[110] This approach has many advantages because the various components of the prior, such as the pseudo-Poisson nature of statistics, nonnegativity of the solution, local voxel correlations (local smoothness), or known existence of anatomic boundaries, may be added one by one into the estimation process, assessed individually, and used to guarantee a fast working implementation of preliminary versions of the algorithms. A Bayesian model also can incorporate prior anatomic information derived from a registered CT[111] or MR[112,113] image in the reconstruction of PET data with the aim of avoiding resolution loss due to the regularization, exploiting the superior resolution of the anatomic images.

This class of algorithms incorporates a coupling term in the reconstruction procedure that favors the formation of edges in the PET data that are associated with the location of noteworthy anatomic edges from the anatomic images. A Gibbs prior distribution is usually used to encourage the piece-wise smoothness of reconstructed PET images. A Gibbs prior of piece-wise smoothness can also be incorporated in the bayesian model. Some groups have published preliminary promising results with segmentation-free anatomic priors based on measures similar to mutual information, but further investigation is required. In this way, the development of dual-modality imaging systems producing accurately

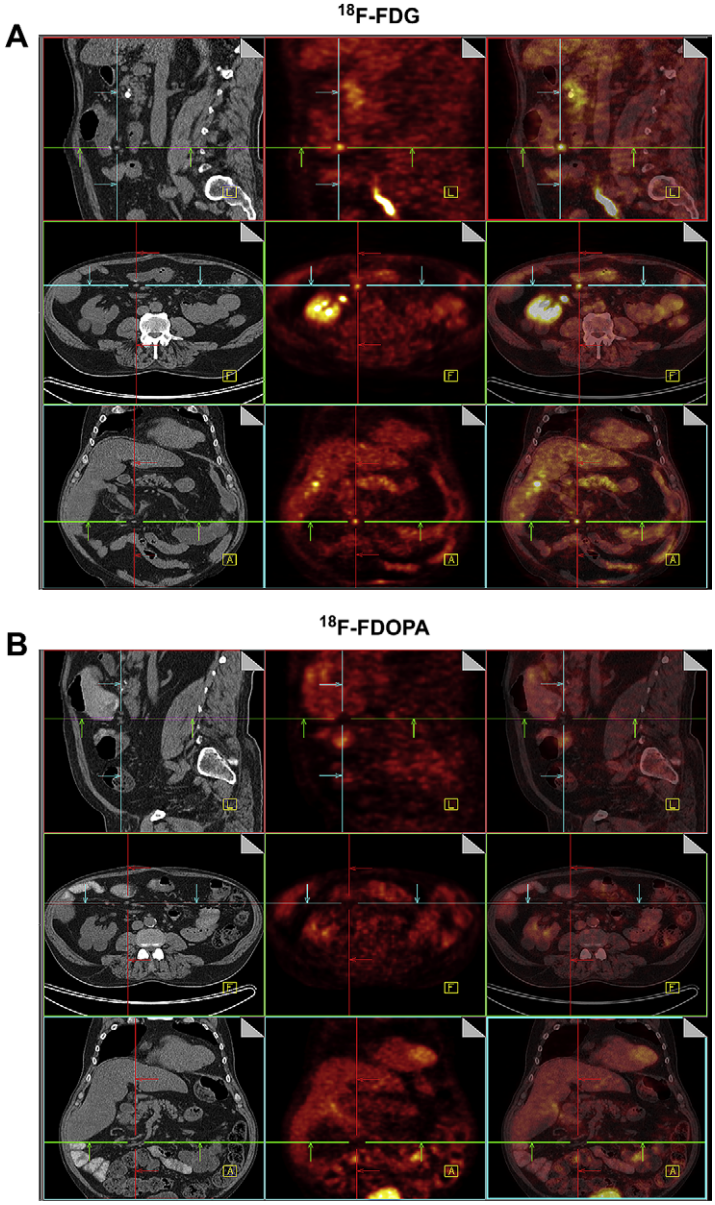

Fig. 6. Illustration of a clinical PET/CT study showing the limitations of ^{18}F-FDG for the detection of hepatic metastases and lymph node involvement, which are clearly visible on the ^{18}F-FDopa study.

registered anatomic and functional image data[23,114] is motivating the further investigation of the potential of bayesian MAP reconstruction techniques.

Anatomically Guided Partial Volume Correction in PET

The quantitative accuracy of PET is hampered by the low spatial resolution capability of currently available clinical scanners. The well-accepted criterion is that one can accurately quantify the activity concentration for sources having dimensions equal to or larger than twice the system's spatial resolution measured in terms of its full-width-at-half-maximum (FWHM). Sources of smaller size only partly occupy this characteristic volume, and, as such, the counts are spread over a larger volume than the physical size of the object owing to the limited spatial resolution of the imaging system. The total number of counts is conserved in the corresponding PET images. In this case, the resulting PET images reflect the total amount of the activity within the object but

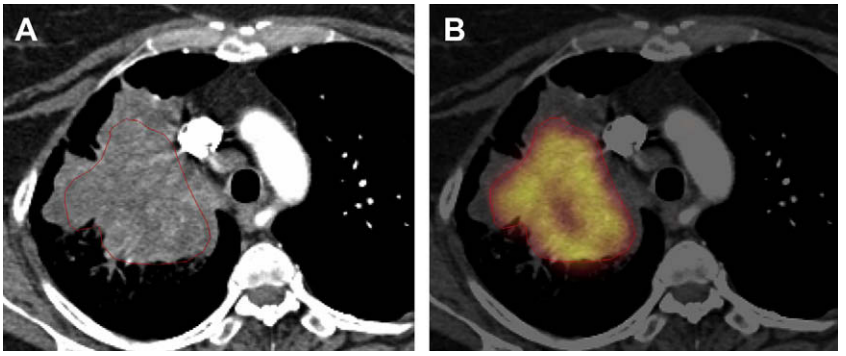

Fig. 7. Transaxial CT (*left*) and FDG-PET (*right*) images of a clinical PET/CT study of a patient with non-small cell lung cancer of the right upper lobe. PET/CT allowed excluding associated atelectasis that was impossible using a diagnostic quality CT alone, modifying the gross tumor volume delineated for radiotherapy treatment planning.

not the actual activity concentration. This phenomenon is referred to as the PVE and can be corrected using one of the various strategies developed for this purpose.[115,116] The simplest technique uses recovery coefficients determined in a calibration measurement for objects of simple geometric shape.[117] This technique works relatively well for objects that can be approximated by simple geometric shapes (eg, tumors of spherical shape).[118] More sophisticated anatomy-based, post-reconstruction approaches have also been developed to correct for this effect knowing the size and shape of corresponding structures as assessed by structural imaging (MR imaging or CT).[119,120]

Fig. 8 shows the principle of the MR imaging–guided partial volume correction approach in functional brain PET imaging. The procedure used follows the approach described by Matsuda and colleagues,[121] which involves realigning the PET and MR image volumes followed by segmenting the MR image into white and gray matter using the statistical parametric mapping (SPM5) segmentation toolbox.[122] The next step of this correction method consists in convolving the segmented white and gray matter images by the PET scanner's spatial resolution modeled by a gaussian response function. The gray matter PET image is then obtained by subtraction of the convolved PET white matter image from the original PET image. The PVE corrected gray matter PET image is then obtained by dividing the gray matter PET image by the convolved gray matter MR image. A binary mask for gray matter is finally applied. The accuracy of MR imaging–guided PVE correction in PET largely depends on the accuracy achieved by the PET–MR imaging coregistration procedure and MR imaging segmentation algorithm. The impact of image misregistration and segmentation errors has been assessed by some investigators.[119,123–127]

More recent techniques using multi-resolution synergetic approaches that combine functional and anatomic information from various sources appear promising and should be investigated further in a clinical setting.[128] The corrections for

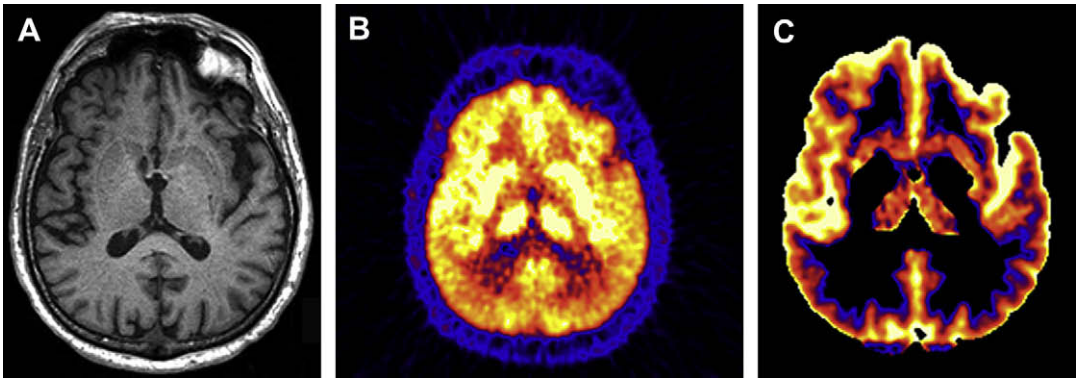

Fig. 8. Illustration of MR imaging–guided partial volume correction approach in functional brain PET showing the original T1-weighted MR image (*A*) and PET image before (*B*) and after (*C*) voxel-by-voxel PVE correction.

the PVE can also be applied during the reconstruction process by incorporating a mathematical model for PVE along with other physical perturbations (photon attenuation, scattered radiation, and other physical effects) directly into the reconstruction algorithm.[129]

SUMMARY AND FUTURE PROSPECTS

This article has attempted to summarize important themes of ongoing advancements by providing an overview of current state-of-the art developments in software- and hardware-based multimodality imaging combining PET with other structural imaging modalities (PET/CT and PET/MR imaging). Clearly, multimodality imaging has changed drastically over the last 2 decades. The pace of change has accelerated rapidly in the last decade driven by the introduction and widespread acceptance of combined PET/CT units in the clinic and the likely deployment of compact PET/MR imaging systems in the near future. Navigating beyond the sixth dimension is now becoming possible with recent progress in multidimensional and multiparametric multimodality imaging combining the latest advances in sophisticated software to make use of existing advanced hardware.[130] A controversy arose recently regarding the future role of SPECT in the era of PET.[131–134] Time will determine whether these predictions are wrong or will come true. Given that the role of any molecular imaging technology is established with respect to the benefits conveyed to patients, dual-modality imaging systems using PET as the key component are here to stay and will definitely maintain an exclusive standing in clinical diagnosis, the assessment of response to treatment, and the delivery of personalized treatments and targeted therapies.

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