Ana M. Franceschi
Dinko Franceschi
Editors

Hybrid PET/MR Neuroimaging

A Comprehensive Approach

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Foreword

I am excited and honored to write the foreword for the book *Hybrid PET/MR Neuroimaging: A Comprehensive Approach* edited by the father and daughter team, Dinko and Ana Franceschi (my trainee!). Dinko has 30 years' experience in nuclear medicine and has clearly recognized hybrid PET-MRI is an important new technology that will completely change our practice futures. I helped train Ana in neuroradiology and PET-MRI – in just a few years, Ana has become a recognized early expert and champion for using this technology in routine clinical practice, first in the New York City area, and now at national meetings for neuroradiology and nuclear medicine. Ana and Dinko have collaborated with established and emerging leaders in this new field to cover the expanding scope and impact of hybrid PET-MRI. My only complaint is that I actually needed this book in the summer of 2012! Now there will be an excellent resource for physicians with different training and clinical backgrounds who are interested in learning more about the utility and interpretation of hybrid PET-MRI for neurological diseases.

My own early personal experience with PET-MRI may be instructive to readers interested in getting started since NYU was one of the first programs to use PET-MRI for clinical practice – i.e. what it was like in the "old days" before this helpful book was available. I suspect many of the chapter authors can tell similar stories. When I arrived at NYU in August 2012 fresh out of fellowship, we had just installed a hybrid PET-MRI scanner in the main outpatient radiology facility. Yvonne Lui, my section chief, asked me to be the neuroradiology liaison for PET-MRI clinical and research studies. After neuroradiology fellowship training, I was quite familiar with the role of MRI in the clinical management of epilepsy and dementia, was an "authorized user," and had decent trainee-level experience with FDG PET for cancer imaging (maybe 50 cases). My proudest accomplishment in nuclear medicine though may have been my autographed copy of Mettler's textbook obtained when he visited UCSF during boards preparation. At that point, I had read three FDG PET brain studies in my "career" – one of those was for the radiology board exam in a hotel room in Louisville in 2011 and to this day I think I failed that case! We were unsure how to apply this new technology, but started using a research protocol that allowed us to pay for a cab and transport patients after their routine FDG PET-CT at the NYU cancer center across midtown Manhattan to be reimaged on the PET-MRI scanner at the radiology outpatient facility on First Avenue using the original decaying FDG dose.

It began as a trickle of patients. Over the next 2 years, I learned on the job how to really analyze and interpret FDG PET from Kent Friedman, chief of NYU nuclear medicine. Kent and I reviewed the MRI and FDG PET images together once a week in a dual-readout format and prepared two separate reports. We were lucky not to have turf wars between sections and combined our expertise to interpret these studies. It was a time of discovery as we encountered real patients that forgot to read the textbooks before they showed up for imaging and we always had lots of questions – it was perhaps my limited knowledge of the FDG PET literature in the 1970–1980s that led me to "rediscover" key features for PET interpretation in epilepsy patients. After only seven patients had consented to both PET-CT and PET-MRI studies, the NYU level IV epilepsy center stopped ordering PET-CT for their patients and switched exclusively to PET-MRI studies. Eighteen months later in summer 2014, we opened the "floodgates"

and agreed to use this new technology to image patients with suspected cognitive impairment from the NYU Pearl Barlow memory and aging center. Our volume immediately doubled, then doubled again over the next 18 months. Today, we typically interpret 25–30 clinical neuroradiology PET-MRI studies a week (~1200 per year) – a volume dominated by cognitive impairment workup, but we also image patients weekly for epilepsy, autoimmune encephalitis, brain, and neck tumors. Last time I checked in 2016, overall brain PET FDG volume was up 300% from 2012. We were one of the few sites to contribute to the original IDEAS study with hybrid PET-MRI data using amyloid tracers and routinely use multiple additional radiotracers in clinical practice and research (e.g., Dotatate, Tau, and TSPO tracers). I would predict that the recent FDA approval of Aduhelm, the amyloid-lowering immunotherapy from Biogen, also may increase our volume substantially.

Hybrid PET-MRI has changed our practice and actually changed the way I interpret MRI even without simultaneous PET. Over time those subtle MRI calls on epilepsy studies I was wary of mentioning in a conference at a well-known level IV epilepsy center for fear of my life were corroborated by the simultaneously acquired FDG PET, then subsequent intracranial EEG and surgical pathology. It is quite humbling to realize that subtle hippocampal sclerosis you were so excited to detect was just the tip of the iceberg in epilepsy patients and many of those "icebergs" were not even detectable with state-of-the-art MRI sequences. Conversely, MRI findings redirected us to recognize subtle extra-temporal FDG abnormalities we missed on an initial review that correlated well with semiology, EEG, and eventually surgical pathology. NYU referrers became very reliant on the PET-MRI reads we provide. Next Monday at our weekly multidisciplinary conference all four epilepsy patients considering surgery will have had hybrid FDG PET-MRI first. We had a similar experience changing the workup for neurodegenerative disease – instead of equivocating on ambiguous FDG PET findings or using MRI only to assess white matter disease, mass, and hydrocephalus, we started providing constellations of multimodal imaging findings to support workup for specific diagnoses. Particularly for dementia, we observed a changing role for radiologists in the triage of patients. Busy general neurology referrers that may not have expertise or time on the initial visit to distinguish the causes for word-finding difficulty would change their follow-up evaluations and management based on our PET-MRI report. Conversely, experts in primary progressive aphasia would use such reports to focus their practice, time, and resources. In epilepsy, neurodegenerative disease, and autoimmune encephalitis, you learn quickly you cannot hide from the limits of sensitivity and specificity for MRI findings we proudly teach residents once you see the much more obvious findings on simultaneously acquired FDG PET. Previous groups had shown the advantages of reinterpreting separately acquired PET and MRI together in epilepsy and dementia respectively [1, 2] – we were just turning that into daily clinical practice with a single efficient imaging session that patients, referrers, and the interpreting radiologists clearly preferred. I expect this phenomenon to continue and to expand to other common neurologic diseases as the technology and radiochemistry develop.

The biggest challenge to this new paradigm is finding physicians comfortable reading these studies by themselves, but this also results in the most powerful diagnostic confidence and efficient workflow. Our rapidly increasing volume showed quite clearly that hybrid PET-MRI was addressing an unmet need for our referrers – I would come back from 2 weeks of relaxing summer vacation with 30–40 cases waiting for me! An individual reader needs to be knowledgeable in several diverse areas that Ana, Dinko, and their chapter authors have made sure are well-covered by this book – neuroanatomy, PET physics and artifacts, potential compromises in imaging physics associated with hybrid PET-MRI (e.g., attenuation correction), FDG and various common radiotracers, software visualization tools and limitations. In 2013–15, I'm not convinced anyone came out of training with that complete skillset. Faculty with dual fellowship training in nuclear medicine and neuroradiology were as common as unicorns with zebra stripes (that is now changing). Very few nuclear medicine fellowship training programs are exposing trainees to even 50 FDG PET brain studies per year. I feel there remains a strong need and responsibility to train more people, and this book will be a tremendous help to that process.

Every year the NYU fellowship program trains 6–7 fellows to read PET-MRI with each fellow reading more than 100 cases during the year. Some may argue the PET is a waste of time for "regular" neuroradiologists, but it teaches them humility regarding the limitations of MRI and makes them better readers. Often we would see something or a question would come up during read up that I did not have a good answer for or could easily find in the PET literature – this book offers an up-to-date comprehensive resource for those frequent situations! In a messianic tone, I always foretell to the fellows that behind the current noise of deep learning, PET-MRI will revolutionize our field and that if they plan to practice for more than 10 years they *will* be reading PET-MRI studies. Ana Franceschi was the fellow who actually listened to me!

With this excellent introductory and first book focused on hybrid PET-MRI in neuroimaging, the secret should be out. I can *finally* retire my lecture titled "PET-MRI will change neuroradiology practice" that I have given over the past 7 years on podcasts and at many US institutions, national, and international meetings. When reading the chapters of this book, I encourage readers to think about our collective future. We all may be anxious about "deep learning" where clinical diagnosis and management are replaced by inscrutable layered algorithms from Skynet based just on existing MRI protocols… yet all the deep learning in the world could not solve the longitude navigation problem in the 1700s without an accurate clock (i.e., the right data). PET tracers increase the dimensionality of imaging data and are already being used to complement big data approaches to clinical imaging challenges in neurological diseases. The underlying reality is that hybrid PET-MRI is already starting to transform imaging for patients with neurological disease. It is not hard to see areas where imaging can improve in 2021; the MS patient with stable-appearing MRI that no longer walks unassisted into their follow-up scan, the young adult patient with smoldering autoimmune encephalitis or TBI that everyone thinks is just depressed, or patients in the early stages of movement disorders with normal-appearing MRI. Research with hybrid PET-MRI in carefully characterized clinical patients should validate new biomarkers particularly with novel MRI contrasts and quantitative approaches. MRI also transforms PET with dose reduction and increased spatial resolution using joint reconstruction techniques. The development of new PET tracers will only accelerate this holistic and synergistic process between two dynamic imaging technologies. Ana and Dinko have picked the perfect time to create a book introducing us to this promising new technology. I hope you find this book helpful and exciting for the future of diagnostic neuroimaging.

New York, NY, USA
June 2021

Tim Shepherd
Associate Section Chief, NYU Neuroradiology

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Part I

Introduction to PET/MRI

Dinko Franceschi

Future Trends of PET/MR and Utility of AI in Multi-Modal Imaging

9

Sheng-Che Hung, Mingxia Liu, Pew-Thian Yap, Dinggang Shen, Weili Lin, and Mauricio Castillo

Recent Advances and Future Trends of PET/ MR

Hardware

Over the past decade, hardware advances, including lutetium-based scintillators, solid-state-based silicon photomultiplier (SiPM)-based detectors, time-of-flight (TOF) imaging, improved detector design, and 3D PET, contributed to improved PET quality [1]. One of the most recent trends is the total-body PET (TB-PET). Standard axial field of view (FOV) in commercial PET scanners ranges from 15 to 26 cm and requires multiple bed translation to acquire a whole-body scan. The idea of TB-PET is to extend the axial FOV to cover the whole body with an increased number of detectors [2]. There are currently two NIH-funded TB-PET systems for human use: the PennPET Explorer (axial FOV, 140 cm) developed by the University of Pennsylvania/KAGE medical team and Philips in 2018, and the uExplorer (axial FOV, 194 cm) developed by the UC Davis/United Imaging team in 2019. Advantages of these TB-PET design are twofold:

1. Whole-body imaging can be acquired in a one-bed position in the same time frame.
2. Detection efficiency is improved by collecting photon pairs emitted from organs that would be originally outside the FOV or the photons emitted from organs inside the FOV but that do not intercept the detector ring.

Overall, TB-PET can contribute to a >40-fold increase in effective sensitivity and a >6-fold increase in SNR compared with current whole-body PET [2]. The large gain of higher detection efficiency can be utilized to optimize scan parameters to achieve different goals, including:

1. Improving imaging quality by controlling the same acquisition time and administered dose
2. Reducing radiotracer dose according to the degree of sensitivity increase by controlling the same acquisition time and the same diagnostic image quality
3. Shortening scan time by maintaining the same radioactive dose and the same image quality

Potential benefits of TB-PET have been elaborated in several reviews [3, 4]. In brief, increased PET sensitivity allows for detection of "lower-density" disease, such as cancer micrometastases, inflammation, or infection. It also allows for imaging of short-lived radiotracers at lower radioactivity or delayed PET to contrast the differential radiotracer uptake in various tissues. The low-dose protocol can significantly reduce radiation dose of each scan and allows for repeated scans for longitudinal and interventional research studies and widens indications to include non-oncological diseases such as imaging of bacterial infections, drug addiction, and neuroinflammation [5–7]. Low-dose PET is also useful in vulnerable populations such as children and pregnant women. Shorter scan times reduce motion artifacts in pediatric or restless patients, reduce patient discomfort, and improve patient throughput [2]. Furthermore, shorter scan times allow for faster dynamic scanning which can be used to monitor radiopharmaceutical pharmacokinetic distribution across multiple organs and systems. Although TB-PET design is currently only combined with CT and the cost of

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total-body PET/MR would be high, the benefits of extending axial FOV in PET/MR will open new windows for research and clinical opportunities.

Imaging Reconstruction

Ordered subset expectation maximization (OSEM) is the most commonly used algorithm to generate the PET images by iterative reconstruction. The OSEM reconstruction methods improve image sharpness with a number of iterations at the expense of reducing signal-to-noise ratio, however. Thus, image reconstruction generally stops after a small number of iterations, and this results in an under-converged image. Technical advances, such as TOF imaging and 3D PET, can reduce noise and allow for a higher number of iterations to achieve higher imaging sharpness at comparable noise levels [8]. Recently, General Electric (GE) introduced a new reconstruction algorithm called "Bayesian Penalized Likelihood Image Reconstruction" that achieves a fully convergent iterative reconstruction and can significantly improve image SNR and accurate quantification compared to OSEM [9].

Quantitative Accuracy

MR-based AC is an important issue because MR images cannot provide metrics that can be converted to attenuation coefficient maps at 511 KeV. Originally, commercial PET/MR scanners generated the attenuation coefficient maps by a 3D "Dixon-VIBE" or "LAVA-FLEX" sequence to classify tissue into four classes (air, fat, lung, and soft tissue) [10]. The main limitation of these methods is that none of the classes truly correspond to bone. Erroneous misclassification of the bone as soft tissue in segmentation can cause spatially biased PET measurements. One of the latest approaches is the atlas-based method, which first derives an atlas based on a population database of CT/MR image pairs and then aligns the atlas to the target patient to synthesize pseudo-CT for AC. Atlas-based methods are proven robust and provide accurate results of brain PET AC [11]. However, these methods may cause a small but significant underestimation of uptake in the temporal lobes or regions near the skull base and cannot be used in patients with anatomic variations [12]. Another approach is direct imaging with ultrashort echo time (UTE) or zero echo time (ZTE). The UTE and ZTE sequences can generate signals in materials with short T2* such as cortical bone and then use this information for bone segmentation in the skull to synthesize pseudo-CT images. This direct imaging approach can overcome the inter-subject anatomic variations and may be applied to regions outside the brain [13]. Several studies have shown similar accuracy of PET measurements between ZTE-based and atlas-based AC maps [14]. However, direct imaging methods are not as robust as atlas-based methods and can be negatively impacted by noise and image artifacts.

Furthermore, in addition to the bones, there are also extrinsic sources of biased AC in the scan, including pads used to keep the patient's head still during the examination, dense hair, and headphones. One study showed that the bias of measurements by the pads is small (<3.1%), but that dense hair and headphones significantly bias the quantification (>10%). Although these issues are not discussed in the current commercial AC methods, it will be important to minimize these quantification biases for quantitative or longitudinal studies [15].

Motion Correction

Longer scan time makes PET/MR prone to motion when compared to PET/CT. A review of motion corrections focusing on PET or MR images alone is beyond the scope of this chapter. Here, we will focus on methods that have been investigated in PET/MR. To correct the motion-induced errors, there are several methods to measure subjects' motion, namely, data-driven and marker tracking methods, respectively. The former approaches use acquired MR images, whereas the latter approaches may require add-on motion tracking systems to obtain motion information [16]. Brain COMPASS™ (Siemens Healthcare GmbH) is a data-driven method, which performs MR-based motion corrections based on a simultaneous acquisition of fast 3D echoplanar images during the scan. This method uses spatially and temporally aligned MR images as references for motion correction of PET [17]. One advantage of data-driven motion correction methods is that no additional hardware is needed. Its disadvantage is that the simultaneous acquisitions during PET prevent the MR unit from scanning other sequences, meaning that the MR-based PET motion correction increases the scan time. Also, the sampling frequency of MR images is limited by the acquisition time and is inferior to that of external tracking systems.

Marker tracking systems require additional optical, radioactive, or MR active fiducial markers temporarily attached to the subject's head [18]. These systems are usually easy to set up but can only track external motions and bring up additional issues, such as patient discomfort, additional patient contact, or fiducial displacement. There are some markerless tracking methods. For example, a commercial system (Tracoline 2.0) can continuously extract the patient's facial features with a synchronized light modulator and a camera outside the scanner [19]. The advantages of this marker-free tracking system include the unnecessary need for fiducials, reduction of the clinical preparation times compared to marker-based methods, and elimination of the possibility of

tracking failure due to marker displacement. However, this system requires additional cross-calibration between the tracking coordinate system and the device coordinate system before each scan and prolongs scan time. Another marker-free tracking system takes advantage of in-bore stereo-optical sensors (HobbitView Inc.) which are directly mounted to the head coil to capture the naive natural or amplified features on the forehead. This approach has been reported to be able to provide sub-millimeter and sub-degree accuracy in phantoms and volunteers [20]. However, the tracking markers of this approach are skin features of the forehead, which may be affected by facial movements, leading to erroneous pose estimation. Besides, the influence of the in-bore cameras on the attenuation maps requires further investigation.

Artificial Intelligence

AI is a rapid-growing field and has already widely impacted various, if not all, fields of PET/MR [21]. For example, deep learning can synthesize a "pseudo-CT" from MR images, or even ^{18}F-FDG non-attenuation corrected images alone can be used for AC [22]. Combining Dixon and ZTE to generate AC maps by the neural network is superior to the approaches based on Dixon images alone or based on the vendor-supplied ZTE segmentation [22]. It is also feasible, by using convolutional neural networks and generative adversarial networks, to denoise PET images and reduce the radiotracer dose to 25% of the standard dose and lower by estimating standard-dose PET images from the low-dose PET images and inputs of multiparametric MRI [23–26].

Utility of AI in Multi-Modal Imaging

MRI and PET have been widely used for the diagnosis of Alzheimer's disease (AD) and conversion prediction of mild cognitive impairment (MCI). A common challenge in multi-modal studies is the missing data problem [27, 28]. In clinical practice, subjects who are willing to be scanned by MRI may reject PET scans due to their high cost and other issues such as concern of radioactive exposure. In the baseline, Alzheimer's Disease Neuroimaging Initiative (ADNI-1) [29], only approximately one-half of subjects have PET scans, although all subjects have MRI data. Previous studies usually tackle this problem by simply discarding subjects without PET scans [30]. However, such a simple approach significantly reduces the number of training subjects for learning a reliable model, thus inevitably degrading diagnostic performance. Another commonly used strategy is to input the missing data/features of a subject using the mean or median feature values of other subjects (with complete data) or even using random values [31], which brings additional noise and is only feasible for handcrafted features. To utilize all available subjects, an intuitive strategy is to impute the missing PET scans directly [32].

In multi-modal neuroimaging-based studies, one usually has a limited number (e.g., tens or hundreds) of training subjects which severely limits the generalization capacity of deep learning models [33, 34]. A commonly used strategy is to include disease-related prior knowledge to guide the extraction of feature representations from neuroimages. For example, prior biological/anatomical knowledge on dementia-associated brain changes/abnormalities has been used to identify local image patches for representing each image. Recently proposed deep learning methods aim to learn task-oriented features of neuroimages based on anatomical landmarks [30, 35]. These methods first define disease-related anatomical landmarks and then automatically extract features based on image patches (located by landmarks) avoiding using non-informative voxels and regions in the brain. Since these methods highly rely on expert knowledge on specific brain diseases, their general performance may be limited in practical applications.

Several advanced AI techniques via deep neural networks have been recently developed for automated brain disorder identification based on incomplete MRI and PET data. Below, we first discuss the problem formulation of neuroimaging-based disease diagnosis based on incomplete MRI and PET scans and then briefly address two recent studies on the topic.

Problem Formulation

It would be desirable to construct a computer-aided diagnosis system based on multi-modality data, such as MRI (denoted as $\mathcal{A}$) and PET (denoted as $\mathcal{B}$). Denote $\mathbf{M} = \left\{\left(\mathbf{A}_i, \mathbf{B}_i, \mathrm{y}_i\right)\right\}_{i=1}^{N}$ as a dataset consisting of N subjects, where $\mathbf{A}_i \in \mathcal{A}$ and $\mathbf{B}_i \in \mathcal{B}$ denote the representations of MRI and PET for the i-th subject, respectively. Also, $\mathrm{y}_i \in \{0, 1\}$ denotes the class label of the i-th subject, e.g., 1 for AD and 0 for healthy control (HC). In practice, not all subjects have complete data of both modalities.

As shown in Fig. 9.1, a general computer-aided disease diagnosis model F using complete multi-modal data can be formulated as

$$\hat{y}_i = F\left(\mathbf{A}_i, \mathbf{B}_i\right), \tag{9.1}$$

where $\hat{y}_i$ is the estimated label for the i-th subject. Let $\hat{\mathbf{B}}_i = G\left(\mathbf{A}_i\right)$ denote data imputation with the mapping function G. Thus, the diagnosis model with complete (after PET synthesis) multi-modal data can be executed as

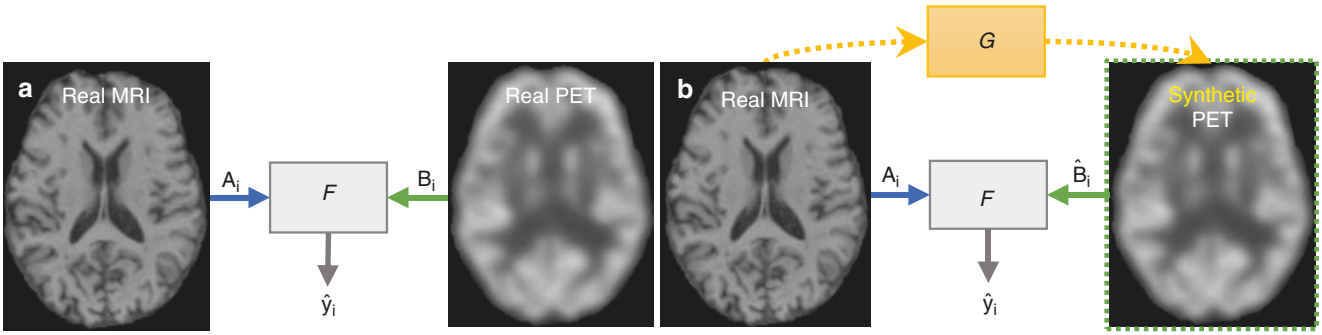

Fig. 9.1 (**a**) A diagnosis model F trained on the complete MRI and PET scans. (**b**) A diagnosis model F trained on the complete (after imputation for missing PET scans) data. $\mathbf{A}_i$ and $\mathbf{B}_i$ represent the MRI and PET scans for the i-th subject, respectively. $\hat{\mathbf{B}}_i = G(\mathbf{A}_i)$ represents the synthesized PET scan via image generator G, and $\hat{y}_i$ is the estimated label for the i-th subject

$$\hat{y}_i = F(\boldsymbol{A}_i, \boldsymbol{B}_i) \approx F \tag{9.3}$$

In the following sections, two AI approaches to synthesize missing PET images for subjects with only MR images will be first discussed, followed by a unified approach capable of imputing missing data and achieving clinical diagnosis.

Hybrid Cycle-Consistent GAN for Synthesizing PET/MRI

Cycle-consistent generative adversarial network (CGAN) [32] has been successfully applied to learning the bi-directional mappings between relevant image domains. Since MR and PET images scanned from the same subject have underlying relevance, Pan et al. [36, 37] resorted to a 3D CGAN model, called hybrid GAN (HGAN), to learn bi-directional mappings between MRI and PET through which a missing PET scan can be synthesized based on its corresponding MRI scan. Specifically, a two-stage deep learning framework was developed [36, 37] to employ all available MRI and PET for brain disease diagnosis. In the first stage, the missing PET images were imputed by bi-directional mappings between MRI and PET via HGAN. In the second stage, based on the complete MRI and PET (i.e., after imputation), a landmark-based multi-modal multi-instance learning method (LDMIL) [30] was used for AD diagnosis, by learning MRI and PET features automatically in a data-driven manner.

The architecture of the HGAN model is illustrated in Fig. 9.2, which consists of two generators (G_1 and G_2) and two adversarial discriminators (D_1 and D_2). As shown in Fig. 9.2, based on the underlying relevance between MRI and PET, a mapping function from MRI to PET is learned in HGAN, i.e., $G_1 : \mathcal{A} \to \mathcal{B}$. A reversed function $G_2 : \mathcal{B} \to \mathcal{A}$ is also learned to encourage G to be a one-to-one mapping, with the constraint of $G_2 = G_1^{-1}$. The adversarial discriminators (e.g., D_1) are used to tell us whether the synthetic MR and corresponding real MR images are distinguishable or not. A cycle-consistent loss is used to learn the bi-directional mapping between MRI and PET aiming to guarantee the interactive relationship between the two modalities. More details on the network architecture and objective function of HGAN can be found elsewhere [36, 37].

Two subsets of the ADNI database [29], i.e., ADNI-1 and ADNI-2, were used for performance evaluation [36, 37]. There were 821 subjects in ADNI-1 and 636 subjects in ADNI-2. While all subjects in ADNI-1 and ADNI-2 had baseline MRIs, only 395 subjects in ADNI-1 and 254 subjects in ADNI-2 had PET images. All MR images were preprocessed via four steps: (1) anterior commissure (AC)-posterior commissure (PC) alignment, (2) skull stripping, (3) intensity correction, and (4) linear alignment to a template MRI. Each PET image was also aligned to its corresponding MRI via linear registration.

To evaluate the quality of the synthetic images, HGAN was first trained on the complete subjects (i.e., containing both PET and MRI scans) in ADNI-1 and then tested on the complete subjects in ADNI-2. Two typical subjects with real and synthetic PET scans are shown in Fig. 9.3. From Fig. 9.3, one can observe that the synthetic PET/MRI looks very similar to their corresponding real images. For instance, the mean and standard deviation of peak signal-to-noise ratio (PSNR) values of synthetic PET images in ADNI-2 are 24.49 ± 3.46. These results imply that the HGAN model is reasonable, and that the synthetic PET scans have acceptable image quality (in terms of PSNR).

Disease-Image-Specific GAN for Joint Image Synthesis and Disease Diagnosis

The HGAN model in [36] equally treats all voxels in each 3D volume, thus ignoring the *disease-image specificity*

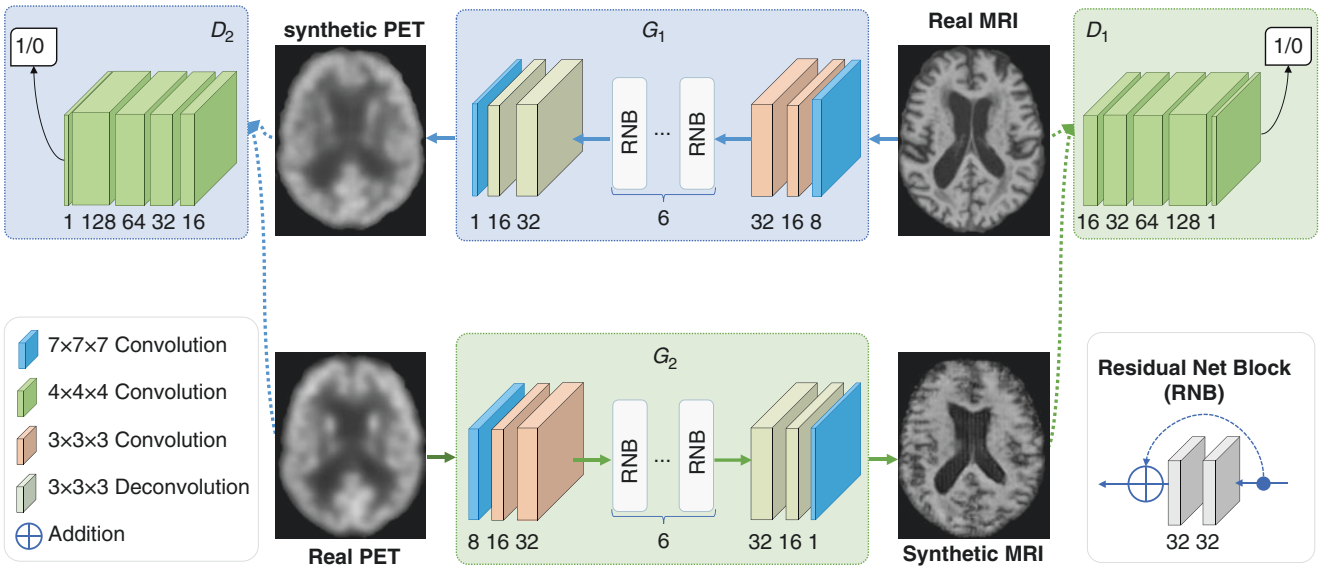

Fig. 9.2 Illustration of the hybrid generative adversarial network (HGAN) for MRI-based PET image synthesis, including two image generators (i.e., G_1 and G_2) and two adversarial discriminators (i.e., D_1 and D_2)

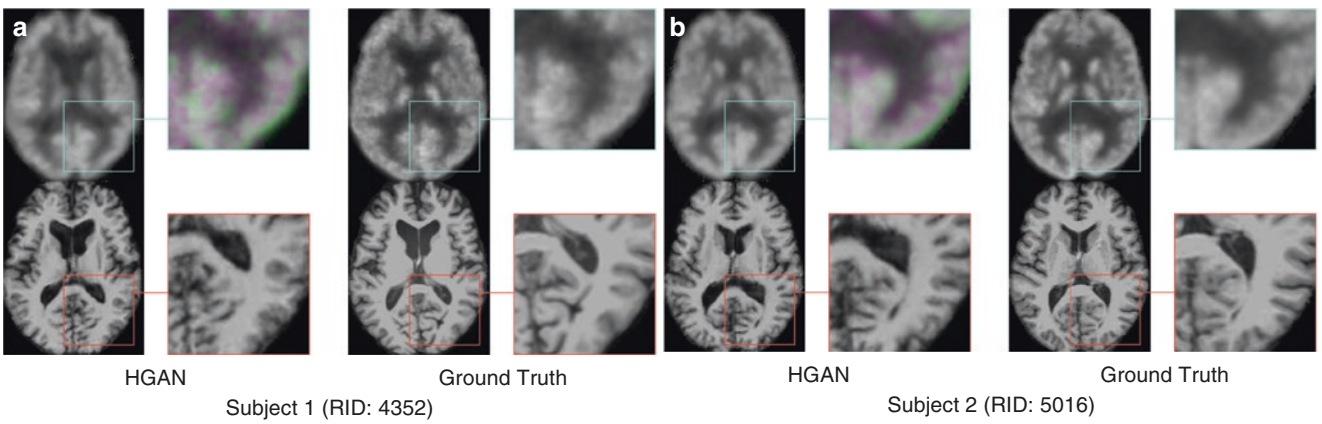

Fig. 9.3 Illustration of synthetic (Syn.) PET/MRI generated by HGAN for two typical subjects (Roster IDs: 4352, 5016), as well as their corresponding real PET/MRI images

conveyed in multi-modality neuroimaging data. Here, the disease-image specificity refers to two types of knowledge: (1) not all regions in an MRI/PET scan are associated with a specific brain disease [38], and (2) disease-associated brain regions may differ in different modalities (e.g., MRI and PET) [27, 39]. Existing deep learning methods usually treat all brain regions equally in the image synthesis process ignoring that several regions (e.g., hippocampus and amygdala) are highly associated with AD/MCI [38, 40–42]. Previous studies have shown that disease diagnosis models can implicitly or explicitly capture the disease-image specificity through regions of interest (ROIs) and anatomical landmarks [30, 35, 41]. To model the disease-image specificity, it is desirable to integrate disease diagnosis and image synthesis into a unified framework by imputing missing neuroimages in a diagnosis-oriented manner.

To this end, Pan et al. [43] proposed a disease-image-specific deep learning framework for joint disease diagnosis and image synthesis using incomplete MRI and PET scans. As shown in Fig. 9.4a, this method contained two single-modality Disease-image-Specific Network (DSNet) for MRI-based and PET-based disease diagnosis and a feature-consistent generative adversarial network (FGAN) for image synthesis. A disease-image specific network (DSNet) encoded disease-image specificity in MRI-based and PET-based feature maps (via $\mathbb{F}_A$ and $\mathbb{F}_B$) to assist the training of FGAN, while FGAN imputed missing images to improve the diagnostic performance of DSNet. Since DSNet and FGAN were trained jointly, missing neuroimages were synthesized in a diagnosis-oriented

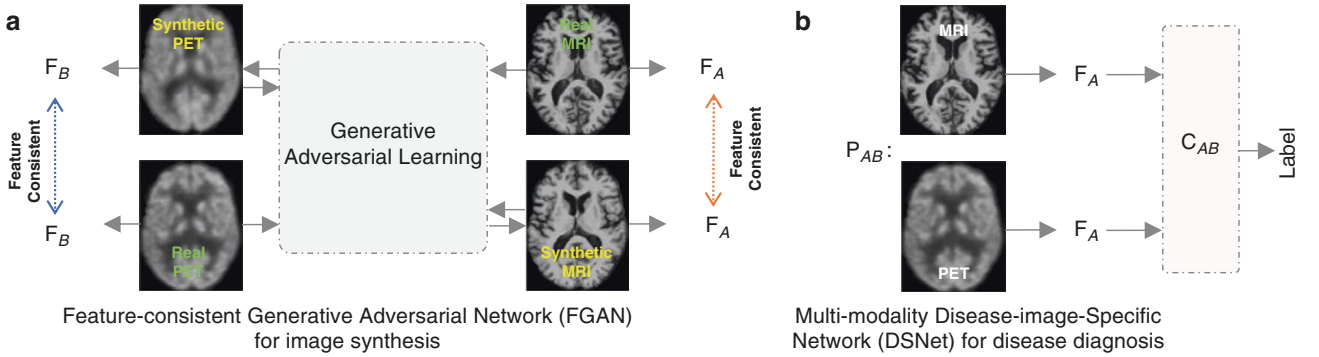

Fig. 9.4 Illustration of a disease-image-specific deep learning framework. (**a**) A feature-consistent generative adversarial network (FGAN) for image synthesis, encouraging feature maps (e.g., generated by $\mathbb{F}_A$) of a synthetic image and its real image to be consistent. Based on complete (after imputation) paired MRI and PET scans, a multi-modality DSNet (i.e., $\mathbb{P}_{AB} = [\mathbb{F}_A, \mathbb{F}_B] + \mathbb{C}_{AB}$) is designed for brain disease identification (**b**). The feature extractors (e.g., $\mathbb{F}_A$ and $\mathbb{F}_B$) in (**b**) are followed by a spatial cosine module (e.g., C_{AB}) for classification

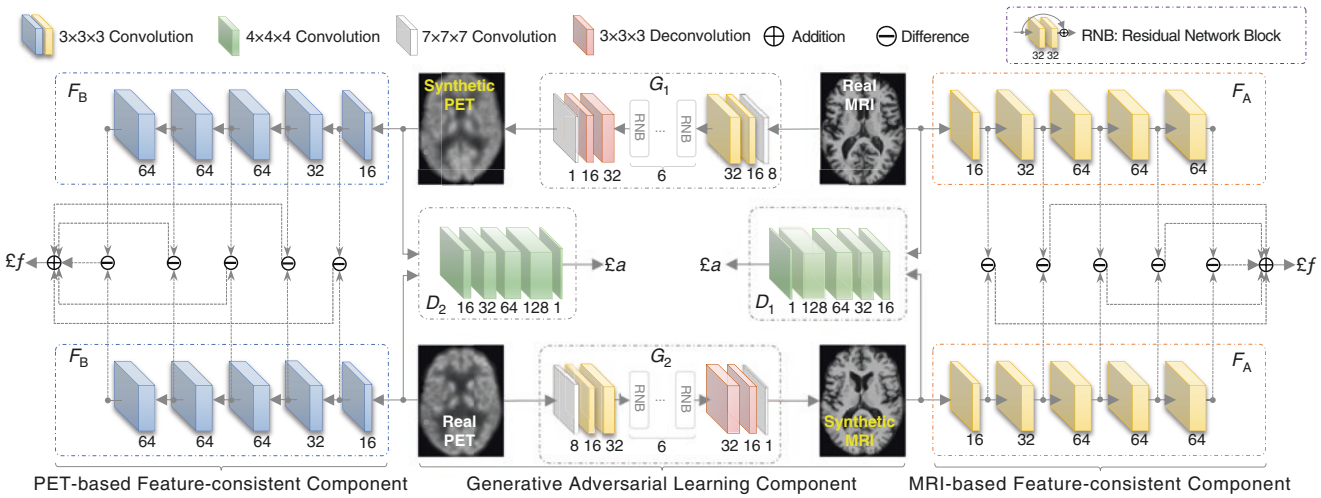

Fig. 9.5 Illustration of a feature-consistent generative adversarial network (FGAN) for image synthesis, including (1) a feature-consistent component (i.e., MRI-based $\mathbb{F}_A$ and PET-based $\mathbb{F}_B$) and (2) a generative adversarial learning component, with two image generators (i.e., G_1 and G_2) and two adversarial discriminators (i.e., D_1 and D_2)

manner. Using complete MRI and PET scans (after imputation), automated disease diagnosis was performed via DSNet, as shown in Fig. 9.4b. More details on the architecture of DSNet can be found elsewhere [43].

The network architecture of FGAN is illustrated in Fig. 9.5. The FGAN model contained two feature-consistent components (i.e., MRI-based $\mathbb{F}_A$ and PET-based $\mathbb{F}_B$) to encourage (1) feature maps of a synthetic image to be consistent with those of its corresponding real image and (2) a generative adversarial learning component to synthesize images under the constraints of feature consistency (i.e., $\mathfrak{L}_F$) and distribution consistency (i.e., $\mathfrak{L}_a$). Note that $\mathbb{F}_A$ and $\mathbb{F}_B$ were learned in MRI-based and PET-based DSNet models, respectively, through which the disease-image specificity learned in DSNet was employed in the image synthesis process, encouraging FGAN to focus on those disease-associated regions in each modality. The adversarial discriminators, i.e., D_1 and D_2, were used to constrain the synthetic MRI and PET scans to follow the same data distribution of those real MRI and PET scans, respectively. Besides, two generators (i.e., G_1 and G_2) were learned to construct bi-directional mappings between two imaging modalities. By jointly training DSNet and FGAN, one encourages that disease-image specificity learned by DSNet can be preserved in the image synthesis process and synthetic images are task-oriented for disease diagnosis.

Based on ADNI-1 and ADNI-2, two generative models were compared with FGAN, including (1) a conventional GAN with only the adversarial loss and (2) the cycle-consistent GAN (CGAN) [32]. These three models (i.e., GAN, CGAN, and FGAN) were trained on subjects with MRI and PET scans in ADNI-1 and tested on subjects with both MRI and PET scans in ADNI-2. Three metrics were used to measure the quality of synthetic images gen-

Table 9.1 Results of image synthesis achieved by different methods for MRI and PET in ADNI-2, with the models trained on ADNI-1

	Synthetic MRI					Synthetic PET				
Method	MAE (%)	SSIM (%)	PSNR	AUC[1] (%)	AUC[2] (%)	MAE (%)	SSIM (%)	PSNR	AUC[1] (%)	AUC[2] (%)
GAN	15.03	55.56	23.48	66.83	53.64	11.62	55.27	27.13	52.92	51.54
CGAN	14.09	59.38	23.96	71.00	57.20	10.70	58.15	27.16	57.50	52.55
FGAN	**12.61**	**64.04**	**25.10**	**92.98**	**77.61**	**8.03**	**68.17**	**29.62**	**83.80**	**71.27**

erated by different methods, including (1) the mean absolute error (MAE), (2) peak signal-to-noise ratio (PSNR) [44], and (3) structural similarity index measure (SSIM). The experimental results are shown in Table 9.1. To further evaluate the reliability of synthetic MR and PET images (generated by FGAN) in disease diagnosis, values of the area under the receiver operating characteristic (AUC) achieved by DSNet in two diagnosis tasks, i.e., AD vs. HC classification (with results denoted as AUC^1) and MCI conversion prediction (with results denoted as AUC^2), are also found in Table 9.1. This table suggests that FGAN can generate high-quality MRI and PET scans in terms of three metrics and that the AUC values obtained by using FGAN-based synthetic images are significantly better than those using CGAN-based and GAN-based synthetic images. This implies that FGAN is effective in generating diagnosis-oriented images.

Future Research Direction

Several technical issues need to be considered in the future. First, even though existing methods [43] can automatically locate disease-related regions to help image synthesis, those regions are only coarsely defined. It is interesting to identify finer regions in the brain image for further improvement. Also, multi-modal neuroimaging data used in existing studies were usually acquired from different imaging sites, and data from different sites may follow different distributions. It is desirable to alleviate the negative influences of different data distributions via data harmonization approaches, e.g., data adaptation techniques [45, 46].

Conclusion

PET/MR has already demonstrated great potentials in both clinical and research applications. The recent advances of instrumental, software, and AI developments contribute to a significant improvement of PET performance, which leads to improved image SNR, reduced scan time, and lower radiotracer dose. We believe that the technology of PET/MR technology will be continuously progressing, and its role in clinical practice will keep growing.

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