PET/MRI of central nervous system: current status and future perspective

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Abstract
Imaging plays an increasingly important role in the early diagnosis, prognosis prediction and therapy response evaluation of central nervous system (CNS) diseases. The newly emerging hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) can perform “one-stop-shop” evaluation, including anatomic, functional, biochemical and metabolic information, even at the molecular level, for personalised diagnoses and treatments of CNS diseases. However, there are still several problems to be resolved, such as appropriate PET detectors, attenuation correction and so on. This review will introduce the basic physical principles of PET/MRI and its potential clinical applications in the CNS. We also provide the future perspectives for this field.

Key Points
• PET/MRI can simultaneously provide anatomic, functional, biochemical and metabolic information.
• PET/MRI has promising potential in various central nervous system diseases.
• Research on the future implementation of PET/MRI is challenging and encouraging.

Keywords PET/MRI · Neurodegenerative diseases · Brain tumour · Epilepsy · Stroke

Abbreviations
AD Alzheimer’s disease
CNS Central nervous system
MRI Magnetic resonance imaging
PET Positron emission tomography
PET/CT Positron emission tomography/computed tomography
PET/MRI Positron emission tomography/magnetic resonance imaging
SUVs Standard uptake values

Introduction
Central nervous system diseases include a series of pathophysiological statuses, such as dementias, epilepsy, stroke and tumours. The pathogenesis of these disorders is complicated and has not been fully understood so far. As reported in the Global Burden of Disease Study 2013, years lived with disability from neurological disorders increased 59.6 % from 1990 to 2013 [1]. Early detection and intervention become the most important countermeasures to control the progress of these diseases.

Recently, multimodal imaging has provided novel opportunities to study neuropsychiatric diseases. Positron emission tomography/computed tomography (PET/CT) has been successfully applied in clinics for decades with results superior to PET or CT alone. However, CT has ionising radiation and lower soft tissue resolution than MRI. The novel PET/MRI can make up for the deficiency of PET/CT and perform better. It can realise a real-time combination of neurological pathophysiological information measured by PET and precise anatomic information shown by MRI for the correct diagnosis and appropriate therapy [2]. With higher security, this new...
technique may be especially suitable for children, pregnant women and patients who need to be imaged repeatedly [3].

This review will introduce the technical principles of PET/MRI and its potential clinical application in CNS diseases as well as the new technique’s challenges and perspectives.

Technical considerations in PET/MRI

Implementations of PET/MR acquisitions

Currently, commercial whole-body PET/MRI is mainly implemented in the following ways: (1) Sequential acquisition in two different rooms: PET/CT and MR scanners are put in two neighbouring rooms to acquire PET and MR images respectively, then the image fusion is carried out using the appropriate software. CT information is used for PET attenuation correction (AC). Motion artefact is one of the distinct problems. (2) Sequential acquisition in a single room (Ingenuity TF PET/MR, Philips): the PET and MRI scanners are in line with each other. Patients can be imaged by moving their bed between two scanners. AC is based on MR data. Similarly, patient’s motion artefacts are still a problem. (3) Simultaneous acquisition approach (Biograph mMR, Siemens): a PET detector is inserted into the 3.0-T MRI (Fig. 1). It can simultaneously obtain PET and MR images to reduce registration errors [2, 4, 5]. However, some technical problems still need to be resolved, including inventing a PET photodetector that is compatible with MR, maintaining the homogeneity of the magnetic field, providing accurate PET AC and so on [2]. In December 2014, General Electric introduced an integrated PET/MRI system (the SIGNA PET/MRI). It is characterised by GE’s digital MR-compatible silicon photomultiplier detector (SiPM) technology, which has high spatial resolution enabling Turbo time-of-flight (Turbo TOF) reconstruction.

PET photodetectors

A major problem of integrated PET/MRI is the interference between the PET and MRI systems [6]. Several solutions have been adopted to deal with the problems. At first, the photomultiplier tubes (PMTs) were placed outside the main magnetic field and linked to the scintillation crystals by long optical fibres; however, the quality of PET imaging was obviously affected because light information was weakened when transmitted on the optical fibre [7]. Avalanche photodiodes (APDs) insensitive to magnetic fields were introduced [8]. However, APDs have some known limitations, including a lower gain of signal amplification, strong temperature dependence and inferior temporal resolution compared with PMTs [9, 10]. The silicon photomultiplier (SiPM), also called Geiger-mode APD, performs much better than APDs. SiPMs have amplification gain and temporal resolution equivalent to those of PMTs and are not sensitive to magnetic fields [9]. A recent study showed a PET/MRI insert detector using an SiPM on a strip line was feasible, with negligible interference between the two imaging modalities [11].

Attenuation correction

AC is a critical requirement for quantitative PET reconstruction. MR-based AC in PET/MRI is challenging because the MR image does not reflect direct photon attenuation information. Currently, the Dixon segmentation method is the most commonly used model of attenuation correction in PET/MRI, but does not take bone into account. Because of the relatively high photon-attenuation coefficient of bone, this method may underestimate the standard uptake values (SUVs) of lesions surrounding osseous structures [12].

A new model-based AC method based on a regular four-compartment segmentation from Dixon sequences could reduce the underestimation of bony tissue from −25.5 % ± 7.9 % (Dixon) to −4.9 % ± 6.7 % to enhance the PET quantification

![Fig. 1 Schematic cross-sectional views of potential designs for combined PET/MR imaging systems. (a) Tandem design with two imagers mounted back to back (similar to that in PET/CT instrumentation) to allow sequential rather than simultaneous acquisition, (b) insert design with the PET imager (P) inserted between the radiofrequency coil (R) and gradient set (G) of the MR imager and (c) fully integrated design with two imagers in the same gantry. Radiofrequency coil, gradient set, PET imager and patient bed (B) are shown for all configurations. With permission, from reference 78](image)
in whole-body hybrid PET/MR imaging, especially in tissue close to bone [13].

An atlas-based approach and combination of Dixon and ultra-short echo time (UTE) sequences have been investigated [12, 14, 15]. An atlas-based approach can predict attenuation values for osseous tissue with a suitable CT template or MRI with appropriate algorithms and co-registered MR-CT pairs. UTE can supplement the Dixon method by providing additional bone contrast or segmentation to achieve high-quality PET data. A recent study showed that the UTE MR-based AC method performed acceptably in the brain, but could not provide enough accuracy for neck and facial structures compared with CT-based AC [16]. Cabel et al. estimated an R₂-based attenuation map (μ map) including bone tissue in which the R₂ map is based on a dual-echo UTE MR sequence. They reported the method could reduce the error of PET AC to deliver more accurate PET data [17].

Other technical considerations

Some other factors such as respiratory motion influence the quality of PET or MR images. Integrated PET/MRI allows using MR images to monitor and correct PET images degraded by motion. Manber et al. proposed an anatomy-independent MR-based respiratory motion correction strategy for PET data and showed the method could improve the quality of clinical PET images using only a short additional PET/MRI acquisition and without external respiratory hardware or modifications of the conventional clinical MR sequences [18].

Optimal parameter selection for image reconstruction is also critical for improving image quality. Leemans et al. used spherical symmetric basis functions (blobs) as image reconstruction algorithms and systematically evaluated the influence of the related parameters on the image quality of brain PET in a PET/MRI system. They showed that the reconstructed image quality was improved with the optimisation of blob parameters (d = 2.0375, alpha = 10.4101, radius = 3.9451) in their study. However, this qualitative improvement is task specific, since a particular application has an individual requirement of image quality considering spatial resolution, contrast, etc. This work may be helpful for selecting the optimal task-specific parameters [19].

Clinical applications

Alzheimer’s disease

In the management of Alzheimer’s disease (AD), PET/MRI facilitates the understanding of the relationship among cerebral blood flow (CBF), glucose metabolism, amyloid plaques and anatomic abnormalities in the pathogenesis [7]. According to the preliminary results, amyloid PET/MRI is feasible and provides imaging biomarkers of amyloid pathology and neuronal injury to help make the diagnosis and differential diagnosis of AD (Fig. 2) [20]. ¹¹C-Pittsburgh compound-B (PIB) is the most widely used amyloid PET tracer in vivo [21], but its clinical use is limited by the short half-life of the ¹¹C isotope [22]. To overcome this disadvantage of the ¹¹C isotope, several ¹⁸F labelled tracers have been developed, including ¹⁸F-florbetaben, ¹⁸F-florbetapir and ¹⁸F-flutemetamol [20, 22]. A multicentre study reported that ¹⁸F-florbetaben PET had a specificity of 91% for distinguishing suspected AD patients from controls [23]. Recently, a human investigation of ¹⁸F-fluorinated imidazo[2,1-b]benzothiazole (¹⁸F-FIBT) showed that ¹⁸F-FIBT is a promising novel radio-pharmaceutical for amyloid PET/MRI with improved binding characteristics and pharmacokinetics, but more detailed studies are required [24].

Hybrid PET/MRI facilitates simultaneously assessing brain functional connectivity, such as the default mode network (DMN) functional connectivity, cerebral blood flow and metabolism in AD. DMN, one of resting-state networks involving in the posterior cingulate cortex/precuneus, medial prefrontal cortex and anterior cingulate cortex, is crucial in cognitive processes [25–29]. Previous studies have demonstrated that abnormality of the DMN measured by resting-state MRI (fMRI) can be useful in the early diagnosis of AD [30, 31]. However, further studies on the functional connectivity, metabolism and inflammation of the DMN in AD are needed. Arterial spin labelling (ASL) MR perfusion imaging can non-invasively quantify the CBF with the water of the inflowing arterial blood as an endogenous tracer [32, 33]. ASL-derived CBF is associated with the progression and severity of AD [34, 35] and is comparable to FDG-PET for making the differential diagnosis of AD, frontotemporal dementia and Lewy body dementia [36–38]. A recent study using PET/MRI reported that in patients with AD dementia, the intrinsic connectivity between the hippocampus and precuneus was significantly reduced, and the glucose metabolism was reduced in the precuneus while unchanged in the hippocampus [39].

Parkinsonian syndromes

With novel emerging PET tracers, such as dopamine transporter (DAT) and α-synuclein tracers, and new MR techniques, such as voxel-based morphometry, diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy (¹H-MRS) and Fe-mapping [20], PET/MRI tends to be increasingly used in the exploration of Parkinsonian syndromes (PD).

Abnormality of the dopaminergic system may be associated with motor symptoms in PD. Lower uptake of DAT tracers or 6-¹⁸F fluoro-L-DOPA (¹⁸F-DOPA) has been proven to be correlated with greater symptom severity in PD, such as bradykinesia and rigidity [40]. The serotonergic system is also
involved in the pathophysiology of PD. Both $[^{11}C]$-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ($[^{11}C]$-DASB) and $[^{18}F]$-DOPA PET are able to assess serotoninergic function in PD [41]. Serotonin transporter availability and $5-HT_{1A}$ receptor density have been shown to be reduced in the raphe nucleus of PD patients [42]. Serotonergic dysfunction in the striatum and limbic system is associated with some non-motor syndromes in PD, for instance fatigue [42]. Besides, central dopaminergic and cholinergic dysfunction may contribute to cognitive impairments in PD patients [43, 44], such as executive dysfunction, attention disturbances and memory deficits [45, 46].

In addition, PET/MRI may also have potential for the differential diagnosis, therapy evaluation and prognostic counselling of Parkinsonian syndromes. $[^{11}C]$-raclopride and $[^{18}F]$-fluorodeoxyglucose (FDG) PET can be used to discriminate multiple system atrophy from PD [40]. $[^{18}F]$-FDG PET can be used to evaluate the response of cholinergic agents in PD patients with dementia [40] and act as an early predictor of survival in patients with atypical Parkinsonian syndromes [47].

### Brain tumours

Multimodality imaging including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), $[^1H]$ MRS and other advanced MR techniques has become an integral part of the medical management of brain tumours [48]. Especially the combined use of fMRI and DTI can provide the spatial relationship between brain tumours and adjacent functional brain areas and white matter fibres, which is helpful for preoperative planning and risk assessment for patients with brain tumours [49, 50].

PET/MRI has the potential to allow an early diagnosis and more targeted treatment of brain malignancies. It can accurately distinguish tumours from surrounding normal tissues for image-guided radiotherapy [51]. $[^{68}Ga]$-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraaceticacid-D-Phe1-Tyr3-octreotide ($[^{68}Ga$]-DOTATOC) PET/MRI has been proven to be clinically feasible in the intensity-modulated radiotherapy (IMRT) treatment planning for meningioma [52]. PET/MRI also holds promise to differentiate post-treatment radiation changes from residual and recurrent tumour by dynamic contrast-enhanced (DCE)-MRI or DWI [7, 53, 54]. Besides, studying tumour biology at the molecular level by PET/MRI can help realise personalised treatment plans for patients with brain tumours and explore new therapies in the future [51].

PET/MRI is useful in the diagnosis, grading and treatment response evaluation of glioma patients [55]. $[^{18}F]$-fluoroethyltyrosine ($[^{18}F$-FET) PET/MRI may be used for the initial glioma grading. Dunet et al. reported that a combination
of tumour FET time-activity-curve and apparent diffusion coefficient histogram analysis could improve the sensitivity from 67 % to 86 % and the specificity from 63-67 % to 100 % when they were used to distinguish between low- and high-grade gliomas [56]. 18F-fluoromisonidazole (18F-MISO) PET/MRI can noninvasively quantify tissue hypoxia for risk stratification of recurrent glioma patients before angiogenesis inhibitor therapy and evaluate the response to angiogenesis inhibitor treatment, such as bevacizumab [57, 58].

PET/MRI may gradually prove superior for children with brain tumours and related studies are increasingly conducted. 18F-fluoroethylcholine (18F-Cho) PET/MRI is feasible and reliable as a potential imaging tool for children with astrocytic brain tumours. It can monitor the morphological and metabolic changes of patients with astrocytoma during therapy [59]. 18F-DOPA PET/MRI is also used to diagnose and stratify patients with infiltrative astrocytomas and assess the treatment and prognosis [60] (Fig. 3).

**Epilepsy**

Epilepsy is a common neurological disease. Frequent epileptic seizures will cripple children’s growth and intellectual development. PET/MRI is able to facilitate interictal detection and help explore the pathogenesis of seizures. A pilot study of 29 patients with refractory focal epilepsy reported PET/MRI increased the diagnostic accuracy of the potential epileptic focus compared with separate MRI and PET/CT [61]. The combination of high-density electroencephalography (EEG) and a PET/MRI scanner can provide reliable interictal clinical data with improved efficiency and reduced bias and cost [62]. Ding et al. recently conducted an initial study using PET/MRI, which showed that left and right post-central gyri were hypermetabolic regions, while the right temporal pole and planum polare were consistently hypo-metabolic regions in epileptic patients compared with healthy controls [63].

**Cerebrovascular disorders**

Cerebrovascular disorder is the leading cause of adult death and functional disability and is characterised by cerebral haemodynamic disorder and brain dysfunction via ischaemia and haemorrhage [64, 65]. In acute ischaemic stroke, it is critical to detect the ischaemic penumbra accurately and quickly to provide individualised therapeutic opportunities. The penumbra is identified as hypo-perfused but viable tissue, which will rapidly evolve to infarction without therapeutic intervention in time [66, 67]. Many MR techniques can be used for detecting stroke. For example, ASL MR perfusion imaging can noninvasively reflect brain perfusion abnormalities to rapidly identify the penumbra, evaluate the cerebrovascular reserve and monitor the post-treatment effect of cerebrovascular diseases [68, 69].

PET/MRI is useful in the management of cerebrovascular diseases with novel PET tracers and multiparameter MR techniques. It can determine the potentially salvageable tissue in ischaemic stroke by H 2 15O PET and special MR approaches and enables direct comparison of the determined hypoperfusion in PWI and low flow-preserved oxygen-supplied tissue to correctly discriminate tissue that can benefit from thrombolytic therapies [70]. In addition, PET/MRI can be used to distinguish ischaemic stroke from haemorrhagic stroke for correct therapy and help better understand the progression or recovery of functional impairment surrounding the ischaemic lesion to evaluate the therapy effect [70].

**Multiple sclerosis**

Multiple sclerosis (MS) is a common disease in young adults and is characterised by chronic inflammatory demyelination [71]. Multimodality MR imaging can be used to detect the disease activity of MS, metabolic changes, iron deposition
and normal-appearing white matter damage [22, 72–75]. Translocator protein (TSPO)-targeted PET imaging has the ability to quantify neuroinflammation to monitor disease progression, predict the prognosis and evaluate the treatment effect in MS [22]. PET with FDG and 18F-fluoromethylcholine (FCho) is used to assess the metabolic features of MS [76]. In addition, initial evidence has suggested that amyloid PET may play a role in studying and monitoring MS [77]. PET/MRI facilitates more specific information on the pathological mechanisms of the disease. A study using PET/MRI showed that the metabolic features were different between two variants of MS, tumefactive MS and Balo’s concentric sclerosis, and may represent different disease activities [76].

Future perspectives

Although PET/MRI has many encouraging potentials in both the clinic and research, several challenges still need to be addressed. First, the technical challenges need to be resolved. It is necessary to better evaluate the safety of PET tracers during simultaneous imaging because static and low-frequency magnetic fields are likely to increase the genotoxicity of ionising radiation [78]. New MRI-compatible PET photodetectors should be developed. More effective algorithms and trails are required to provide appropriate strategies for MR-based AC of PET data. Second, workflow and image acquisition parameter optimisations are the next step for PET/MRI. Specific disease statuses, patient populations and body parts of interest need individualised radiotracer dose and acquisition parameters or sequences for optimised evaluation. Third, standardised appropriateness criteria should be developed for PET/MRI [78]. A large randomised controlled trial is necessary to further confirm the superiority of PET/MRI to some existing imaging tools such as CT, MR and PET/CT. Finally, we believe that a future use of PET/MRI will be to explore the connection between the metabolic, molecular information provided by PET and anatomical, functional, blood flow information provided by multimodality MRI concerning the physiological or pathological status [79], especially in AD and psychopathies such as schizophrenia and depression.

Conclusions

PET/MRI shows some unique superiorities to the existing imaging modalities, performing especially well in CNS diseases, including the diagnosis and management of brain disorders and the exploration of the connection between brain metabolism and function. PET/MRI has promising potential to improve our understanding of the pathophysiology, diagnosis and prognosis evaluation of CNS diseases.

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