Published in final edited form as:

Magn Reson Imaging Clin N Am. 2017 May ; 25(2): 297–313. doi:10.1016/j.mric.2016.12.003.

Neurological Applications of PET/MR

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Synopsis

PET/MR benefits neurological clinical care and research by providing spatially and temporally matched anatomic MR imaging, advanced MR physiologic imaging, and metabolic PET imaging. MR imaging sequences and PET tracers can be modified to target physiology specific to a neurological disease process, with applications in neuro-oncology, epilepsy, dementia, cerebrovascular disease, and psychiatric and neurological research. Simultaneous PET/MR provides efficient acquisition of multiple temporally matched datasets, and opportunities for motion correction and improved anatomic assignment of PET data. Current challenges include optimizing MR based attenuation correction and necessity for dual expertise in PET and MR.

Keywords

PET/MR; Neuro-oncology; Epilepsy; MR perfusion-weighted imaging; MR diffusion-weighted imaging; Dementia

Introduction

PET and MRI are both established imaging modalities for the study of disorders of the central nervous system, with applications in neuro-oncology, epilepsy, dementia syndromes, cerebrovascular disease, neurological disease, and psychiatric disorders. The two modalities offer complimentary information, with conventional MRI providing structural imaging of the brain with high spatial resolution and high tissue contrast and PET providing physiologic information about brain metabolism. In the last two decades, advanced MR imaging

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Disclosure statements:

Michelle M. Miller-Thomas, MD has no commercial or financial conflicts of interest. Tammie L.S. Benzinger, MD PhD receives grant support from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), participates in clinical trials for Avid Radiopharmaceuticals, Eli Lilly, and Roche, prepares continuing medical education materials for Medscape and Quintiles, and receives travel support from the National Multiple Sclerosis Society.

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techniques, including perfusion-weighted imaging (PWI), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and diffusion-weighted imaging (DWI), and several PET imaging agents targeting numerous metabolic pathways in the brain have expanded the tools available for studying the nervous system in the normal state and in various diseased states. Fusion of MRI and PET images obtained at different time points is commonly performed for clinical and research purposes, but the possibility that the physiologic processes studied by PET and by advanced MR techniques may differ slightly during the two different imaging sessions limits the ability to cross-validate emerging imaging techniques and may leave open questions about how the findings on the two imaging modalities relate to each other as there may be changes in the disease between imaging sessions. Brain imaging was one of the first applications of simultaneous PET/MR and the development of commercial simultaneous PET/MR units allows for true multiparametric analysis of the brain using the two modalities.¹ This review will focus on applications suited to hybrid PET/MR scanners that acquire PET and MR imaging simultaneously.

PET/MR Imaging Protocols

Simultaneous PET/MR of the central nervous system is most beneficial when conventional MR imaging sequences are optimized for depicting the relevant structural anatomy, advanced MR imaging sequences are utilized to study the relevant physiological state of the brain, and the PET radiotracer and image acquisition are chosen to best depict the metabolic state of the brain. MR imaging protocols targeted to specific clinical or research questions, such as oncology, epilepsy, and dementia imaging, may be easily replicated on the simultaneous PET/MR unit allowing for straightforward comparison to MR examinations performed without simultaneous PET. Similarly, PET imaging protocols are easily replicated with results of PET brain imaging acquired on PET/MR units with MR attenuation correction performing similarly to PET brain imaging acquired with conventional CT attenuation correction.² Initial studies showed good performance of hybrid PET/MR compared to PET/CT.²⁻⁵

Most commonly, PET/MR brain imaging will be performed alone without additional body imaging, although PET/MR may be used to study the remainder of the body, particularly for the workup of metastatic disease to the brain from a source outside the CNS.⁵⁻⁸ The minimum MR sequences necessary include the MR attenuation correction sequences, which depend on the MR attenuation correction technique used by the manufacturer and clinical or research site, and basic anatomic brain imaging sequences as dictated by the local site (Box 1). Commercial software for viewing simultaneous PET/MR imaging studies can fuse the PET images with any acquired conventional MR imaging sequence, including T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), DWI, susceptibility-weighted imaging (SWI), and contrast-enhanced T1WI. At our institution, we optimize imaging for epilepsy by acquiring high spatial resolution imaging of the brain utilizing T1WI, fluid-attenuated inversion recovery (FLAIR), and T2WI sequences in the coronal plane, for tumors by acquiring high spatial resolution post-contrast T1WI and FLAIR sequences, and for dementia by acquiring high spatial resolution magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences for quantitative volumetric analysis and PWI for

assessment of cerebrovascular disease. Advanced imaging sequences including PWI, MRS, DTI, and fMRI may be obtained as well with results comparable to images acquired on a dedicated MRI.

Box 1

PET/MR Brain Imaging Protocols

MR Acquisition

- Dixon sequence for PET attenuation correction (modify if using an alternative method of attenuation correction)
- Conventional brain MRI sequences
- For tumor evaluation consider including PWI, MRS, fMRI, DTI
- For epilepsy evaluation consider including coronal plane T1WI, T2WI, FLAIR
- For dementia evaluation consider including MPRAGE for quantitative volumetric analysis and PWI

PET Acquisition

- PET tracer may be injected either prior to scan or during scan depending on the indication
- Simultaneously acquire PET data during MR acquisition
- Tumor evaluation: ^{18}F -FDG, amino acid analogs, ^{18}F -FLT, ^{18}F -MISO
- Epilepsy evaluation: ^{18}F -FDG
- Dementia evaluation: ^{18}F -FDG, amyloid-specific tracers, tau-specific tracers

Numerous PET imaging agents targeted to specific disease processes may be used with PET/MR. 2-[fluorine-18]fluoro-2-deoxy-D-glucose (^{18}F -FDG) is the most well-known PET radiotracer and the most commonly used Food and Drug Administration (FDA)-approved radiotracer for clinical tumor imaging, epilepsy imaging, and dementia imaging. It is widely available in areas of the world that routinely perform clinical PET. There are currently three FDA-approved ^{18}F -labeled amyloid- β PET imaging agents including ^{18}F -florbetaben, ^{18}F -florbetapir, and ^{18}F -flutemetamol. Multiple other radiotracers, including those targeting tau protein in Alzheimer disease research and amino acid metabolites in brain tumor research, are not currently FDA approved. Limited access to cyclotron facilities capable of producing many of these PET tracers limits their use to research facilities.

The portion of the PET/MR exam specific to PET imaging includes the injection and uptake period for the PET tracer, acquisition of the MR images required for PET attenuation correction, and collection of PET data. Brain-only PET imaging may allow for the injection and uptake phase of the PET exam to occur while the targeted MR imaging is being acquired, thus increasing efficiency of the exam acquisition for both the patient and the PET/MR facility. Some PET studies benefit from the collection of dynamic PET data or PET

images at more than one time point after injection which is easily coordinated within the sequence of MR image acquisition since PET data can be collected simultaneously. Long PET acquisition times are also possible, thus increasing total collected counts and signal to noise ratio.

PET/MR Benefits and Challenges

PET/MR offers several advantages over separately acquired conventional PET/CT and MRI (Box 2). The practical advantage of simultaneously acquiring PET and MRI during a single imaging session eliminates possible delays in scheduling two separate exams; potentially improves patient satisfaction as the patient only needs to travel to the imaging facility and take time away from other daily activities for a single exam rather than two exams; and patients requiring sedation for PET and MRI only need to undergo sedation a single time for a shorter total time length. A PET/MRI only utilizes ionizing radiation for the radiotracer used for the PET imaging, saving the added radiation necessary for attenuation correction and anatomic correlation utilized in the CT portion of a PET/CT which is beneficial in young patients, pregnant patients, and patients with a potentially long lifespan who may need multiple PET imaging studies during their remaining lifetime. PET/MR may add value by promoting multidisciplinary interpretations with PET and neuroimaging experts.⁶ While commercially available fusion software does a good job of fusing separately acquired PET/CT with MRI, only simultaneous PET/MR can provide temporally matched information for disease states that may change between the time it takes to acquire two separate imaging studies. Patient head motion during PET acquisition may interfere with appropriate attenuation correction or lead to misregistration of the PET data to the MR images. MR-based motion tracking may be used to realign the PET data.^{9,10} The PET spatial resolution obtained from the Siemens mMR Biograph simultaneous PET/MR (Siemens, Erlangen, Germany) has been measured at 4.3mm, which is greater than typical human cortical thicknesses.¹¹ Activity in the thin cortical layer may be falsely localized to adjacent areas. The MR component of the scan may be used to create an anatomical mask for gray matter and white matter to improve assignment of PET activity to tissue on the MRI.¹⁰ Quantitative brain PET relies on an input function obtained from arterial sampling to estimate delivery of the tracer to the binding site. PET/MR provides a means for noninvasively measuring the arterial input function from the internal carotid artery, validated against conventional arterial blood sampling and ¹⁵O-H₂O measurement of cerebral blood flow.¹²

Box 2

PET/MR Benefits and Challenges

Benefits

- Improved efficiency by acquiring PET and MR datasets during a single examination
- MR-based attenuation correction reduces total radiation dose

- Temporally and spatially matched anatomic MRI, PWI, DWI, and MRS data with PET metabolic data
- Simultaneous acquisition reduces error in combined interpretation of MR physiologic and PET metabolic data which may fluctuate across time as disease states and therapies change
- Opportunity for combined interpretations from PET and MR experts that may provide added benefit over separately interpreted PET and MR studies
- Potential for MR-based motion correction for PET
- Potential for MR-based gray-white matter mask to improve localization of PET activity
- Noninvasive MR-based tools for measuring arterial input function for quantitative brain PET

Challenges

- MR attenuation correction techniques require further validation
- Availability of PET/MR scanners for clinical use remains limited to large medical centers
- Two sets of technologists and physicians with expertise in PET and MR, or a single technologist and physician with dual training in PET and MR, are required to acquire and interpret PET/MR studies

PET/MR poses challenges for the PET and MR imaging communities (Box 2). MR-based attenuation correction strategies for the brain, discussed in detail elsewhere, are an ongoing area of research. The most common strategy used for pure MR-based attenuation correction in clinical scanners uses the Dixon MR technique creating an attenuation correction map consisting of tissue, air, fat, and water. This technique does not account for attenuation due to bone which is relevant to brain imaging since the brain is surrounded by the skull. Studies are ongoing evaluating the impact of this attenuation correction technique on brain imaging as well as developing alternative methods.^{13,14} Hitz and colleagues reported that the measured uptake of ¹⁸F-FDG in the brains of dementia patients was lower on a PET/MR scanner compared to a PET/CT scanner. This was true for both attenuation corrected and non-attenuation corrected data. A new cohort of normal control patients imaged with PET/MR may be necessary for future clinical trials which may require quantitative PET.¹⁵ There are few physicians with dual expertise in both modalities. The American College of Radiology and the Society of Nuclear Medicine and Molecular Imaging recommend that the MR component and PET component should be interpreted by physicians that meet qualifications standards in the two modalities.¹⁶ PET/MR is ideally interpreted as a single study utilizing both PET and MR information to arrive at a final interpretation. At some institutions, this may require joint interpretation by PET and MR experts. Cross-modality training should also be considered in residency and fellowship programs as well as professional societies offering continuing medical education. Similarly, the skill set and knowledge base required for meeting the technical and safety standards for acquiring PET

and MRI differ, necessitating the crosstraining of PET and MRI technologists in the complimentary modality in order to safely acquire a PET/MR. The Society of Nuclear Medicine and Molecular Imaging Technologist Section and the Section for Magnetic Resonance Technologists recommend that technologists involved in acquiring PET/MR meet qualification standards for MR and PET individually which may either require MR and PET technologists, or a single dual trained technologist with advanced training in the field secondary to their area of expertise.¹⁷

Applications

Oncology

Contrast-enhanced MRI is the first line imaging study for diagnosis, presurgical planning, and treatment monitoring of both primary brain tumors and metastatic brain tumors. Advanced MR imaging techniques including perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), MR spectroscopy (MRS), diffusion tractography (DTI), and functional MR imaging (fMRI) provide physiologic information about the tumor and adjacent brain which complements conventional MRI in both clinical and research settings.

PET utilizes radiotracers targeted to different aspects of tumor metabolism: glucose metabolism (¹⁸F-FDG), amino acid transport and protein synthesis (¹¹C-MET, ¹⁸F-FET, ¹⁸F-DOPA), proliferation rate and DNA synthesis (¹⁸F-FLT), oxygen metabolism and hypoxia (¹⁸F-MISO). Although not practical for clinical use due to short half-life, ¹⁵O-H₂O is used to study tumor perfusion.¹⁸ While PET does not have a primary clinical role in oncologic imaging of the brain, ¹⁸F-FDG PET of the brain is used clinically most commonly to differentiate radiation necrosis from recurrent tumor.^{19,20} The radiotracers targeting other metabolites are promising because of improved signal to background ratio and specificity for tumor compared to ¹⁸F-FDG. PET has been used in glioma research utilizing multiple tracers beyond ¹⁸F-FDG targeting different aspects of tumor metabolism to study tumor grading, tumor extension, treatment planning, treatment follow up, and prognosis, as well as to validate physiologic information gained from advanced MR imaging. The combination of MR-based anatomic and physiologic imaging with temporally and spatially matched PET-based molecular imaging allows us to answer questions pertaining to prognosis, plan therapeutic approaches, and assess response to treatment with greater confidence than is possible with either modality alone (Box 3).²¹

Box 3

Oncology Applications

Simultaneous PET/MR provides benefit by ensuring that MR physiologic data and PET metabolic data reflect the same biological state, eliminating the chance that change in therapy between separate imaging sessions may cause discordant results

Glioma Grading

- Contrast enhancement, elevated rCBV, lactate peak on MRS, and low ADC suggest HGG

- ^{18}F -FDG, ^{11}C -MET, ^{18}F -DOPA, and ^{18}F -MISO can differentiate HGG from LGG

Tumor Extension

- PWI, DTI/DWI, MRS, and amino acid analog PET tracers aid in determining nonenhancing tumor margins

Treatment Follow Up

- MRS, PWI, DWI, ^{18}F -FDG PET, and amino acid PET aid in differentiating radiation necrosis and pseudoprogression from recurrent high grade glioma

Metastatic Disease

- Conventional contrast-enhanced MRI is primarily used for detection of intracranial metastatic disease and follow up after treatment
- Whole-body ^{18}F -FDG PET/MR including dedicated contrast-enhanced brain imaging may be equivalent to PET/CT and brain MRI for staging metastatic lung cancer

Tumor Grading and Differential Diagnosis—The differential diagnosis of intracranial masses and initial estimation of tumor grade begins with conventional MRI. Contrast-enhancement due to breakdown of the blood brain barrier is the imaging marker used in MRI to differentiate high grade gliomas (HGG) from low grade gliomas (LGG), and to detect transformation of a LGG to a HGG. Histopathologic evaluation of brain tumors remains the gold standard for assessing tumor grade since as many as a third of HGG may not enhance.²² Additionally, stereotactic biopsy may undersample a tumor, leading to an inappropriately lower histologic grade.²³ PWI, DWI, and MRS provide additional physiologic information and PET provides additional metabolic information to delineate regions of the tumor of highest grade for biopsy planning and to detect transformation of a LGG to a HGG with greater confidence.

PWI interrogates the vascularity of tumor and the surrounding tissue. Within the astrocytoma line of tumors, higher rCBV corresponded to higher tumor grade. rCBV aids in differentiating neoplastic from non-neoplastic lesions, provides an estimate of tumor grade, and may be used to direct biopsy towards the portion of the tumor with the potential highest grade.^{24–26} Caution is necessary in utilizing results as there is variability in techniques for processing and interpreting MR perfusion which influence results, and the major techniques do not yield the same values when applied to the same tumor.^{27,28} The apparent diffusion coefficient (ADC) value obtained from DWI corresponds to high cellularity seen at pathology in HGG.²⁹ DWI can predict glioma grade, with higher grade tumors having lower ADC values.^{30,31} An altered metabolite spectrum with ^1H -MRS suggests tumor grade. ^1H -MRS demonstrates increased choline due to increased cellular membrane synthesis and reduced *N*-acetylaspartate due to neuronal loss in the setting of HGG. Elevated lactate suggests tumor hypoxia and lipid indicates necrosis as is seen in HGG histopathology.³² MR spectroscopy is technically challenging to acquire in clinical practice with overlap seen between tumors and tumor mimickers.

High grade tumors have a high rate of glucose metabolism and increased ^{18}F -FDG uptake. ^{18}F -FDG uptake correlates with high glioma grade and reduced survival.³³ New elevated ^{18}F -FDG uptake within a LGG signals conversion to HGG.^{33,34} Inherent high ^{18}F -FDG background activity in the brain results in poor delineation of some primary brain tumors and small metastases compared to MRI, preventing routine use of ^{18}F -FDG in brain tumor imaging.^{8,35,36} Coregistration of ^{18}F -FDG PET with MRI is critical as ^{18}F -FDG uptake of tissue must be correctly assigned to white matter, gray matter, or abnormal tissue for proper interpretation.³⁷ Alternative PET tracers, including ^{18}F -DOPA, ^{18}F -MISO and ^{11}C -MET, have been studied as well for predicting tumor grade and time to progression but are not in routine clinical use.^{38–41}

Tumor Extension and Treatment Planning—MRI defines the margins of enhancing and nonenhancing primary and metastatic tumor for surgical resection, but there is overlap in the appearance of nonenhancing glioma margins and vasogenic edema on T2WI.²² Advanced MRI sequences, including diffusion tensor imaging, MRS, and PWI, and PET imaging with amino acid analogs aid in differentiating tumor margin from edema. PWI, particularly rCBV, and fractional anisotropy derived from diffusion tensor imaging differ between nonenhancing tumor and peritumoral edema.^{26,30} Amino acid analogs are well suited to this problem because they have high uptake in tumor and low uptake in normal brain which improves tumor-tissue contrast compared to ^{18}F -FDG.⁴² ^{11}C -Methionine and ^{18}F -FET PET have been shown to differentiate tumor margin from edema, with ^{18}F -FET PET shown to be superior to ^{18}F -FDG PET in determining extent of tumor.^{43–45} ^{18}F -DOPA also shows promise in ability to delineate tumor margins for surgical resection and radiotherapy planning (Fig. 1). Multiparametric maps including MRI and PET sequences may lead to maps of the brain delineating on a voxel by voxel basis the expected grade of tumor and delineate the full extent of tumor.⁴⁶ Simultaneous PET/MR efficiently combines structural MR imaging with advanced MR data and metabolic PET data for complete pretreatment evaluation of the tumor.^{3,6,38,47}

fMRI and tractography play a role in presurgical planning prior to biopsy or resection of gliomas and metastases by delineating eloquent cortex and the associated fiber tracts. Incorporating fMRI and DTI into the presurgical workup facilitates maximal resection with reduced risk of loss of neurologic function as a result surgery.^{48,49} Neuschmelting et al. recently reported using PET/MR including ^{18}F -FET PET, contrast-enhanced MRI, tractography, and navigated transcranial magnetic stimulation to map the relationships between enhancing tumor, metabolically apparent tumor, and eloquent cortex and tracts for surgical planning.⁵⁰

Treatment Follow Up—Contrast-enhanced MRI is the key imaging study for following response to therapy, recurrence, and development of treatment-related changes. Conventional MRI is fraught with problems in the post-treatment brain because of difficulties in assessing nonenhancing tumor, following response to anti-angiogenic therapy, differentiating pseudoprogression from true early progression, and differentiating recurrent tumor from delayed radiation necrosis.^{51–54} Although structural detail is superior with MRI, overlap in the appearance of treatment-related changes and recurrent high grade glioma or

metastases supports a role for PET imaging. Simultaneous PET/MR is especially useful as it is a common conundrum in clinical practice that results from MR differ from the results of ^{18}F -FDG PET. Differences may be due to changes in therapy initiated between the scans or reflective of complex tumor biology. Simultaneous acquisition of MR physiologic imaging and PET metabolic imaging provides more confidence that all imaging data reflects the same state.

rCBV has been shown to aid in differentiating delayed radiation necrosis from recurrent high grade tumor.⁵⁵ Fink et al. showed that multivoxel MRS, specifically Choline/Creatine and Choline/*N*-acetylaspartate ratios, and rCBV ratios had equivalent performance in differentiating radiation necrosis from recurrent high grade glioma.⁵⁶ Multiparametric maps incorporating ADC, rCBV have been shown to correlate with response to treatment.^{57,58} Prat et al. showed that MRS and PWI reached 100% positive and negative predictive values for detecting the presence of high grade glioma in treated patients, compared to a positive predictive value of 75% and negative predictive value of 61.1% for ^{18}F -FDG PET.⁵⁹

One of the earliest applications of ^{18}F -FDG PET in the brain was differentiating radiation necrosis from recurrent tumor (Fig. 2).²⁰ ^{18}F -FLT, ^{18}F -DOPA, ^{18}F -FLT, and ^{11}C -MET with their more favorable tumor-to-background activity characteristics, may perform better than ^{18}F -FDG.^{19,60–63} In a meta-analysis published in 2013, Nihashi et al. reported that ^{11}C -MET had a summary sensitivity of 0.70 (95% confidence interval, 0.50–0.84) and specificity of 0.93 (95% confidence interval, 0.44–1.0) across 7 studies for detecting recurrence of HGG after treatment compared to a summary sensitivity of 0.77 (95% confidence interval, 0.66–0.85) and specificity of 0.78 (95% confidence interval, 0.54–0.91) across 16 studies for ^{18}F -FDG PET.¹⁹ The mean lesion-to-normal tissue ratio of ^{11}C -MET uptake was a good tool for differentiating tumor recurrence from radiation necrosis for both gliomas and metastatic disease.⁶⁴ Two studies found that ^{18}F -DOPA was more accurate than rCBV in detecting recurrent brain metastases from radiation necrosis.^{65,66} While the body of evidence comparing PET to other imaging modalities is growing, the body of knowledge is still small.

Evaluation of Metastatic Disease—Brain metastases are best detected with contrast-enhanced MRI. Many brain metastases may be small and therefore masked by normal cortical ^{18}F -FDG uptake. Whole body PET/MR has been proposed as a one-stop shop approach to screening for metastatic disease in newly diagnosed lung cancer, evaluating the body with ^{18}F -FDG PET with MR for attenuation correction and anatomic correlation and the brain with dedicated contrast-enhanced brain MRI sequences.^{6–8} Other cancers requiring initial staging with brain MRI and whole-body PET/CT may be candidates for whole-body PET/MR as well.

Role of PET/MR in Neuro-Oncology—Multimodality imaging of brain tumors with MRI and PET at initial diagnosis and in follow up imaging adds information that may benefit treatment planning and decision making.^{21,67} PET/MR has emerged as an important tool in neuro-oncologic research providing spatially and temporally matched molecular, physiologic, and anatomic data for the study of tumor biology and therapies as well as a means for cross-validating advanced MR techniques with PET-derived data. Studies are

emerging showing that multiparametric tumor maps incorporating PWI, DWI, and MRS with molecular PET data predict tumor grade, define tumor extent, and correlate with response to therapy.^{46,57,58} The combined data obtained from PET/MR may provide a better estimate of tumor extent, higher accuracy in tumor grading, more prognostic information, optimization of surgical, chemotherapeutic, and radiation-based therapy, and better delineation of tumor recurrence from radiation necrosis than either modality alone.

Challenges still remain for PET/MR in the field of neuro-oncology. Filss et al. found that areas of high grade tumor predicted by elevated rCBV differed from those predicted by ^{18}F -FET uptake.⁶⁸ Sacconi et al. studied accuracy of ^{18}F -FDG and PWI for differentiating HGG from LGG and tumor recurrence from treatment-related changes. They found differing spatial distribution between regions of elevated rCBV and increased ^{18}F -FDG uptake.⁶⁹ Future challenges for the PET/MR community include defining the optimal set of MR imaging parameters and standardizing their acquisition and processing for reproducibility, identifying the best PET radiotracer for each clinical question, and justifying the clinical utility of multimodal imaging.

Epilepsy

Diagnostic imaging plays a crucial role in the evaluation of patients with medically refractory epilepsy, including patients with temporal lobe epilepsy (TLE), focal cortical dysplasia (FCD), and tuberous sclerosis complex (TSC). Both structural imaging with MRI and metabolic imaging with interictal ^{18}F -FDG PET are utilized to confirm the location of epileptogenic cortical lesions suspected by clinical observation, EEG, and intracranial monitoring in preparation for surgical resection (Box 4). PET may provide additional diagnostic support for a suspected epileptogenic focus identified on MRI, or it may provide independent information regarding a potential epileptogenic focus in the setting of either a normal MRI or an MRI with multiple structural abnormalities. In addition to surgical planning, the combination of structural and PET imaging informs outcomes, alters treatment plans, and increases confidence in surgical therapy.

Box 4

Epilepsy Applications

- Structural imaging with MRI can identify lesions responsible for medically-refractory epilepsy
- Combined MRI and ^{18}F -FDG improves detection of focal cortical dysplasia over either modality alone
- Unilateral reduced ^{18}F -FDG uptake in temporal lobe epilepsy predicts a better outcome following surgery
- Simultaneous PET/MR may show lesions not detected by PET/CT and MR evaluation alone

^{18}F -FDG is the dominant PET radiotracer used in clinical practice, with epileptogenic foci demonstrating hypometabolism (Fig. 3).^{70,71} Fusion of separately acquired MRI with ^{18}F -

FDG PET improves detection of FCD over either modality alone and supports planning for surgical resection.⁷² Fusion of separately acquired high spatial resolution MRI to ¹⁸F-FDG allows limited cortical resection of metabolically abnormal foci.⁷³ In a study of TLE patients, subjects with a positive ¹⁸F-FDG PET and a normal MRI did as well after temporal lobe resection, suggesting that a PET scan lateralizing clinically suspected TLE may obviate the need for intracranial monitoring when MRI is normal.⁷⁴ Gok et al. demonstrated that TLE patients with unilateral reduced temporal lobe ¹⁸F-FDG uptake had excellent postsurgical outcomes, with 96% Engel class I and II.⁷⁵

While the vast majority of research has been performed with separately acquired PET and MRI, recently simultaneous PET/MR has been reported to perform well in detecting clinically confirmed epileptogenic foci.⁷⁶ Simultaneous PET/MR has also been reported to show new lesions that were not detected on PET/CT and MR evaluation alone.⁷⁷

Dementia

Dementia is a major cause of disability in the elderly. Alzheimer's disease (AD) is present either alone or coexisting with another type of dementia in approximately 60–80% of patients with dementia, with cerebrovascular dementia (CVD), frontotemporal lobar dementia (FTLD), and dementia with Lewy bodies (DLB) accounting for the majority of the remaining causes of dementia.⁷⁸ Mild cognitive impairment (MCI) is a state in which there is impairment in memory in combination with cognitive impairment, but it does not interfere with the patient's ability to function in usual activities.⁷⁹ MCI often precedes AD, but not all patients with MCI will progress to AD. Pathologic accumulation of amyloid- β plaques within the brain initiates a cascade that results in tau protein accumulation in the form of neurofibrillary tangles and eventual neuronal loss.^{80–83} The diagnosis of AD and MCI relies primarily on meeting core clinical criteria for AD without meeting core criteria for other disorders such as CVD, FTLD, or DLB. The diagnosis of AD may be supported by imaging and cerebrospinal fluid biomarkers.⁷⁹ There are currently no therapies that can halt or reverse AD, but cholinesterase inhibitors and memantine are approved by the Food and Drug Administration to temporarily improve the cognitive symptoms of AD.

The evaluation of dementia begins with structural imaging to exclude causes other than AD. Advanced MR techniques, including volumetric MRI, susceptibility-weighted imaging (SWI), fMRI, and PWI, and PET molecular imaging with ¹⁸F-FDG, amyloid-specific radiotracers, and tau-specific radiotracers serve as biomarkers of the pathogenesis of AD (Box 5)^{79,84–97}.

Box 5

Dementia Applications

- Quantitative volumetric MRI can provide patterns of atrophy that suggest AD, FTLD, or normal pressure hydrocephalus
- PET provides imaging biomarkers of AD physiology within the brain
- A negative amyloid-PET scan suggests that AD is unlikely to be the cause of dementia

- Tau-PET tracer accumulation displays the spatial distribution of tau protein deposition in AD and correlates with clinical severity of dementia and degree of neurodegeneration seen at autopsy
- ^{18}F -FDG PET reflects neuronal injury in AD, helps differentiate AD from other causes of dementia, and predicts decline from MCI to AD with good sensitivity and specificity
- Simultaneous PET/MR provides both the convenience of a single imaging session as well as confidence that all imaging biomarker data reflects the same biological state of the brain

Structural MRI—Structural imaging first excludes imaging patterns that support other explanations for dementia including multiple infarcts in the cortex and deep gray nuclei (CVD), frontotemporal-predominant atrophy (FTLD), ventriculomegaly disproportionate to cerebral atrophy (normal pressure hydrocephalus), and marked intracranial mass effect (large intracranial tumors or subdural hygromas). The pattern of cortical volume loss reflects the pathophysiology of AD, with volume loss more prominent in the temporal and parietal lobes, with the entorhinal cortex and hippocampus most severely affected.⁸⁸ Cortical atrophy is a normal part of aging, but the rate of cortical atrophy is accelerated in AD. Hippocampal atrophy is reported in 70–95% of patients with AD and has a sensitivity of 85% and specificity of 88% for distinguishing patients with AD from healthy control patients.^{88,93}

Perfusion Weighted Imaging—There is a growing recognition that vascular disease influences the cognitive impairment of AD.⁹⁸ PWI using dynamic-contrast enhanced technique (DCE) displays regional alterations in cerebral hemodynamics and blood-brain barrier integrity.⁹⁹ As research into the role of cerebral hemodynamics in AD continues, assessment of cerebrovascular disease may be viewed alongside the metabolic imaging markers of AD pathophysiology (amyloid-PET, tau-PET, FDG-PET) and structural MR imaging data in determining progression of MCI to AD or guiding future therapy for AD.⁹⁹

Amyloid-PET—Amyloid- β in the brain can be imaged by radiotracers that specifically bind amyloid- β , including ^{11}C -labeled Pittsburgh compound B (PiB, GE Healthcare) and ^{18}F -labeled florbetapir (Avid Radiopharmaceuticals), flutemetamol (GE Healthcare), and florbetaben (Piramal Imaging).⁸⁹ Amyloid- β accumulation demonstrated by a positive amyloid-PET study is not unique to AD and can be seen in cognitively normal adults, patients with dual causes for dementia, and patients with other amyloid-related disease such as DLB. A positive amyloid-PET study may not indicate the presence of AD or may not indicate that AD is the sole cause of cognitive impairment. A negative amyloid-PET scan does indicate that AD is unlikely to be the cause of the dementia disorder.^{86,87} In patients with MCI, a positive amyloid-PET study is associated with progression to dementia.⁹⁰ Amyloid-PET is most commonly used in drug treatment trials and other research settings since it is not currently reimbursed by Medicare and Medicaid.

Tau-PET—Several PET radiotracers that bind tau with high affinity are available including ^{11}C -PBB3, ^{18}F -T807(AV-1451), ^{18}F -1808, ^{18}F -THK-5105, and ^{18}F -

THK-5117.⁸⁵ Tau-PET displays the spatial distribution of tau protein deposition over time, which correlates with the neurodegeneration of AD. Tau accumulation begins in the entorhinal cortex and hippocampus, and then it spreads to the temporal and parietal cortices.^{80,91} Amyloid-PET may be positive before tau-PET since amyloid- β accumulation precedes tau-mediated damage to the brain.^{91,92} Tau-PET is closely associated with clinical severity of dementia and has a high association with neurodegeneration seen at autopsy.^{84,100}

¹⁸F-FDG PET—¹⁸F-FDG preceded amyloid- and tau-specific PET imaging agents. It serves as a biomarker for neuronal injury in AD. A pattern of hypometabolism in the parietotemporal associate cortices, posterior cingulate, and precuneus differentiates AD from the healthy elderly brain and from FTLN, DLB, and CVD based on differing distribution of hypometabolism in the brain.⁹⁶ As more and more complex patients are presenting for dementia workup, patients with dual diagnoses of CVD and AD may complicate interpretation of ¹⁸F-FDG PET as blood flow influences ¹⁸F-FDG PET imaging. Inclusion of PWI with simultaneous ¹⁸F-FDG PET/MR can help differentiate between altered cerebral blood flow impacting the distribution of ¹⁸F-FDG and it can assess for dual physiologic process of AD and CVD. ¹⁸F-FDG PET predicts a decline from MCI to AD with sensitivity and specificity ranging from 75% to 100% and predicts early AD with high sensitivity (approximately 90%).⁹⁶ ¹⁸F-FDG PET distinguishes AD from FTLN with 93–98% specificity.⁹⁴ As the dementia disorders have differing clinical manifestations, fMRI has shown that AD, FTLN, semantic dementia, and progressive nonfluent dementia show disruption of differing brain networks. ¹⁸F-FDG PET, structural MRI, and fMRI acquired with PET/MR have shown that patterns of regional hypometabolism, network disruption, and cortical atrophy perform well in differentiating these neurodegenerative syndromes.⁹⁷ Currently, ¹⁸F-FDG PET is reimbursed by the Centers for Medicare and Medicaid for differentiating AD from FTLN, and for patients participating in approved clinical trials utilizing ¹⁸F-FDG PET for the diagnosis and treatment of AD.⁸⁹

PET/MR in Dementia Research—The key hallmarks of Alzheimer's pathology are all captured by neuroimaging which can be used to classify patients as positive or negative for amyloid, tauopathy, and neurodegeneration (Fig. 4).¹⁰¹ PET/MR provides a convenient tool for acquiring high resolution structural imaging with concurrent data for detecting neurodegeneration with the molecular imaging for detecting amyloid and tau proteins in AD clinical trials, prediction of progression of MCI to AD, and differentiation of AD from other clinical dementia syndromes.

Cerebrovascular Disease

Cerebral Perfusion—In acute ischemic stroke, MRI utilizing semi-quantitative PWI and DWI are able to evaluate infarct volume, potentially reversible tissue ischemia, and collateral circulation. These MRI parameters have been used in clinical trials to select patients for intravenous medical therapy and endovascular mechanical thrombectomy for revascularization of acute infarct.^{102–105} ¹⁵O-H₂O PET, and subsequently PWI, have been used to study cerebral blood flow (CBF) in reversible cerebral ischemia.^{106,107} Validation of PWI techniques, including DSC and ASL, remain necessary as the lack of standardization

and variability in values produced by the techniques contributes to the lack of clinical consensus in adopting them for routine use. PET/MRI is the ideal imaging tool for cerebrovascular perfusion research as it allows temporally matched correlation of DWI with quantitative $^{15}\text{O-H}_2\text{O}$ PET CBF, and evaluation of CBF with MRI and with the gold standard $^{15}\text{O-H}_2\text{O}$ PET.¹⁰⁸ The practical application of $^{15}\text{O-H}_2\text{O}$ PET to stroke research is challenging, however, because of difficulties in supplying a radiotracer with a short half-life within the appropriate timeframe to study cerebral hemodynamics during an acute stroke.

Carotid Plaque Imaging—PET/MR has been used for vessel wall imaging in the setting of ischemic stroke of cryptogenic origin with complicated MR features of a carotid plaque combined with evidence of vessel wall inflammation on $^{18}\text{F-FDG}$ PET suggesting a causal role for these plaques in the stroke.¹⁰⁹ Conventional MR coregistered to $^{18}\text{F-FDG}$ PET/CT has been used to correct partial volume error in vessel walls, suggesting that PET/MR may add benefit to vessel wall imaging in the evaluation of plaques at risk for rupture.¹¹⁰

Neurological and Psychiatric Disorders

Advances in the understanding of psychiatric disorders, including autism, depression, and schizophrenia, brought about by fMRI and DTI, and the potential of novel radiotracers in PET to study neurotransmitters in the brain make PET/MR an attractive modality for the future study of mental disorders.¹¹¹

Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are areas ripe for study with PET/MR. $^{18}\text{F-FDG}$ PET has been used to study TBI in human subjects and animal models, correlating alterations in patterns of $^{18}\text{F-FDG}$ uptake in the brain with cognitive and behavioral abnormalities.¹¹² The effects of TBI on the functional connectivity and white matter tracts of the brain are well studied by fMRI and DTI.¹¹³

Conclusion

Prior to the introduction of hybrid PET/MR technology, the role of PET and MRI in disease processes in the brain were studied independently. Post hoc fusion of the two modalities provided good spatial registration, but the possibility of the physiological state of the disease process changing between MR and PET imaging sessions limited interpretation of some datasets. Hybrid PET/MR allows temporal and spatial matching of datasets displaying different physiological and metabolic information about a disease process. As the body of research incorporating the information derived from PET and from MR grows and the utility of multimodal diagnostic evaluation in neuro-oncology, neurodegenerative disease, epilepsy, cerebrovascular disease, psychiatry, and neurology is evaluated, PET/MR shows promise in providing an efficient means for acquiring these studies and may show added benefit beyond separate acquisition and interpretation of PET and MRI alone.

Acknowledgments

Funding statements:

Work published in this article was supported NIH grants P50 AG05681, P01 AG003991, P30NS048056, P01AG026276, [R01AG043434](#) and UL1TR000448, through the generous support of the Hope Center for

Neurological Disorders and the Barnes-Jewish Hospital Foundation, and through by grants from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), including provision of the 18F-Florbetapir and of the technology for synthesis and precursor for 18F-AV1451.

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Key Points

1. Simultaneous PET/MR acquires spatially and temporally matched anatomic MR imaging, MR-based physiological imaging, and PET metabolic imaging of the brain for the purposes of clinical care and research.
2. The combined data obtained from PET/MR may provide a better estimate of tumor extent, higher accuracy in tumor grading, tools for optimization of therapy, and better differentiation of tumor recurrence from radiation necrosis than either modality alone.
3. While MRI is the first line imaging modality for evaluating potential surgical therapy for medically-refractory epilepsy, PET may provide additional diagnostic support for a suspected epileptogenic focus identified on MRI, or it may provide independent information regarding a potential epileptogenic focus in the setting of either a normal MRI or an MRI with multiple structural abnormalities.
4. ^{18}F -FDG PET, amyloid-PET, tau-PET, and volumetric MRI analysis provide imaging biomarkers of the pathological processes involved in Alzheimer's disease, aiding in the prediction of progression to Alzheimer's disease and confirmation of Alzheimer's disease for the purpose of clinical trials.

Fig. 1. ^{18}F -DOPA PET/MR obtained for defining extent of nonenhancing WHO grade III oligodendroglioma. Axial post-contrast T1WI (A) and FLAIR (B) shows nonenhancing tumor in the right frontal lobe. ^{18}F -DOPA PET unfused (C) and fused to FLAIR (D) shows uptake in a portion of the abnormal tissue with a region of interest demarcating greatest ^{18}F -DOPA uptake and suspected nonenhancing high grade tumor margin on FLAIR (B), unfused PET (B), and fused PET (C) images. The ^{18}F -DOPA activity corresponds well to increased rCBV (E) and reduced ADC (F) which are additional MR markers of high grade tumor.

Fig. 2.

45 year old man with a history of a resected WHO grade IV GBM treated with chemotherapy and radiotherapy presents with worsening FLAIR (A) signal changes and new enhancement on contrast-enhanced T1WI (B, C) adjacent to the treatment site. Increased ^{18}F -FDG uptake on unfused PET (D) and fused PET/MR (E), and elevated rCBV (F) support recurrent GBM.

Fig. 3. PET/MR for presurgical workup of a 47 year old woman with medically refractory temporal lobe epilepsy shows classic signs of hippocampal sclerosis on the coronal FLAIR images (A) including increased signal intensity and reduced size of the hippocampus (arrow) with reduced ^{18}F -FDG uptake on the unfused PET (B) and fused PET/MR (C) (arrowhead).

Fig 4.

Axial ^{18}F -Florbetapir amyloid PET (A), axial ^{18}F -Flortaucipir tau PET (B), and axial and coronal T1WI (C, D) of a cognitively normal 78-year old male. The amyloid PET scan is negative for amyloid pathology with visually greater uptake of tracer in white matter than in gray matter. The tau PET scan is normal with no specific uptake in the cortex to suggest tauopathy. The brain MRI is normal, without temporal lobe atrophy to suggest neurodegeneration. Axial ^{18}F -Florbetapir amyloid PET (E), axial ^{18}F -Flortaucipir tau PET (F), and axial and coronal T1WI (G, H) of a 76-year old female with AD. The amyloid PET scan is positive for amyloid pathology, with visually equal uptake of tracer in white matter and in gray matter. The tau PET scan is positive, with left parieto-occipital uptake (arrowhead) supporting an AD pattern of tauopathy. The brain MRI demonstrates hippocampal atrophy, with concomitant enlargement of the adjacent temporal horn of the lateral ventricle (arrow), a pattern of neurodegeneration supportive of AD.