Diagnosis of Brain Diseases in Fusion of Neuroimaging Modalities Using Deep Learning: A Review

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Abstract

Brain diseases, including tumors and mental and neurological disorders, seriously threaten the health and well-being of millions of people worldwide. Structural and functional neuroimaging modalities are commonly used by physicians to aid the diagnosis of brain diseases. In clinical settings, specialist doctors typically fuse the magnetic resonance imaging (MRI) data with other neuroimaging modalities for brain disease detection. As these two approaches offer complementary information, fusing these neuroimaging modalities helps physicians accurately diagnose brain diseases. Typically, fusion is performed between a functional and a structural neuroimaging modality. Because the functional modality can complement the structural modality information, thus improving the performance for the diagnosis of brain diseases by specialists. However, analyzing the fusion of neuroimaging modalities is difficult for specialist doctors. Deep Learning (DL) is a branch of artificial intelligence that has shown superior performances compared to more conventional methods in tasks such as brain disease detection from neuroimaging modalities. This work presents a comprehensive review paper in the field of brain disease detection from the fusion of neuroimaging modalities using DL models like convolutional neural networks (CNNs), recurrent neural networks (RNNs), pretrained, generative adversarial networks (GANs), and Autoencoders (AEs). First, neuroimaging modalities and the need for fusion are discussed. Then, review papers published in the field of neuroimaging multimodalities using AI techniques are explored. Moreover, fusion levels based on DL methods, including input, layer, and decision, with related studies conducted on diagnosing brain diseases,

are discussed. Other sections present the most important challenges for diagnosing brain diseases from the fusion of neuroimaging modalities. In the discussion section, the details of previous research on the fusion of neuroimaging modalities based on MRI and DL models are reported. In the following, the most important future directions include Datasets, DA, imbalanced data, DL models, explainable AI, and hardware resources are presented. Finally, the main findings of this study are presented in the conclusion section.

KeyWords: Brain Diseases, MRI, Neuroimaging, Fusion, Multimodality, Deep Learning

1. Introduction

The brain is the most crucial organ in the human body and is responsible for controlling thoughts, memory, emotions, motor skills, vision, and breathing [1]. The human brain consists of 100 billion neurons connected to over 100 trillion synapses [2]. From an anatomical perspective, these connections are organized at various spatial scales, while from a functional standpoint, they interact with each other at various time scales. Due to these complexities, evaluating and identifying the neural mechanisms of brain activities are incredibly important for researchers [2].

Neurological and mental disorders are diseases affecting the central or peripheral nervous system [3-4]. Due to the complexity of the nervous system, the probable causes and forms of brain diseases are diverse. Genetic, epigenetic, and external factors, such as physical trauma, infection, and various environmental factors, can be involved in the onset and progression of brain diseases [5-6]. Some of the most important brain diseases include multiple sclerosis (MS) [7], Alzheimer's disease (AD) [8], Parkinson's disease (PD) [9], cerebral palsy [10], autism spectrum disorder (ASD) [11-12], amyotrophic lateral sclerosis (ALS) [13], myasthenia gravis (MG) [14], traumatic brain injury [15], and epileptic seizures [16-18].

Neuroimaging is important for diagnosing and identifying brain diseases [19-20]. Neuroimaging records thpatient's brain's structural form and functional behavior [19-20]. Neuroimaging modalities are primarily divided into structural and functional categories [21-22]. Structural neuroimaging modalities are used for displaying the anatomical structure of the brain and diagnosing neurological disorders that cause structural changes in the brain; a few of the well-known structural modalities include Computerized tomography (CT) [23], structural MRI (sMRI) [24], and diffusion tensor imaging (DTI) [25]. In contrast, functional neuroimaging modalities are used for evaluating the behavior and metabolism of the brain when performing a specific task, such as sensory, motor, and cognitive tasks [26]. Positron emission tomography (PET) [27], single-proton emission computed tomography (SPECT) [29], functional magnetic resonance imaging (fMRI) [28], and magnetoencephalography (MEG) [30] are among the most important functional imaging modalities based on medical imaging. Following are the details of each neuroimaging modality and its advantages and disadvantages. It is emphasized that neuroimaging modalities are flawless and that there are alternatives for selecting each one to identify brain diseases.

CT, also known as computerized x-ray imaging, combines a set of x-ray images obtained from different angles around the body and creates cross-sectional images using computerized processing [23]. The CT scanner uses a motorized x-ray source that rotates around a gantry, i.e., a circular frame in a donut-shaped structure [23]. CT scans' benefits include high resolution, short scanning time, and high penetration depth [23]. However, some disadvantages of this medical imaging method include limited tissue characterization, exposure to X-rays, expensive and high radiation doses in each examination [31].

PET is a combination of nuclear medicine and biochemical analysis. Biochemical changes can reveal the development of the disease even before other imaging techniques show the anatomical changes related to that disease [27]. Some advantages of PET imaging include high sensitivity, high penetration depth, and the possibility of imaging physiological and biochemical phenomena [27]. Nonetheless, limited resolution,

radiation, high cost, motion artifacts, problems interpreting images, and radioactive material usage limitations are well-recognized disadvantages [32-33].

SPECT is a nuclear medicine tomographic imaging technique using gamma rays [29]. This technique is highly similar to conventional nuclear medicine flat imaging using gamma cameras (scintigraphy); however, it can provide real 3D information [29]. Attenuation reimbursement is not probable because of multiple-electron scattering. Some disadvantages of using SPECT include blurring effects, limited resolution, radiation, and high cost [29]. Nevertheless, the benefits of SPECT include sensitivity, higher penetration depth, and the lack of background in the images [34].

MRI is one of the most popular medical imaging techniques that allow the observation of anatomical structures, physiological functions, and molecular composition of tissues [35]. MRI has various structural and functional modalities [11-12]. The most important advantages of MRI are high-contrast brain tissue presentation, high-resolution (1mm cubic voxels), adequate signal-to-noise ratio, and no radiation exposure [36]. However, the long recording time compared to CT and the Complex analysis of the obtained images by physicians are disadvantages of MRI [37].

In order to diagnose brain diseases, physicians have recently started fusing various neuroimaging modalities [38-44]. Usually, a structural modality, such as sMRI, is fused with a functional modality, such as PET [45]. One of the advantages of using fusion techniques is that various modalities can complement each other, i.e., a modality can cover the information not provided by another modality [46-47]. For instance, PET or SPECT data do not provide high-resolution 3D anatomical information. On the other hand, high-resolution structural images can be obtained using CT and/or MRI. These neuroimaging techniques complement each other, providing a complete image of the anatomy, physiology, and pathology of the brain. Using complementarity, we merge a hyper-temporal resolution image with a hyper-spatial resolution image to obtain a spatiotemporal resolution fusion image [48-49].

There are various technical challenges in image fusion due to brightness, differences in resolution, the presence of noise, variety of image modalities, lack of a sufficient number of images in each modality, increased imaging costs, and extensive computational complexity [50-51]. In recent years, to overcome these challenges, extensive research has been carried out in the field of diagnosis of brain diseases based on multimodality neuroimaging using AI techniques [52-86]. AI techniques can be divided into machine learning (ML) and deep learning (DL) methods [87-90]. ML is a sub-branch of AI based on the concept that systems can learn from the data, identify patterns, and make decisions with minimum explicit coding on how to do so [87-88]. As a standard procedure, ML algorithms are evaluated and picked by trial and error in the diagnosis of diseases, which is difficult [87-88]. Two review papers in this field include: Yadav et al. [66] discussed the process of image fusion, its application in medicine, and its advantages and disadvantages. They explore the fusion of MRI, PET, and CT medical images Using AI-based approaches. Yousif et al. [68] presented a review paper on brain disorders detection using data fusion techniques. They evaluated the most important challenges facing the diagnosis of brain disorders. Then, they analyzed various image fusion techniques, fusion levels, methods based on multiscale decomposition, and their advantages and disadvantages.

DL models can automatically learn representations from raw data and optimize them [89-90]. In addition, these models automatically learn robustness against natural changes in the data [89-90]. As a general rule, in DL models, the larger the training data size, the better the model's performance [89-90]. Furthermore, DL models can learn from unstructured data, providing the possibility of using different data formats. Labeling the data is expensive and time-consuming; however, some DL models can use and process non-labeled data [89-90]. Zhou et al. [69] presented a general view of DL-basemultimodal medical image

segmentation approaches. They first discuss the main idea behind DL and multimodal image segmentation. Then, they explain various DL architectures. Afterward, they analyze different fusion techniques and compare their respective results. Finally, they provide a conclusion and perspectives on future research.

When diagnosing brain diseases using DL techniques, image fusion techniques can increase the performance for the diagnosis of brain diseases. Fusion is performed at three levels: the input, the layer, and the decision level [91-93]. At the input level (also known as the pixel level), the information is directly fused into the raw image domain or the image's multi-resolution transformations [91]. The main objective of layer-level fusion methods, also known as the feature level, is to fuse the extracted features from the image since features are more valuable and informative than the pixels, and it is easier to perform fusion in feature space [92]. Finally, the decision level integrates the outputs from several DL algorithms to reach a final decision. Each image is processed separately in this method, and its output is fed into a final classifier for fusion [93].

The current paper reviews prior research on the diagnosis of brain diseases based on neuroimaging multimodalities and DL techniques. Section 2 discusses all the review papers on diagnosing brain diseases using neuroimaging multimodalities and AI techniques. Section 3 introduces the search strategy based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [94]. Section 4 is about brain disease detection based on the fusion of neuroimaging modalities. The most important DL models used for brain disease detection based on neuroimaging multimodalities are discussed in Section 5. Section 6 deals with various levels of medical imaging fusion using DL techniques. In this section, the most important studies in each part are summarized in tables 3 to 6. The challenges facing the diagnosis of brain diseases using neuroimaging multimodalities and DL models are presented in Section 7. Section 8 presents the discussion. The most important future works are presented in section 9. Finally, the conclusion and the findings of this review study are provided in Section 10.

2. Diagnosis of Brain Diseases using Fusion Neuroimaging Modalities and AI Methods

In this section, all review papers focusing on diagnosing brain diseases using the fusion of neuroimaging modalities and AI methods published from 2016 to 2022 are explored. The summary of these review papers is presented in Table 1. Table 1 shows the details of review papers, including publication year, publisher, AI methods, modalities, and the number of citations. The current study evaluated papers on brain disease detection using the fusion of neuroimaging modalities based on MRI data and DL models. As the first novelty, we review all papers on diagnosing brain diseases from neuroimaging multimodalities based on MRI data using DL methods. The second novelty of the current study is reviewing papers on the diagnosis of brain diseases from neuroimaging multimodalities based on MRI in three fusion levels: input, feature, and decision. The papers related to the input, layer, and decision level are reported in Tables 3 to 6, respectively. Moreover, a few researchers have combined different fusion levels to increase the performance for brain disease diagnosis. In this review study, these papers are also explored and reported in Table 1.

Table 1. Summary of review papers published on the diagnosis of different brain diseases in fusion neuroimaging modalities using AI methods.

Works	Year	Publisher	Method	Approach	Modalities	Number of Citations
[52]	2016	Elsevier	ML	Multi-Modal Medical Image Fusion	MRI, CT, PET, SPECT	210
[53]	2016	Elsevier	AI	Multimodal Fusion of Brain Imaging Data	fMRI, dMRI, sMRI	252
[54]	2016	IEEE	ML	Image Fusion Models based on pixel level	Different Data	9
[55]	2016	I-Scholar	ML	Multimodal Medical Image Fusion Techniques	CT, MRI, PET, SPECT	12
[56]	2016	IEEE	ML	Multi-Modality Medical Image Fusion	MRI, CT, PET	10

[57]	2017	IEEE	DL	Deep Multimodal Learning	Different	323
[58]	2017	IEEE	ML	Image Fusion based on Multi-Scale Decomposition to Non-Multi-Scale Decomposition Techniques	CT, MRI PET, SPECT, and etc.	112
[59]	2017	IEEE	ML	CT - PET Fusion Using Hybrid Algorithm	CT, PET	5
[60]	2017	A and V Publication	ML	Image Fusion Methodologies and Applications	MRA, MRI, CT, PET, fMRI, X Rays, Ultrasound	10
[61]	2018	IEEE	ML	Image Fusion Techniques for Medical Diagnosis	CT, MRI	0
[62]	2019	Elsevier	DL	Medical Image Segmentation from Multi-Modality Fusion using DL Models	PET, MRI, CT	230
[63]	2019	IEEE	ML	Different Multimodal Medical Image Fusion Techniques	MRI, CT, PET	4
[64]	2019	IEEE	ML	Medical Images Fusion Using A Wavelet Models	CT, MRI	5
[65]	2019	IEEE	ML	Multi-Model Medical Image Fusion	MRI, PET, CT, SPECT	9
[66]	2019	Elsevier	ML	Region-Based Image Fusion Methods	CT, MRI	113
[67]	2019	Springer	DL	Multimodal Medical Image Analysis using DL Methods	CT, MRI, PET	11
[68]	2020	IEEE	ML	Present Solutions of Medical Image Fusion	CT, MRI, PET, SPECT	19
[69]	2020	Springer	ML	Image Fusion in Multimodality Medical Images	MRI, CT, PET	33
[70]	2020	Elsevier	ML	Advances in Multimodal Data Fusion in Neuroimaging	CT, PET, SPECT, MRI	90
[71]	2020	MIT Press	DL	DL Techniques for Multimodal Data Fusion	Different Modalities	102
[72]	2020	Hindawi	ML and DL	Multimodal Medical Image Fusion Techniques	MRI, PET, CT, SPECT	34
[73]	2020	MDPI	ML and DL	Image Fusion for Diagnosis of Liver Cancer	CT, MRI, PET, Ultrasound	14
[74]	2020	Springer	ML	Different Image Fusion Techniques in Brain	CT, MRI	4
[75]	2020	Nature	DL	Medical Imaging Fusion and Electronic Health Records Using DL Models	Medical Imaging With EHR	83
[76]	2021	Elsevier	ML	Medical Image Fusion Methods	MRI. CT, PET, Echo	0
[77]	2021	Springer	ML	Various Image Fusion Algorithms Performance Metrics	CT. MRI, PET	0
[78]	2021	Elsevier	ML and DL	Multimodal Medical Image Fusion Review in Medicine	CT, PET, MRI, SPECT	20
[79]	2021	IEEE	ML and DL	Various Multimodal Medical Image Fusion Techniques	MRI, SPECT, PET, CT, Ultrasound, X-Rays	0
[80]	2021	IEEE	ML	Medical Image Fusion Based on Sparse Representation	CT, MRI, SPECT	3
[81]	2021	Elsevier	DL	Image Fusion Meets DL	Different Modalities	29
[82]	2021	Springer	ML and DL	Image Fusion Techniques	Different Modalities	34
[83]	2021	Springer	ML	Multimodality Medical Image Fusion Methods	MRI, CT, PET, SPECT	17
[84]	2022	NCBI	--	Decision Fusion in Healthcare and Medicine	Different Modalities	0
[85]	2022	Elsevier	--	Multimodal Medical Image Fusion	Different Modalities	0
[86]	2022	ArXiv	ML and DL	Deep Multi-modal Fusion of Image and Non-image Data in Disease Diagnosis and Prognosis	Image and Non-Image Data	0

Table 2. Exclusion and inclusion criteria used during the selection of papers.

Inclusion	Exclusion
1. Neuroimaging multimodalities 3. MRI-PET, MRI-CT, MRI-SPECT, etc. 3. Different types of brain diseases 4. Fusion level methods 5. DL models (CNNs, RNNs, AEs, CNN-RNN, CNN-AE, GAN, Transfer Learning, etc.)	1. Treatment of brain diseases 2. Clinical methods for brain diseases treatment

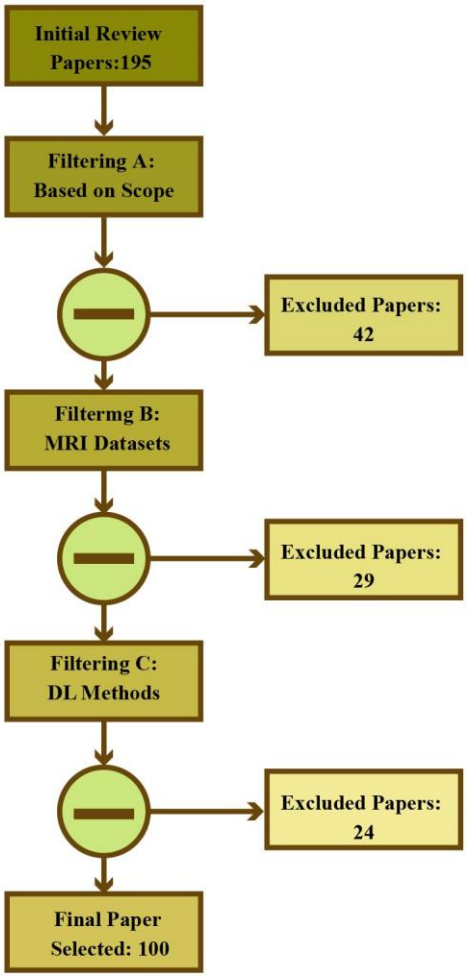

Fig 1. PRISMA flow diagram used to select the relevant papers.

3. Search Strategy Based on PRISMA Guidelines

This section searched papers according to PRISMA guidelines [94]. In our study, papers published from 2016 to 2022 focusing on the diagnosis of brain diseases using the fusion of neuroimaging modalities were chosen. To identify such papers, we used keywords including “fusion”, “multimodality”, “deep learning”, “sMRI”, “fMRI”, “sMRI-fMRI”, and “fMRI-EEG”, “MRI-CT”, and the like. These keywords were used for searching various databases, including Science Direct, Frontiers, MDPI, IEEE Xplore, Nature, Springer, ArXiv, and Wiley. The process of selecting and evaluating papers focusing on brain disease detection using neuroimaging modalities fusion and DL was carried out based on the PRISMA guidelines at three levels. 195 papers focusing on neuroimaging modalities fusion were identified in the first stage. Then, 42 papers were eliminated from the next evaluation stages since they were out of scope. In the following, the 29 papers are filtered because these papers were not based on MRI modalities. In the next stage, another 24 papers were eliminated because they did not use DL methods or because of the type of the publishing database. This left 100 papers that were retained for reviewing, and their details were discussed. Figure 1

depicts the process of selecting the papers based on the PRISMA guidelines. Moreover, the inclusion and exclusion criteria are presented in Table 2.

Based on Table (2), the most important inclusion criteria for selecting papers are neuroimaging modalities, fusion techniques (the most popular ones are picked), types of brain diseases, fusion levels, and finally, DL models. Neuroimaging multi-modality was selected as the first inclusion criterion for searching for papers. As mentioned earlier, various methods have been introduced to diagnose brain diseases; here, the focus is on neuroimaging multi-modalities based on MRI, such as MRI-PET or MRI-CT. The type of brain disease is the second inclusion criterion for our search because the primary purpose of this review paper is to examine the research in the field of brain disease diagnosis based on neuroimaging multi-modalities, and therefore other diseases are not considered in this work. Fusion levels are one of the most important inclusion criteria for searching papers in this work; the authors of this paper have summarized and reported different types of brain disease detection research based on fusion levels, including pixel, feature, decision, and hybrid, in tables 3 to 6. DL is the last inclusion criterion for searching articles in this field. Until now, numerous papers have been presented on brain disease diagnosis from neuroimaging multi-modalities using different AI techniques, and we aim merely to review articles with DL methods. On the other hand, the exclusion criteria include the treatment of brain diseases and clinical methods, which are not discussed in this work.

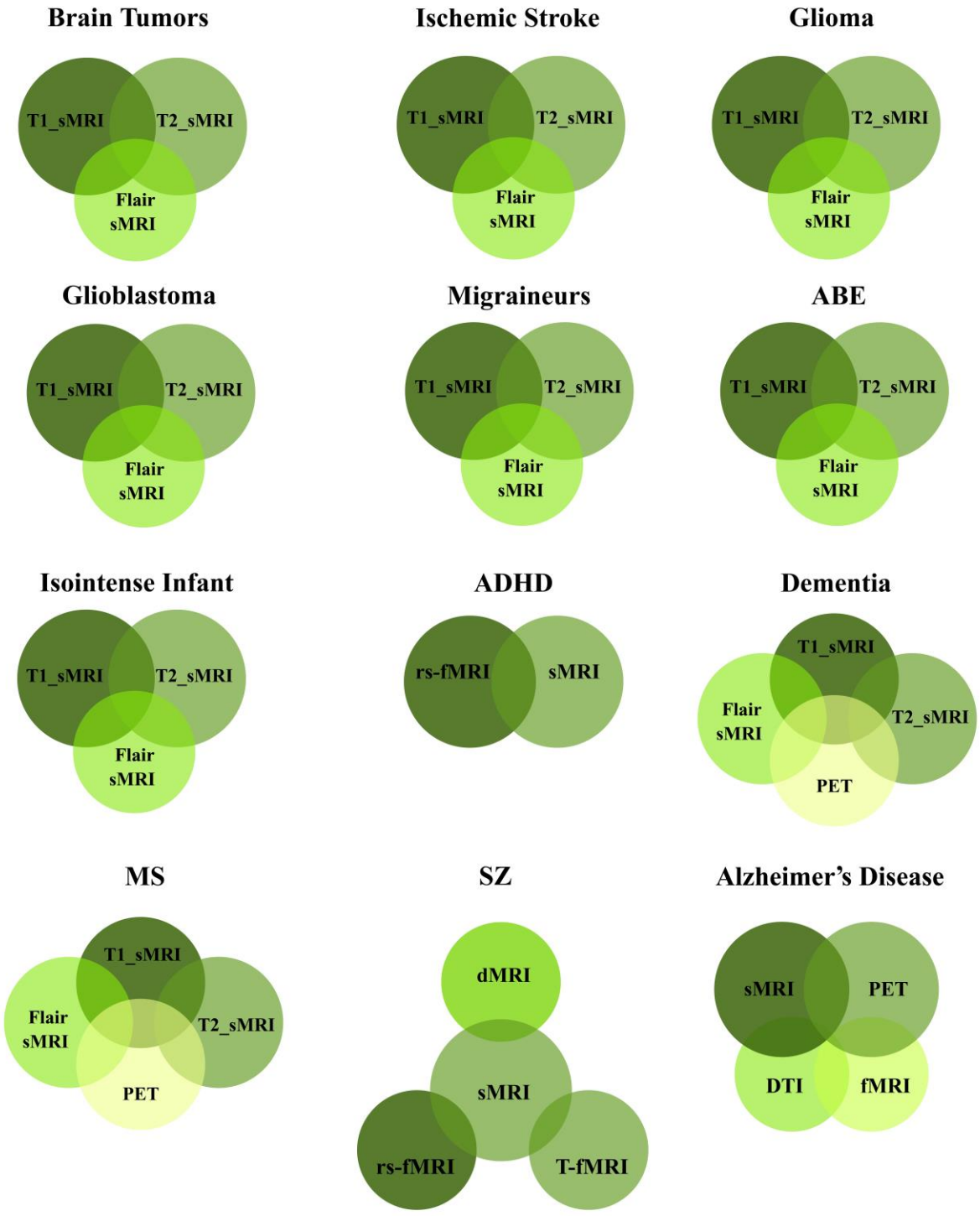

Fig. 2. Brain disease detection using neuroimaging multimodalities and DL methods.

4. Brain Diseases Detection using Fusion of Neuroimaging Modalities

Neuroimaging modalities are an essential category of brain disease diagnosis techniques, and numerous clinical trials are undertaken in this sector. Each neuroimaging modality offers distinct advantages and disadvantages for the diagnosis of brain diseases. In order to diagnose brain diseases, different neuroimaging modalities are typically registered and evaluated by specialists. In other words, medical professionals use a variety of neuroimaging modalities to diagnose brain diseases more accurately. Investigators typically combine MRI imaging techniques with other neuroimaging modalities in clinical settings to diagnose brain diseases. The diagnosis of ADHD, SZ, brain tumors, ischemic stroke, glioma, glioblastoma, acute bilirubin encephalopathy (ABE), Migraineurs, MS, isointense infant brain, Alzheimer's disease, and dementia is made using fusion neuroimaging modalities in combination with DL approaches, as shown in tables 3 to 6. As discussed in the manuscript, several levels of fusion are used for diagnosing brain diseases, such as pixel, feature, decision, and hybrid; reviewed papers are also categorized by their fusion level and reviewed in tables 3 to 6, respectively. Fusion neuroimaging modalities for brain applications are depicted in Figure 2. As can be observed in this figure, researchers have used a fusion of structural neuroimaging modalities, such as T1-sMRI, T2-sMRI, or Flair, to diagnose brain tumors (such as ischemic stroke, glioma, glioblastoma, Migraineurs, and ABE). Structural neuroimaging modalities play a significant role in detecting these tumors; therefore, researchers mainly fuse them to reach a robust detection system. On the other hand, for MS and dementia (two of the most important neurological disorders), we can see that physicians use both structural and functional modalities. As shown in figure 2, the fusion of T1-sMRI, T2-sMRI, or Flair with PET as the functional modality is common for diagnosing MS and dementia. Moreover, SZ is another mental disorder, and as illustrated in figure 2, sMRI-TfMRI, dMRI-sMRI, and sMRI-fMRI are commonly used for SZ diagnosis. Lastly, researchers have used a fusion of structural and functional modalities (fMRI, DTI, sMRI, and PET) to diagnose AD.

5. Deep Learning Models

Recent developments in DL models have increased their prominence in applications for medical diagnosis, particularly brain diseases [338-340]. This section is devoted to providing details on different DL techniques used by researchers for brain disease diagnosis from the fusion of multi-modality. Researchers apply DL approaches for segmentation, feature extraction, and classification when analyzing neuroimaging modalities to diagnose brain abnormalities [341-342]. These tasks usually shape most of the AI system used in any model; therefore, the whole AI system of papers is generally considered a one-unit DL method. Development of DL methods, and even new types and groups of models and architectures, is usually outside the scope of biomedical-AI literature. In that literature (which we can call DL literature), researchers focus on creating new layers, new optimization techniques, or even a new type of method for specific data types. Here in biomedical AI, however, we mostly see researchers focusing on finding the best-suited architecture for their case; researchers mostly play with the number and configuration of layers and loss functions [343-344]. But the particular problem of finding and creating networks for brain disease detection using neuroimaging multimodalities is more challenging, as researchers are forced to fuse different types of data. Therefore, they are forced to use different types of networks and also fuse them on different levels. Given these challenges, this section aims to review the most influential architectures used in reviewed works to help new researchers learn about them faster and, hopefully, create a suiting model for their task easier.

The most used DL networks for brain disease detection using neuroimaging multimodalities include CNNs, GANs, RNNs, AEs, CNN-RNNs, and CNN-AEs. In the training phase, CNN architectures, among the DL models, employ supervised learning and are split into classification and segmentation techniques. Pretrained CNNs, 2D and 3D CNNs, and FC layers are all included in CNN models with classification

approaches. CNN-based segmentation models also encompass U-Net and FCN architectures. GANs are a well-known class of DL approaches employing various methodologies depending on how they are used in the training phase. GAN models are typically employed for DA in studies on the diagnosis of brain diseases. Two other significant categories of DL approaches are RNNs and AEs models, which rely on unsupervised learning during the training phase. These networks are employed in applications involving feature extraction or classification, and several of their hybrid models, including CNN-RNNs, CNN-AEs, and RNN-AEs, have also been introduced.

5.1 Convolutional Neural Network

Convolutional Neural Networks (CNNs) started a revolution in machine learning around a decade ago and initiated the field known today as deep learning. The idea behind training convolutional filters is not new, though, as it has been suggested before in [95-97]. Nevertheless, their first important appearance is usually recognized as the AlexNet paper [95-97], which scaled up the benchmark for image classification tasks. CNNs are also great representation learners, and they are applied in various fields such as image enhancement [98] and medical diagnosis [99-102]. Nowadays, a few well-known network structures, such as VGG [95] and ResNet [95] are usually used, and it is not common to develop the CNN architecture from scratch; also, these models are considered baselines in the process of model development. CNNs are not limited to tasks where the underlying data has a 2D image-like structure. An influential variant for medical diagnosis is 3D CNN, which is perfect for 3D data such as MRI brain scans. 3D CNN works by taking account of spatial information in all three directions; however, they are harder to train and require far more data and computational resources [95-97]. In addition to being suited to extracting features from image data, given their structures, convolutional neural nets are among the popular options for information fusion, especially at the feature level. This is arguably due to the quality of their features; however, they still face a considerable performance drop when faced with distributional drifts in datasets.

1) Pretrained Models

When looking at what each filter has learned in CNNs, researchers have found that early layers of these networks learn to extract low-level features, such as edges [95], while high-level features are usually extracted in the last layers. This encourages re-using weights, considering that low-level features are usually the same between different tasks [95]. Doing so has been known as transfer learning (i.e., transferring knowledge from one domain to another), and typically, the previously trained networks are called pre-train nets. Pre-train nets allow one to train deep neural nets without having a tremendous amount of data. Usually, pre-trained weights for well-known structures (trained on ImageNet) are available publicly. Researchers usually use these weights as an initial point for their network and freeze some of the layers to reduce the number of learnable parameters [95-98]. Pre-training networks are essential in many medical diagnosis tasks, as limited dataset size is usually one of the challenges biomedical machine learning faces. Nevertheless, by pre-training networks, an initial direction is given to the model for convergence, which might, in nature, contradict the idea of representing various aspects of data and fusing them in information fusion. Figure 3 shows a general form of a deep pre-trained model used for diagnosing brain diseases in neuroimaging multimodalities based on MRI.

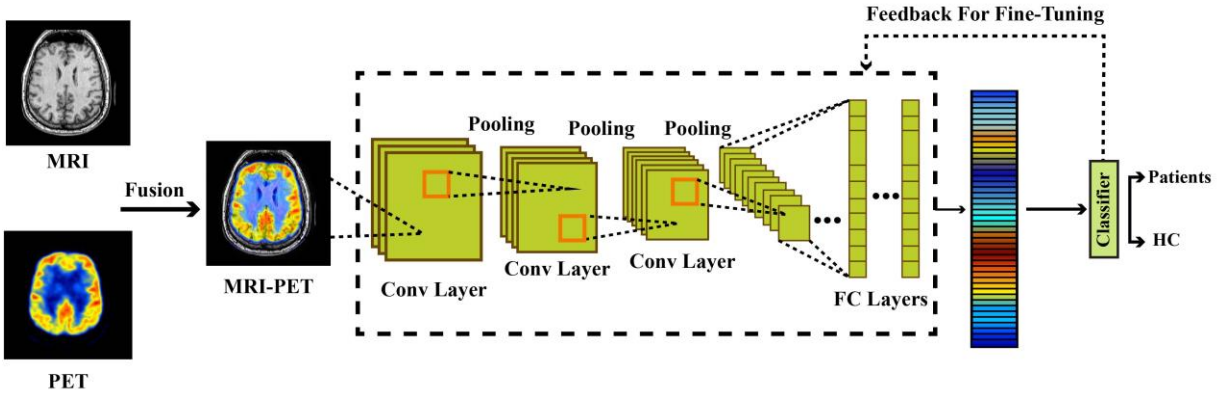

Fig. 3. A typical pre-trained model for brain diseases detection from neuroimaging multimodalities based on MRI.

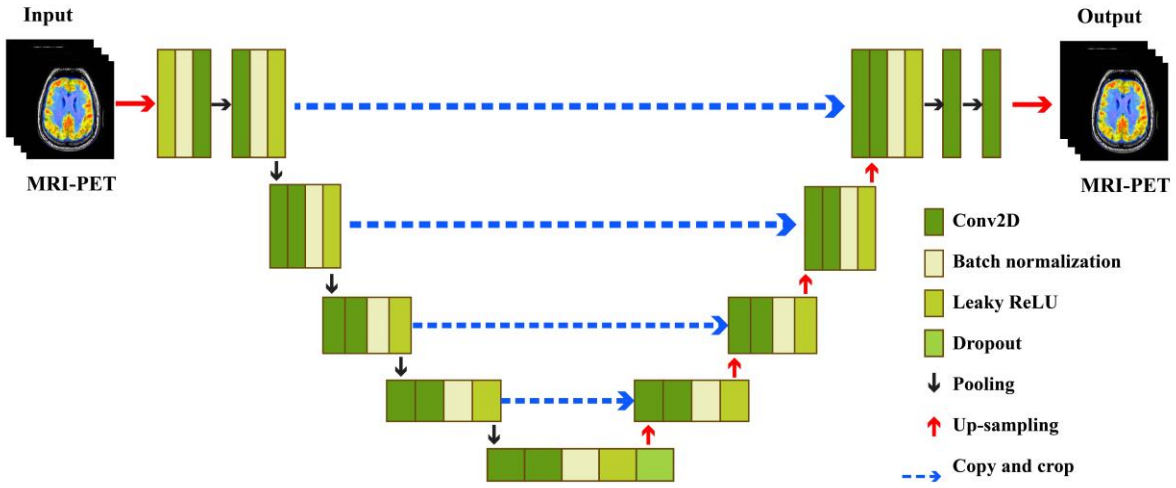

Fig. 4. A typical U-Net model for brain disease detection from neuroimaging multimodalities based on MRI.

2) U-Net Models

Image segmentation tasks are slightly different from routine classification problems, as the network needs to generate an image-sized mapping from each pixel to the corresponding label [103]. To this end, segmentation methods are usually created in an encoder-decoder paradigm and can be viewed as CNN-AEs. A few famous segmentation network structures, such as FCN and U-Net, have already been widely applied in medical image segmentation [103]. In addition to the encoder-decoder structure, U-Net also has skip connections, which has helped dramatically improve performance [103]. U-net and FCN are both powerful networks when it comes to image segmentation.

Nonetheless, these networks are limited to spatial information by merely using convolutional layers. This might be reasonable when the task at hand is solely segmentation, but when fusing information for higher-level tasks, this might prevent network learning. Figure 4 shows a general form of a U-Net model used for diagnosing brain diseases in neuroimaging multimodalities based on MRI.

3) FCN Models

FCN was first proposed in [104] by Long et al. for the segmentation of images. This unique type of CNNs, with an encoder-decoder structure, does not have any fully connected layer [104]. In these networks, a raw image is given to the model as input, and mapping with a comparable size to the image is provided as the output of the model. In its basic form, the output is the segmentation mapping, but it can be used for other purposes (such as localization of a specific region of an image [104]). As expected from the encoder-decoder structure, inputs are first transformed into a latent space. Then by using up-sampling and convolutional layers are converted back to the original space to produce the desired mapping [104].

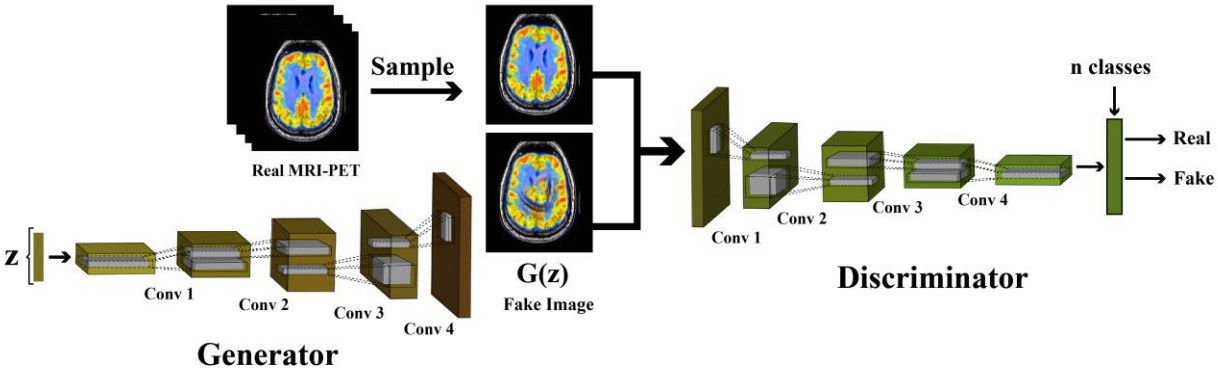

Fig. 5. A typical GAN model for brain disease detection from neuroimaging multimodalities based on MRI.

4) GAN Models

Learning the underlying distribution of data is key for many data science problems, but it is also arguably the most complicated task in all learning paradigms [105-106]. One path to tackle this task is to learn a generative model that tries to generate data similar to the primary dataset. While there are numerous generative methods, Generative Adversarial Networks (GANs) have a special place among researchers due to their high-quality generated data [105-106]. The idea behind these models is to simultaneously train two models, one discriminator that tries to discriminate between real and generated images and a generator that tries to fool the discriminator. GANs and their variations, such as CycleGAN [107-108] and WGAN [109], have been widely used in medical diagnosis for tasks such as data augmentation (DA), representation learning, and image enhancement. GANs have helped many research disciplines by introducing new data generation and augmentation methods. Nonetheless, as the dimensionality of data increases, the quality of generated synthetic data drops. This issue can prevent them from being used in information fusion as here as the model requires generating multi-modal data simultaneously. Figure 5 shows a general form of a GAN model used for diagnosing brain diseases in neuroimaging multimodalities based on MRI.

5) Autoencoder Models

Ideas and applications of Autoencoders (AE) go far back before the appearance of deep learning [95]. The primary idea is quite simple: taking the data to an underlying smaller latent space (by an encoder) and then reconstructing it from the latent representation (by a decoder) [95]. Professionally trained, one expects that the encoder learns to extract and encode essential patterns in data and the decoder to reconstruct an acceptable output [95]. AEs are used in medical imaging not merely due to their ability to learn representation but also for denoising and compression [110-111]. Numerous variants of AEs, such as denoising AE, stacked AE, and sparse AE, have been suggested, each aiming to solve a problem of priors [112]. One variant of AE is convolutional AE (CNN-AE), specifically created to handle image and signal data types [113]. Without convolutional layers, AEs cannot learn spatial patterns in data. However, the

applications of CNN-AE are not limited to this, as some forms of them (VAEs) can be used to generate data, and, with a few changes, they are widely used for image segmentation [114] and forgery detection [115]. AEs are among the most preferred choices for unsupervised re-presentation learning. They are great options for feature-level fusion, and as they have many variants (such as CNN-AE), they can easily be matched to any data format. Still, when switching to pixel-level fusion, they lag as unsupervised signals prevent them from learning the combination of information that can distinguish different data classes. Figure 6 shows a general form of an AE model used for diagnosing brain diseases in neuroimaging multimodalities based on MRI.

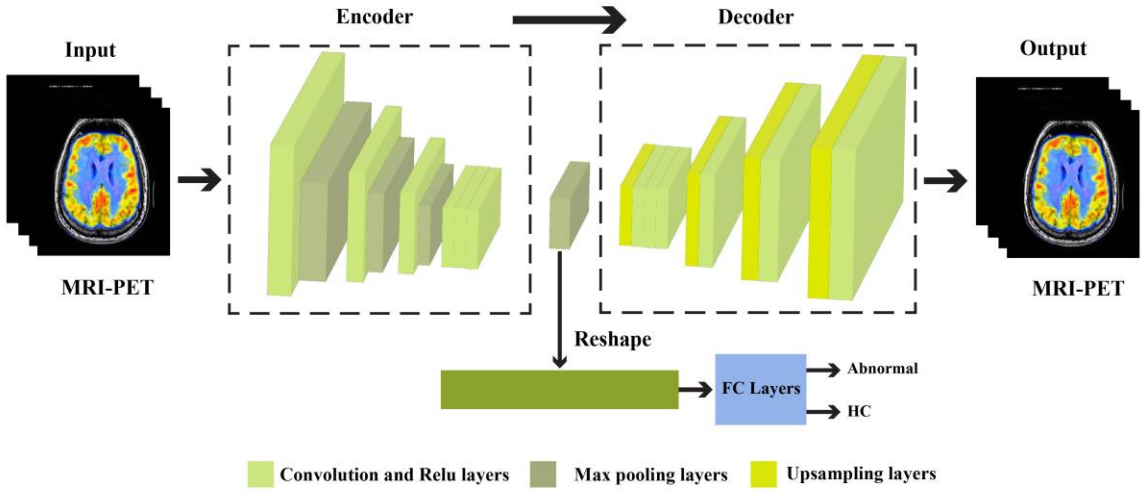

Fig. 6. A typical AE model for brain disease detection from neuroimaging multimodalities based on MRI.

6) RNN Models

Most of the networks discussed in this section aim to find spatial patterns in data; however, temporal patterns are also presented in some data, such as texts and signals [95-98]. The difficulty with these patterns arises from the fact that they might be close or far [95]. Basic recurrent neural networks (RNNs) were first suggested to handle the time series challenges, such as various lengths of different data instances [95]. As their name suggests, they use an identical set of weights, recurring on each time slice of data. Nevertheless, models such as long short-term memory (LSTM) and gated recurrent units (GRU) [95] were later suggested to find temporal patterns of various lengths efficiently. Nowadays, RNNs are used widely for natural language processing (NLP) [116], signal processing [117], and volume 3D scan analysis [118]. Learning temporal patterns is essential in processing any time series, but combining them can be painful, as different data points can have varying lengths and different behaviors. Fusing information from functional and structural modalities requires extracting both temporal and spatial patterns and spatio-temporal ones. Nonetheless, RNNs can be utilized to help researchers extract this information after resolving the mentioned challenges. Figure 7 shows a general form of an RNN model used for diagnosing brain diseases in neuroimaging multimodalities based on MRI.

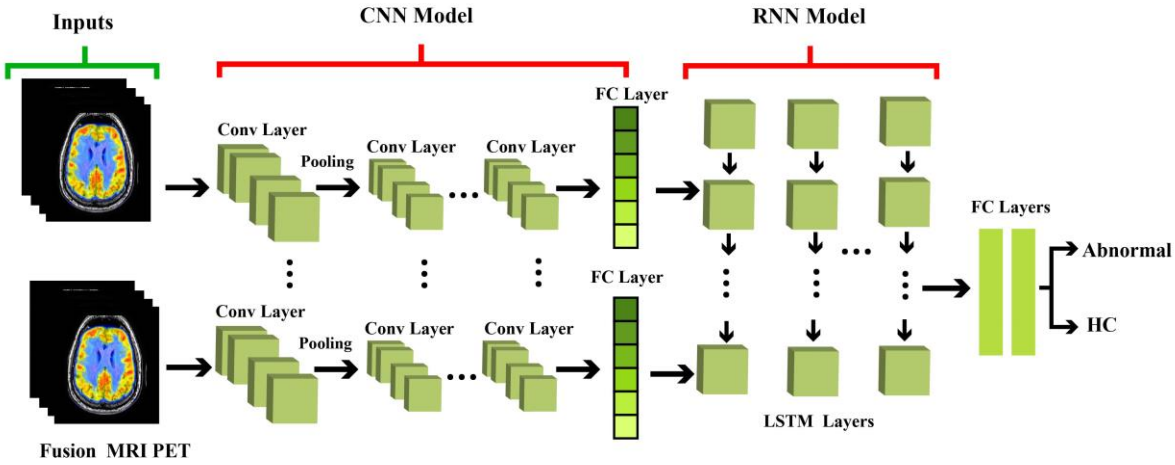

Fig. 7. A typical RNN model for brain disease detection from neuroimaging multimodalities based on MRI.

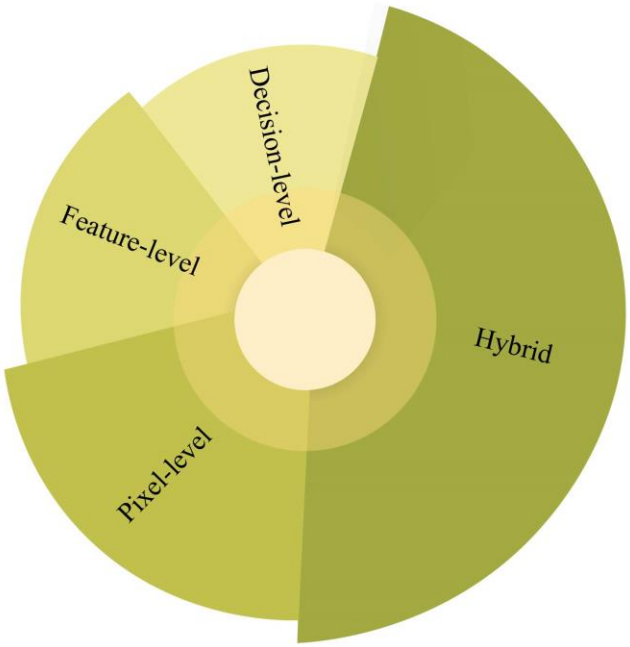

Fig. 8. Fusion levels used for brain disease detection using neuroimaging multimodalities based on MRI.

6. Fusion Levels

Medical imaging technologies are evolving rapidly, and various modalities of medical images have significant applications in clinical diagnosis and disease analysis [119-121]. Due to the differences in imaging technologies, different medical imaging modalities have complementary information and features [122-123]. The main objectives of medical imaging fusion are to extract more useful information from the input images, improve the application of medical images, and help physicians in the diagnosis of different diseases. Therefore, investigating medical imaging fusion is important. In general, image fusion techniques

are divided into three levels, namely, the input [91], layer [92], and decision level [93]. Figure 8 shows the different fusion levels for the diagnosis of brain diseases in neuroimaging multimodalities based on MRI and DL models.

6.1. Pixel/ Input-Level Fusion

In the input-layer/pixel-level fusion, multimodality images are integrated with the raw input domain in channel-to-channel integration, known as multichannel input [91]. We train the network to extract an integrated feature representation using this combined input. Pixel-level fusion is directly applied to the pixels of the original images [91]. However, there are requirements for the fused image: (i) all prominent and important features of the original images must be maintained, and (ii) no artifacts or inconsistencies should occur during the fusion process [91][124]. Techniques presented for pixel-level fusion are divided into four groups: multi-scale decomposition (MSD) [125], sparse representation [126], component substitution [127], and hybrid model-based methods. These methods with higher microscopic information work are based on several concrete similarity criteria [91][124].

Architectures at the pixel level can be divided into six steps: imaging, registration, preprocessing, fusion, post-processing, and display [91][124]. The imaging step consists of several modalities. Various imaging modalities have different recording parameters. Therefore, the alignment of the images, both spatially and temporally, is crucial. This is done in the registration step. The intelligent and appropriate preprocessing effectively eliminates artifacts and significantly improves performance. Post-processing depends on the type of display and the purpose of the fusion. The most basic post-processing involves gain and offsets correction for the fused image. The display subsystem depicts the fused image. The display determines the quality of the final output image to some extent. Table 3 describes the pixel-level fusion research for brain disease detection using DL methods. In addition, Figure 9 shows a general block diagram of a pixel-level fusion used for diagnosing brain diseases in neuroimaging multimodalities based on MRI data.

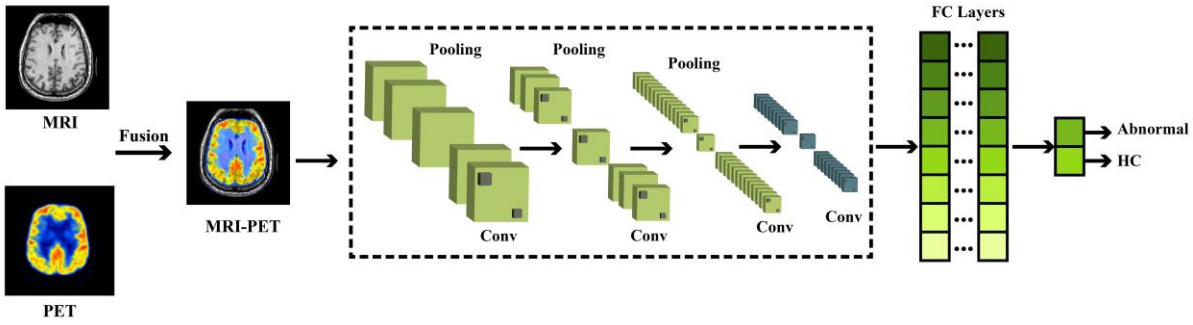

Fig. 9. Pixel-level fusion for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Table 3. Pixel-level fusion research for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Work	Application	Modality (Fusion)	Dataset	Pre-Processing	DL	Classifier	Post-Processing	Performance (%)
[128]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2017	Standard Procedure	Multi-Modality Fusion Network Based on Attention Mechanism	--	--	Dice=87.1, 79.1, 73.9 For WT, TC, ET
[129]	Multi-Modality Medical Image Fusion Technique	MRI, CT	Clinical	NSCT, Multi-Objective Differential Evolution	Xception	--	Inverse NSCT	Entropy= 6.81 MI=0.64 FF=1.29

[130]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2013	Normalization	FCN, Spatial Texton Features	RF	--	Dice=88, 80, 73 Sen= 89, 77, 70 For WT, TC, ET
[131]	Glioma Segmentation	MRI (Multimodality)	BraTS 2017, Rembrandt Dataset	Normalization	Voxel-Wise BCN, FCN, FIFCN	--	--	Dice=86
[132]	Ischemic Stroke Lesions Segmentation	MRI (Multimodality)	Clinical	Standard Procedure, Data Annotation, DA	MASK R-CNN	Softmax	--	Prec= 85
[133]	Acute Ischemic Stroke Lesion Segmentation	T2-MRI, DWI	SPES, LHC	Data Fusion Using Structured and Sparse Canonical Correlation Analysis (ssCCA) Technique and DA	Res-CNN	Conv Layer (Sigmoid)	--	Dice=74.20 HD=2.33 m
[134]	Deep Brain Regions Segmentation	MRI, Ultrasound	Clinical	Patch Extraction	CNN	Hough Voting	--	Dice=85
[135]	Isointense Infant Brain Image Segmentation	MRI (Multimodality)	Clinical	Standard Procedure	2D-CNN	Softmax	--	Dice=84.92, 88.48, 88.24 MHD=63.20, 43.98, 43.62 For CSF, GM, WM
[136]	Detecting Acute Bilirubin Encephalopathy in Neonates	MRI (Multimodality)	Clinical	ADC Map Calculation, Registration, Cropping, Resizing, Normalization, Logistic Regression, DA	ResNet18, DenseNet201	Softmax	--	Acc=92.9 Sen=87.56 Spec=98.22 Prec=98.19 F1-S=92.29
[137]	Glioma Segmentation	MRI (Multimodality)	BraTS 2015	N4ITK Method, Normalization	3D CNN	Softmax	Connected Domain Labeling Method	Sen=82, 75, 86 Dice=84, 79, 75 For WT, TC , ET
[138]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2018	Standard Procedure, DA	U-Net	Softmax	--	Dice=78.3, 86.8, 80.5 Sen=82.6, 89.5, 80.7 Spec=99.7, 99.1, 99.7 For ET, WT, TC
[139]	MS Detection	MRI (Multimodality)	CombiRx	Standard Procedure, MRIAP Segmentation, DA	Multi-Class U-Net	--	--	Dice WM and GM=94 CSF=97 T2 hyperintense Lesions=85
[140]	IDH Genotype Prediction in Gliomas	MRI (Multimodality)	BraTS 2017, TCGA-BRCA	Masking, Cropping, Reshaping, DA	M3D-DenseNet	Softmax	--	Acc=84.6 Sen=78.5 Spec=88 AUC=85.7
[141]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2018, BraTS 2019	Standard Procedure	3D DFP-ResUNet	Sigmoid	--	Sen=87.6, 91.5, 90.1 Spec=99.7, 99.1, 99.8 Dice=84.3, 89.7, 90.6 For ET, WT, TC Sen=80.9, 92, 84.3 Spec=99.8, 99.3, 99.6 Dice=79.8, 90.2, 84.5 For ET, WT, TC
[142]	Identify Glioblastoma Progression Phenotype	MRI (Multimodality)	Clinical	Standard Procedure, ROI Extraction	VGG16, ResNet50	Sigmoid	Grad-CAM	Acc=95.8 Sen=96.9 Spec=94.2
[143]	Glioma Segmentation	MRI (Multimodality)	BraTS 2015	Distortion Correction, Normalization	TLN and ITCN	Softmax	--	Sen=87, 84, 76 Dice=90, 81, 81 For WT, TC, ET
[144]	Ischemic Lesion Segmentation	MRI (Multimodality)	ISLES 2015	Skull Stripping, Normalization, DA	U-Net	Sigmoid	--	Acc=70

[145]	MS Detection	MRI, PET	Clinical	Lesion Filling Procedure, Segmentation, Logan Graphical Reference Method, Brain Extraction, Intensity Inhomogeneity Correction, Registration, Cropping	Sketcher-Refiner GAN	Softmax	Visual Attention Saliency Map	MSE= 0.0083 PSNR= 30.044
[146]	Brain Tumor Detection	MRI (Multimodality)	BraTS 2018	Cropping, Nearest Neighbor Interpolation, DA	Multi-CNNs	Softmax	--	Sen=92.8 Spec=99.8 Dice=92.7
[147]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2018	3D Samples are Converted Into 2D Array Slices, Removing Redundancy, Intensity Normalization, Intensity Zero-Centering	Adaptive U-Net	Sigmoid	--	Dice=92 Mean IoU=88 Sen=94 Spec=99
[148]	Multimodal Fusion, Shared and Cross Learning on Medical Images	MRI, CT	TCGA-GBM	Segmentation	SAEs	Sigmoid	--	Acc= 82.39
[149]	Intervertebral Disc Segmentation	MRI (Multimodality)	Prof. Guoyan Zheng from University of Bern	Multi-Modality Analysis, DA	Multimodal 3D U-Net	Conv Layer (Sigmoid)	Binary Thresholding, Assembling	Dice= 89
[150]	Prediction of High Amino Acid Uptake Regions and Survival in Patients with Glioblastoma	MRI (Multimodality)	Clinical	Standard Procedure, DA	U-Net	--	--	Acc=98 Sen=85 Spec=100
[151]	Unsupervised MRI Super-Resolution	MRI (Multimodality)	NAMIC	Down Sampling, DA	Unsupervised Multimodal Guided SISR Framework	--	--	PSNR=41.48 SSIM=0.990
[152]	Multimodal Neuroimaging Synthesis	MRI, PET	ADNI	Registration, Field Correction, Intensity Normalization, Filtering, Nonuniform Field Inhomogeneity Correction, Eddy Current Distortion Involuntary Movement Correction, Masking	3D SC-GAN	--	--	NRMSE= 76 PSNR= 32.14 SSIM= 96.2
[153]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2013, BraTS 2015, BraTS 2018	Skull Stripping, Co-Registration, Resampling	AFPNet	--	3D Fully Connected Conditional Random Field	Dice=86.58, 76.88, 74.43 For WT, TC, EC
[154]	Alzheimer Disease Diagnosis	MRI, PET	ADNI	Post-Acquisition Correction of Gradient Warping, B1 Nonuniformity Correction, Intensity Non-Uniformity Correction, Phantom-Based Scaling Correction, ITK N4 Bias Correction, Resampling, Cropping	3D RevGAN	Softmax	--	Acc=89.26 Sen=82.69 Spec=96.48 AUC=90.98
				PET Image Quality Control, Normalization, Averaging, Registration, Resampling	3D CNN			
				ROI Extraction				
[155]	MRI Synthesis	MRI (Multimodality)	BraTS 2015	Patch Extraction	GAN	--	--	NMAE=5.8 PSNR= 30.158 SSIM=95 VIF=67.2

								NIQE= 1.401
[156]	Distinguish Between Migraineurs and Healthy Controls and Between the Two Subtypes of Migraine	rs-fMRI	Clinical	Standard Procedure, AAL Atlas, Combination of 3 Functional Measures (ALFF, ReHo, RFCS), DA	Inception Module-Based CNN	Softmax	--	Acc= 99.25
[157]	Identifying Early MCI	sMRI, DTI	ADNI	Skull-Stripping, Intensity Normalization, Registration Skull-Stripping, Eddy Current Correction, Head Motion Correction, Diffusion Tensors Estimation Generating FA and MD Maps, Registration Multi-Modality Fusion Strategy	VGG16 + LASSO	SVM	--	Acc= 94.2 Sen=97.3 Spec=92.9 AUC=95.3
[158]	PET Synthesis	PET, MRI, DTI	Simulated Data, Clinical Data	Locality-Adaptive Fusion Network	LA-GANs	--	--	PSNR=25.19 SSIM=98.43
[159]	Multi-Modality Medical Image Fusion	MRI, CT	2 Public Datasets	Discrete Shearlet Transform, EMBO	RBM	--	Reconstruction	SD= 97.78 EQ= 0.96 MI= 5.71 FF= 6.53 Entropy= 7.43 CF= 0.97 SF= 25.78
[160]	Alzheimer Disease Diagnosis	DTI, fMRI	Clinical	Standard Procedure, ALL, DTI Structural Connectivity Network (DTISCN), Functional Connectivity Network (FCN), Data Enhancement	CNN	Softmax	--	Acc=92.06
[161]	Glioma Segmentation and Survival Prediction	MRI (Multimodality)	BraTS 2018	Standard Procedure, 3D Patch Extraction, Radiomic Features	Modifier 3D U-Net	MLP	3D Connected Component Analysis	Acc= 57.1 Dice =88, 83, 75 For WT , TC , ET
[162]	SZ Detection	sMRI, rs-fMRI, T-fMRI	Clinical	Registration, Masking, 5 Brain Maps Generation	1D CNN	--	--	Acc=84
[163]	Alzheimer Disease Diagnosis	MRI, PET	ADNI	Gradwarp, B1 Non-Uniformity, N3, Cropping, Sampling Co-Registered Dynamic, Averaging, Standardization, Intensity Normalization, Uniform Resolution, Cropping, Sampling Fusing MRI and PET Scans at The Image Field (GM-PET), Cropping, Sampling	3D Simple CNN, 3D Multi-Scale CNN	Softmax	3D Grad-CAM	Acc=94.11 Sen=93.33 Spec=94.27
[164]	Multimodal Brain Medical Image Fusion	MRI, PET, SPECT	Whole Brain Atlas	Multi-Scale Local Extreme Scheme (MSLES), Adaptive Dual-Channel Spiking Cortical Model (ADCSCM) Based on The Information Entropy (EN)	Siamese Network	--	--	EI=97.66 AG=11.87 SD=82.96 MI=3.24 MSSIM=69.20
[312]	Brain Tumor Classification	Structural and Texture Information of Four MRI Sequences	BRATS 2012, BRATS 2013, BRATS 2015, BRATS 2013 Leader board	DWT, Partial Differential Diffusion Filter (PDDF), Global Thresholding Method	CNN	Softmax	--	Acc=99 Sen=98 Spec=97

			and BRATS 2018					

6.2. Feature/ Layer-Level Fusion

In layer-level/feature-level fusion, various modalities are fed into different sub-networks as input [92]. Then, the modalities are processed in these sub-networks [92]. Afterward, the extracted features are integrated into the subsequent layers. Finally, the result of this fusion is applied to the fully connected (FC) layers for classification to obtain the results [92]. The fusion network at the layer level can effectively integrate multimodality images and efficiently use their information [92].

The DL networks provide the possibility of combining multimodalities in each intermediate layer of the network, which is known as layer-level fusion. In principle, since DL networks are hierarchical, giving each modality a set of sub-networks for processing is possible, followed by fusing the representations obtained from each sub-network [92]. Lastly, all the representations are concatenated and sent to the fully connected (FC) layer [92]. The layer-level fusion method can be more beneficial than pixel-level fusion since different sub-networks architectures can be used based on the nature of different modalities to effectively make the best use of the information contained in each modality [92]. Moreover, since there is no need to meet the two requirements of pixel-level fusion, the implementation and training at this level are easier than at the pixel level [92]. However, it is impossible to simultaneously learn information from two modalities at the low levels at the layer level since the model is limited to high-level information [92]. Table 4 describes the feature-level fusion research for brain disease detection using DL methods. Also, Figure 10 shows a general block diagram of feature-level fusion for the diagnosis of brain diseases from neuroimaging multimodalities based on MRI data.

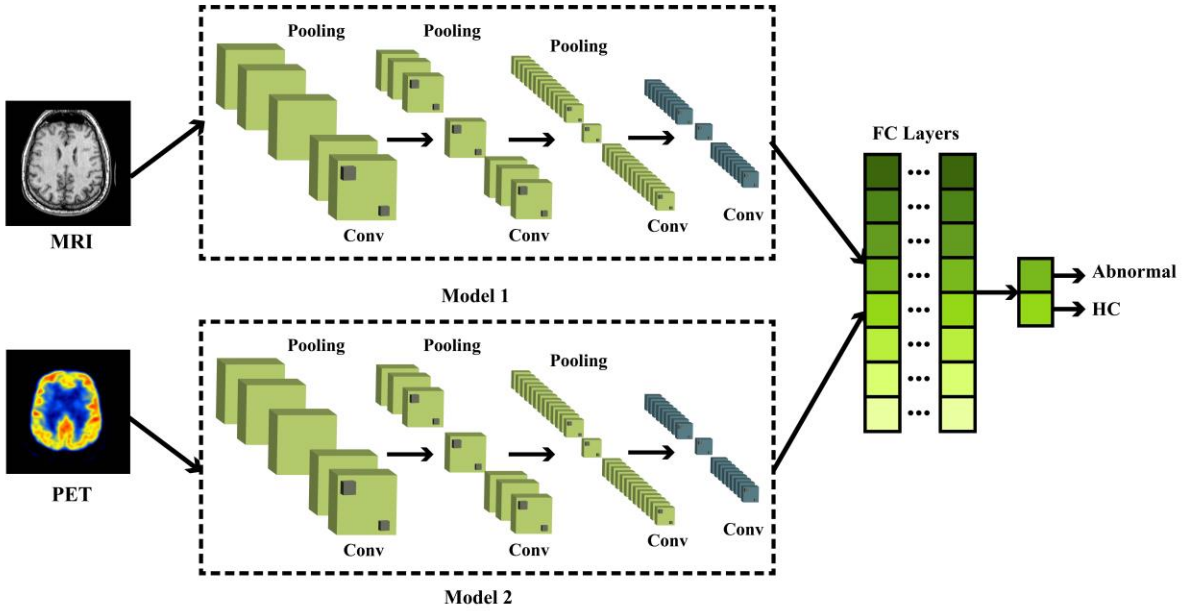

Fig. 10. Feature-level fusion for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Table 4. Feature-level fusion research for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Work	Application	Modality	Dataset	Pre-Processing	DL (Fusion)	Classifier	Post-Processing	Performance
[165]	Alzheimer Disease Diagnosis	MRI, PET	ADNI	AC-PC Correction, Intensity Inhomogeneity, Skull Stripping, and Cerebellum Removal, Segmentation, Registration, ROIs Extraction, Gray Matter Tissue Volumes (Features), PET Alignment to MRI, Average Intensities (Features)	MM-SDPN	SVM	--	Acc=97.13 Sen=95.93 Spec=98.53
[166]	Alzheimer Disease Diagnosis	MRI, PET, Demographic and Genetic Information	ADNI	Standard Procedure, ROI-Based Features	MTDL	Softmax	--	Acc= 63.6
[167]	Alzheimer Disease Classification	MRI, PET	ADNI	Standard Procedure	Two 3D-CNN and 2D-CNN	Softmax	--	Acc= 89.64 Sen=87.10 Spec=92 AUC=94.45
[168]	Tumor Segmentation	PET, CT	Clinical	ROI Extraction, DA	3D FCN	Softmax	--	Dice=85
[169]	Multi-Modality Missing Data Completion	MRI, PET	ADNI	--	GAN	--	--	Acc= 72.91 PSNR= 34.90 SSIM= 0.9854
[170]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2019, BraTS 2018	Cropping Images, Random Slice, Z-Score Normalization	3D Multi-Pathway FCN	--	Necrosis Label, Transformed Output Matrix to NiBabel (3D Image) Format and Submit to Online Evaluated Platform.	Dice= 89, 78, 76 Dice= 90, 79, 77
[171]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2017, BraTS 2018	N4 Bias Field Correction, Dimensionality Reduction	Multi-Modalities Fusion, Tumor Extractor, Tumor Segmenter	Sigmoid	--	Dice=92, 91, 84 For WT, TC, ET
[172]	Meningiomas Detection and Segmentation	MRI (Multimodality)	Clinical	Manual Segmentation, Standard Procedure	DLM	Softmax	--	Acc= 98 Dice=81, 78 for TTV, T1CE TV
[173]	Brain Metastases Detection and Segmentation	MRI (Multimodality)	Clinical	Manual Segmentation	DeepMedic	Softmax	--	Sen=98 Dice=79
[174]	Isointense Infant Brain Image Segmentation	MRI (Multimodality)	Clinical	Alignment, Up Sampling, Skull Stripping, Segmentation	3D FCN	--	--	Dice=91.90, 94.01, 96.10 MHD=36.76, 35.30, 18.90 For WM, GM, CSF
[175]	Image Synthesis	MRI (Multimodality)	BraTS 2018	Cropping, Patch Extraction	Hybrid-Fusion Network (Hi-Net)	Conv Layer	--	PSNR=25.05 NMSE=0.0258 SSIM=0.8909
[176]	Alzheimer Disease Diagnosis	PET, MRI	ADNI	Standard Procedure	3D-cGAN, LM3IL	Softmax	--	Acc=92.50 Sen=89.94 Spec=94.53 F-Score= 91.37 MCC= 84.78 AUC= 95.89
[177]	Reconstruction of Under Sampled MRI	MRI (T2W and FLAIR)	Public Dataset	Co-Registered with Bias Correction by Algorithm N4, Resizing, Slice	Multimodal U-Net	--	--	Acc=97

	Related to MS Patients			Extraction, Intensity Normalization				
[178]	Image Fusion Model	PET, MRI	Whole Brain Atlas Database	Registration, Cropping	CSpA-DN	--	--	Entropy=5.5289 Q_{abf}=0.7111 FMI_pixel=0.8770 FMI_dct=0.3933
[179]	Alzheimer's Disease Diagnosis	MRI, PET	ADNI	AC-PC Correction, N3 Algorithm, Skull Stripping, Segmentation, Realignment, Normalization, Spatial Filtering, Slice Extraction, DA	Deep Multi-Modal Fusion Network (DMFNet)	Softmax	--	Acc=95.21 Sen=93.56 Spec=97.48
[180]	Image Synthesis	MRI (Multimodality)	BraTS 2015	Slice Extraction	Multi-Scale Gate Mergence Based Generative Adversarial Network Model (MGM-GAN)	Sigmoid	--	PSNR=26.801 SSIM=0.918 NRMSE=0.231
[306]	Brain Tumor Radio Genomic Classification	MRI	RSNA-MICCAI dataset	DA	Attentive Multi-Modal CNN	Sigmoid	--	Acc=63.71
[309]	Image Fusion	MRI, PET	Harvard University	Registration, Image Conversion, Resizing	VGG19	--	--	Entropy=3.0319 MI=2.3993 Discrepancy=3.8187 OP=0.9899
[310]	Brain Tumor Segmentation	Multimodal MRI	BraTS 2018	Cropping, Resizing, N4ITK, Intensity Normalization	Proposed Model	--	--	Dice=82.9, 74.9, 59.1 For WT, TC, ET
[311]	Medical Image Fusion	CT, MRI, SPECT, MRI, PET	Whole Brain Atlas of Harvard Medical School	Hybrid MDWT-Shearlet	CNN-HOD	Softmax	--	--

6.3. Decision-Level Fusion

In decision-level fusion, each modality is used as a separate input for an individual branch of a parallel network [93]. Using different branches leads to the extraction of the unique information of each modality. Then, the final outputs of all the branches are integrated to achieve the results [93]. The decision-level fusion has been proposed for learning complementary information of various modalities since multimodality images have low levels of complementary information in their main domains because of the difference in the techniques used for recording the images [93]. The most famous methods are average and majority voting [93].

Two different cases are possible in decision-level fusion. In the first case, each set of features is sent to its specific classifier. Then, the outputs of these classifiers are fused to achieve the final output for multimodality prediction [93]. Compared to pixel-level fusion, decision-level fusion can be used for a wider range of problems [93]. In the second case, various modalities are given to different branches of single network architecture [93]. After processing by the intermediate layers of the network, the extracted features are sent to a fusion neural network instead of being given to their specific classifiers for classification [93]. This fusion network input consists of the features of various branches, and its output is the final fused decision. In its most basic form, this fusion network consists of several FC layers along with the SoftMax activation function [93]. While implementation and training at this level are easier than at the two previous levels, it does not allow the possibility of integrating information at low levels and simultaneously using

the resolutions of both modalities [93]. Table 5 displays the decision-level fusion research for brain disease detection using DL methods. In addition, Figure 11 shows a general block diagram of decision-level fusion for brain disease detection from neuroimaging multimodalities based on MRI data using DL architectures.

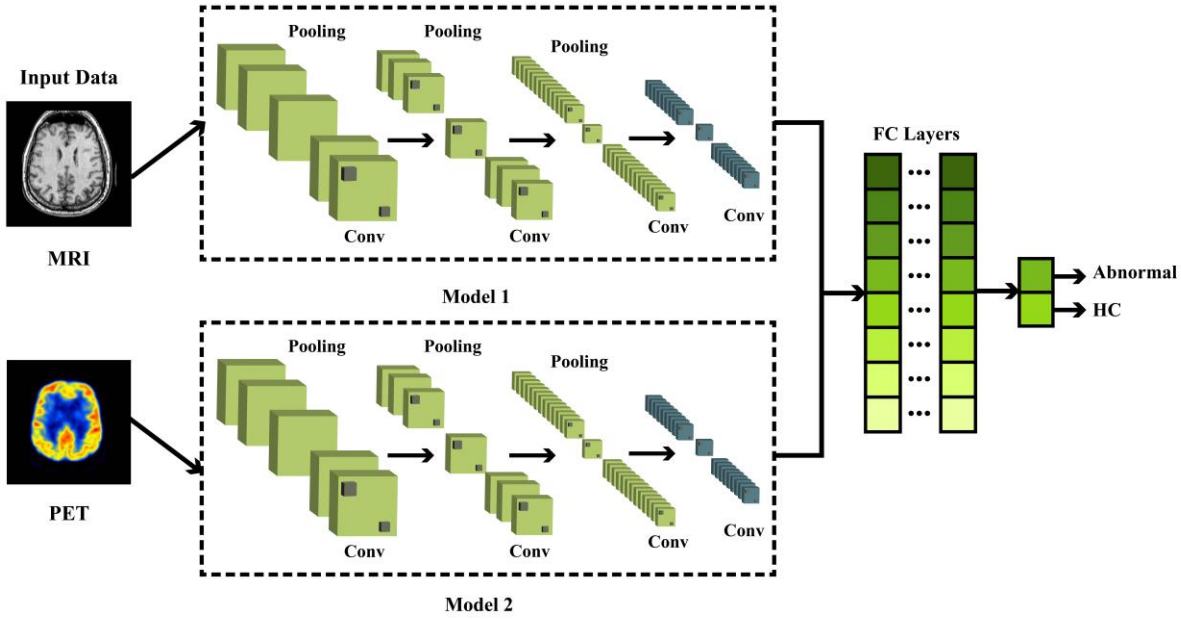

Fig. 11. Decision-level fusion for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Table 5. Decision-level fusion research for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Work	Application	Modality	Dataset	Pre-Processing	DL	Classifier (Fusion)	Post-Processing (Fusion)	Performance
[181]	ADHD Classification	Rs-fMRI, sMRI	ADHD-200	Standard Procedure, Feature Extraction	3D-CNN	SoftMax	--	Acc=69.15
[182]	Brain Tumor Segmentation	MRI	BrainWeb, Internet Brain Segmentation Repository (IBSR 20, IBSR V2.0)	CMA Autoseg Routine, CLAHE, Gamma Adjustment Method, Construction of Probabilistic Brain Atlases, Patch Extraction	Multi-Model, Multi-Size, Multi-View Deep Neural Network (M 3 Net)	Conv Layer (SoftMax)	--	Acc=91.31 Dice=93.05
[183]	Brain Tumor Segmentation	PET, CT	Clinical	ROI Extraction, DA	3D FCN	SoftMax	Fuzzy Variational Model	Sen=86 Dice=86
[184]	Predict Alzheimer's Disease Progression	sMRI, fMRI	ADNI	Time-Varying FC	ResNet	Softmax, CCA, SVM	--	Acc= 78
[185]	Fusion	MRI, PET	Harvard Medical School	--	CNN	Weight Map and Masking	--	SNR= 69.17 Entropy=5.5
[186]	Alzheimer Disease Diagnosis	sMRI, DTI	ADNI	Standard Procedure, ROI Extraction, DA	3D Inception-Based CNN	SoftMax	--	Acc=93.3 Sen=93.3 Spec=93.3
[305]	Predicting Functional Outcome in Stroke Patients	MRI, DWI, DSC-PWI	HIBISCUS-STROKE cohort	Parametric Maps Extraction, Co-Registration, Resizing, Skull Stripping, Normalization	CNN-LSTM	Weighted Average	--	Acc=74 Spec=69 Sen=72 AUC=77

6.4. Hybrid-Level Fusion

Recently, researchers have combined fusion levels to improve performance for various applications known as hybrid fusion. Four different cases are possible in hybrid fusion. In the first case, pixel- and layer-level fusion are used together [187-202]. In [187], MRI multimodality and 3D CNN-GMU were used for glioma grading. In another study, Huang et al. [200] used different fusion modalities along with the MGMDcGAN architecture. In the second case, fusion is simultaneously performed at pixel and decision levels [203-207]. In [204], sMRI and DTI modalities were used for schizophrenia (SZ) detection. Then, neuroimaging multimodality data were applied to the input of the CNN model. Afterward, the majority voting method was used for classification. In [207], Fu et al. presented the neuroimaging multimodality framework using MRI, CT, PET, and SPECT data. Then, they used the VGG-16 model for the classification of input data. In the third case, researchers used feature-level and decision-level fusion [208-216]. In [211], to diagnose dementia, 3-stage DNNs were used along with majority voting. Finally, in the fourth case, researchers combine all three fusion levels [217-219]. Authors in reference [218], first used the MRI multimodalities segmentation for the diagnosis of glioma. In this paper, two-stage segmentation was implemented using several U-Net networks. Finally, another U-Net was used for post-processing. Table 6 displays hybrid fusion research for brain disease detection using DL methods.

Table 6. Hybrid fusion research for brain disease detection from neuroimaging multimodalities based on MRI using DL methods.

Work	Application	Modality	Dataset	Preprocessing	DL	Classifier	Post-processing	Performance
[187]	Glioma Grading	MRI (Multimodality)	BraTS 2015	--	3D CNN with GMU Fusion	Softmax	Privileged Learning in Distilled-CNN Model	Acc= 82.1 Sen= 88.9 Spec=57
[188]	Intervertebral Disc Localization and Segmentation	MRI (Multimodality)	IVDM3Seg	Normalization	IVD-Net	Softmax	--	Dice=91.91
[189]	Brain Tumor Classification	MRI (Multimodality)	BraTS 2015	2D Slices Extraction, Normalization, Inhomogeneity Alteration, Manual Segmentation	MSMCNN–LSTM	Softmax	--	Acc= 96.36 Sen= 92.14 Dice=90.36
[190]	Isointense Infant Brain MRI Segmentation	MRI (Multimodality)	iSeg 2017	Standard Procedure	3D-CNN	Voting Approach	--	Acc=92.84
[191]	Standard-Dose PET Image Estimation from Low-Dose PET/MRI	PET, MRI	Clinical	Standard Procedure	Deep Auto-Context CNN	--	--	Average PSNR=24.76 NMSE=0.0206
[192]	Isointense Infant Brain MRI Segmentation	MRI (Multimodality)	iSeg-2017	DA	Context Guided, Multi-Stream 3D FCN	3 Down-Scaled Branch Classifiers in Addition to The Classifier of The Main Network	--	Dice =95.4, 91.6, 89.6 For CSF, GM, WM
[193]	Isointense Infant Brain MRI Segmentation	MRI (Multimodality)	Clinical	Standard Procedure, Manual Segmentation	3D U-Net	3D Binary Segmentation Map Construction	--	Dice= 92.92 3D MHD=43.19
[194]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2019	--	GAN, 3D FCN	--	--	Sen= 76.88, 91.32, 77.71 Spec= 99.85, 99.39, 99.76 Dice= 76.65, 89.65, 79.01

								For ET, WT, TC
[195]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2015, BraTS 2018	Skull Stripping, Co-Registration, Interpolation, Slice Extraction, Normalization, DA	WRN-PPNet	--	--	Dice=91 Sen=94 PPV=89
[196]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2018	--	CNN with NABL	Softmax	--	Dice=59.44, 80.27, 69.44 for ET, WT, TC Prediction Acc=59
[197]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2017, BraTS 2018	Standard Procedure	3D U-Net	--	--	Dice=88.5, 84.5, 73.4 for WT, TC, ET
[198]	Automated Simultaneous Intervertebral Disc (IVDs) Identification and Segmentation	MRI (Multimodality)	MICCAI-2018 IVD challenge	--	RIMNet	--	--	Acc= 94 MDOC=91.2 Dice= 91.7 JAC= 0.87 F1=90
[199]	MRI Synthesis	MRI (Multimodality)	BraTS 2015	Slice	GAN	Sigmoid	--	PSNR= 24.8 SSIM=88 NRMSE=25
[200]	Medical Image Fusion	MRI, CT, PET, SPECT	Harvard	--	MGMDcGAN	--	--	--
[201]	MRI Synthesis	MRI (Multimodality)	BraTS 2015	Pre-Registration, Resizing	LR-cGAN	Sigmoid	--	PSNR= 26.727 SSIM= 0.918 NRMSE= 0.231
[202]	Paramagnetic Rim Lesion Assessment in MS	MRI (Multimodality)	Clinical	Registration, Segmentation, Annotations of Paramagnetic Rim Lesions, Patch Extraction, DA	RimNet	Softmax	Error Analysis	Acc=89.5 Sen=70.6 Spec=94.9 AUC=94.3 Dice=83.5
[203]	Classify Low/High Grade Gliomas	MRI (Multimodality)	BraTS 2017, Mayo Clinic	2D Brain Image Slices, Tumor Masks, DA	Multi Stream 2D CNN	Fusion Layer + Bilinear Layer+ 3 FC Layers (Softmax)	--	Acc=90.87
	Glioma Detection							Acc=89.39
[204]	SZ Detection	sMRI, dMRI	NUSDAST, IMH	Skull Stripping, Registration, Segmentation Modulation, Head Movements and Eddy Current Distortion Correction, Diffusion Gradients Rotation, Visual Inspection, Tensor Fitting	Pre-Trained 2D CNN, Naive 3D CNN	Majority Voting	Gradient Class Activation Map Approach	Acc=81.02 Sen=86.44 Spec=70.42 AUC=84
[205]	Head and Neck Tumor Segmentation	CT, PET, MRI	Clinical	Registration, Parch Extraction, DA	4 Residual 3D U-Net	Ensemble Learning	--	Dice=74 HD95= 7.9 mm MSD= 2.4 mm Prec=87
[206]	Alzheimer Disease Diagnosis	T1-MRI, FDG-PET	ADNI	The Segmented Dataset and The Paired Dataset Generation	3D-CNN	FC (Softmax)	--	Acc= 90.10 Sen=90.85 Spec=89.21 AUC=90.84

[207]	Multimodal Biomedical Image Fusion	MRI, CT, PET, SPECT, PC, GFP	Whole Brain Atlas, GFP Database of John Innes Center	Rolling Guidance Filter	VGG-16	--	Three Different Fusion Strategies, Image Composition	Different Results for Different Image Fusion
[208]	MCI Diagnosis	MRI, MMSE, LM Test Data	National Alzheimer Coordinating Center (NACC)	ROIs Extraction	Three VGG-11, Two MLP	Max, Mean, Majority Voting	Subgroup Analysis	Acc=90.9 Prec=92.6 Recall=96.3 F-Score=94.4 MCC=71.9
[209]	Alzheimer Disease Diagnosis	MRI, PET	ADNI	Standard Procedure	3D-CNNs and 2D-CNNs	Softmax	--	Acc=93.26 Sen= 92.55 Spec= 93.94 AUC= 95.68
[210]	Intervertebral Disc Localization and Segmentation	MRI (Multimodality)	IVDM3Seg	--	MsFCN	Score Volume, Thresholding, Centroids	--	Dice=91.2 Mean Localization Error=0.62 mm
[211]	Dementia Diagnosis	MRI, PET, Genetic Data (i.e., SNP)	ADNI	Standard Procedure, ROI Extraction	3 Stage DNNs	Majority Voting	--	Acc=90
[212]	Brain Tumor Segmentation	MRI (Multimodality)	BraTS 2017	Intensity Normalization	2CNet, 3CNet	Ensemble Net	--	Sen=82, 82, 69 Spec=74, 77, 78 Dice=89, 76, 81 For WT, TC, ET
[213]	Alzheimer Disease Diagnosis	sMRI, FDG-PET	ADNI	Segmentation, Patch Extraction, Feature Extraction	Multimodal and Multiscale Deep Neural Network (MMDNN)	Ensemble Classifier	--	Acc=84.6 Sen=80.2 Spec=91.8
[214]	Brain Tumor Segmentation and Survival Prediction in Glioma	MRI	BraTS 2018	Intensity Normalization, DA	Ensembles of CA-CNN, DFKZ Net, 3D U-Net	Majority Voting	--	Acc=61 Dice=71.71, 87.62, 79.77 HD= 4.9782, 7.2009, 6.4735 mm For ET, WT, TC
				Filtering, Wavelet Decomposition, Radiomic Features, Decision Tree and Cross Validation (Feature Selection)		RF		
[215]	Data Integration Framework	Cognitive Performance, CSF, MRI, Demographic Information	ADNI	Feature Extraction	GRU	Linear Regression	--	Acc=79 Sen=83 Spec=77
[216]	Alzheimer Disease Diagnosis	MRI, PET	ADNI	Reorientation and Resample, N3, Skull Stripping and Cerebellum Removal, Segmentation, Registration	3D CNN, FSBi-LSTM	Softmax	Visualization Analysis	Acc= 94.82 Sen=97.70 Spec=92.45 AUC=96.76
				Alignment, Gaussian Kernel Down Sampling				
[217]	Image Segmentation	MRI, CT, PET	STS-TCIA	Patch Extraction	CNN	RF	Label Maps	Dice Type-I= 85 Dice Type-II= 85 Dice Type-III= 84

[218]	Glioma Segmentation	MRI (Multimodality)	BraTS LGG Subset Data	Patch Extraction, DA	3D U-Nets	Conv Layer	U-Nets	--
[219]	Improving Alzheimer Stage Categorization	sMRI, DTI	ADNI	Noise Correction, Alignment, Normalization, Co-Registration for DTI-MD, ROI and Patch Extraction, DA	CNN	Majority voting	--	Acc=92.30 Sen=93.95 Spec=90.65
[307]	Brain Tumor Classification	MRI and CT	BraTS 2020	Hybrid Probabilistic Wiener Filter (HPWF)	BTFSC-Net	Softmax	--	Acc=99.46
[308]	Brain Tumor Segmentation	Multimodal MRI	BraTS 2019, BraTS 2020	DA	PIF-Net + MSFF Module +V-Net	--	--	Dice= 82.65

7. Challenges

This section addresses the most important challenges in data fusion for the diagnosis of brain diseases using DL techniques. In general, there are numerous challenges in neuroimaging multimodalities, including dataset limitations, imbalanced data, DL models, and hardware resources. Accessing datasets of the multi-modality of neuroimaging is the first challenge and is discussed in detail in this section. Datasets based on multimodality neuroimaging play a key role in developing brain disease diagnosis research using DL techniques, so accessing these datasets is of utmost importance. Also, data privacy is a challenge in this field. In the rest of this section, challenges faced by unbalanced data are discussed, another critical issue researchers face. The available multi-modality neuroimaging datasets for diagnosing brain diseases have different classes and subjects, and this issue challenges the creation of tools for diagnosing these diseases using DL techniques. DL models and hardware resources are two other significant challenges faced in research in this field; solving them can lead to software development or real-time hardware to diagnose brain diseases in the future.

7.1. Limited Datasets

Lack of access to large datasets of medical images is one of the most common challenges facing studies focusing on diagnosing brain diseases. DL models require large volumes of data for training; hence, a lack of access to ample medical images in these DL models can result in overfitting [220-221]. Unavailable neuroimaging multimodality datasets based on MRI data are another challenge for the diagnosis of various brain diseases. So far, numerous clinical studies have been performed for diagnosing brain diseases using fusion neuroimaging modalities, sMRI-fMRI [222-223], MRI-PET [224], MRI-CT [225], and MRI-SPECT [226]. In contrast, few studies have been conducted on brain disease detection using neuroimaging multimodalities and DL techniques. This is caused due to lack of access to available datasets with sMRI-fMRI, MRI-PET, MRI-CT, and MRI-SPECT modalities for brain disease detection.

7.2. Data Privacy

In medical applications, privacy and security of patient data are generally considered of utmost importance. Many of the collected data can only be used with the patient's consent; even with consent, they mostly can not be shared [321-322]. However, a good amount of data sharing (between hospitals or even different researcher groups) is generally required when it comes to multi-modality fusion. Considering this, there need to be newer policies developed and established for data sharing to keep the confidentiality of patient data and also allow researchers enough sharing to create multi-modality fusion models without any problem

[323]. Moreover, the means of data transmission and sharing also need to change so that the security of patient data is never compromised.

7.3. Class Imbalance

Imbalanced data is another important challenge in the field of medical images for the diagnosis of brain diseases. In medical applications, the number of subjects (or images) used in each class is not balanced, resulting in various challenges [227]. As the first challenge in this section, training DL models using data with class imbalance will bias the network toward the class with the largest volume of data. In imbalanced data, classes do not include identical images, and to resolve this challenge, we reduce the data size, which may cause some data to be neglected.

7.4. Deep Learning

This section deals with the challenges related to DL models and their use for the diagnosis of brain diseases from neuroimaging modalities based on MRI. In the standard case, sMRI data are recorded in 3D form. Therefore, the main approach is to use 3D DL models [228]. However, this requires high levels of hardware resources. Furthermore, fMRI data are recorded as 4D [229]; however, it is not possible to implement 4D DL models. In MRI-based fusion data, other neuroimaging modalities are integrated into MRI data. This will result in the high complexity of DL models, significantly increasing the hardware resources required for training the network. The previous section discussed the lack of access to available datasets with large numbers of subjects. This makes implementing advanced DL models for brain disease detection much more difficult.

7.5. Hardware Resources

Having access to computational resources is a necessity in DL research, but researchers in information fusion suffer more from this as they usually need to work with high-dimensional datasets. In the standard case, sMRI data are recorded in 3D form. Therefore, the main approach is to use 3D DL models [228]. However, this requires high levels of hardware resources. Furthermore, fMRI data are recorded as 4D [229]; however, it is not feasible to implement 4D DL models. In MRI-based fusion data, other neuroimaging modalities are integrated into MRI data. This will result in the high complexity of DL models, significantly increasing the hardware resources required for training the network. Some solutions to these issues are; using the services of Google and Amazon and providing researchers with servers to implement DL models. Nonetheless, they also have some limitations, like providing their services only to some countries or time limits. Also, implementation of DL models in hardwares platforms based on cloud computing is another challenge that mentioned in the following.

7.5.1 Cloud Computing

DL methods are now mainly considered too much hardware demanding to run and train on personal computers. Therefore, many have switched to cloud computing for model development or real-life applications and tools [335]. While these models generally help researchers open their hands to develop models of any size, two main downsides also come with them. Firstly and most obviously, access to a powerful cloud system, which has unfortunately forces researchers without funding to stop working, as they can not compete with more computation power [336-337]. Secondly, this makes the models dependent on internet connections; therefore, creating models can not be used in remote areas. This contradicts one of the primary goals of creating automated models, which is to help patients in places without access to physicians [336-337].

8. Discussion

This section discusses the details of research studies focusing on the fusion of neuroimaging modalities using DL techniques. The studies conducted based on the fusion levels are summarized in Tables 3 to 6. These tables present valuable information for each paper, including applications, modalities, fusion levels, DL models, and classification techniques. In this section, first, this work is compared with other review papers. In subsection 2, the number of fusion levels for the diagnosis of brain diseases is discussed. The following shows the number of fusion levels each year for brain disease detection. In subsection 4, the number of applications of the papers in this field is reported. Subsection 5 presents the number of brain diseases detected using fusion neuroimaging modalities with DL models. In subsection 6, various fusion neuroimaging modalities are discussed. Then, the number of DL models in the fusion of neuroimaging modalities is reported. Finally, the number of classification techniques used in DL models is shown.

8.1. Comparison of This Work with Other Review Papers

In recent years, tremendous progress has been made in diagnosing brain diseases by employing neuroimaging multimodalities and AI approaches. Table 1 summarizes review articles by several researchers on the diagnosis of brain diseases using neuroimaging multimodalities with various ML, and DL approaches. The review papers included in Table 1 frequently highlight the usage of ML and DL to the diagnosis of brain diseases using neuroimaging multimodalities; however, they do not elaborate on fusion levels. On the other hand, all papers on the diagnosis of brain diseases based on fusion levels have been examined and published in this research. The DL review papers for neuroimaging multimodality-based brain disease detection are summarized in Table 7. The most significant advantage of our study is the review of all the papers on the diagnosis of brain diseases utilizing DL techniques and their fusion levels, as shown in Table 7. The review of papers has not been conducted in this manner in other works. The literature review on the diagnosis of brain diseases from neuroimaging multimodalities based on MRI is an additional novelty of this work. This work assists researchers in analyzing and comparing publications regarding the diagnosis of brain diseases using the fusion of neuroimaging multimodalities based on MRI. Additionally, this study enables researchers in brain diseases to utilize superior ideas in upcoming investigations. Our work is compared with other review papers and shown in Figure 12. It can be noted from the figure that our review paper is unique and does not overlap with other similar review papers.

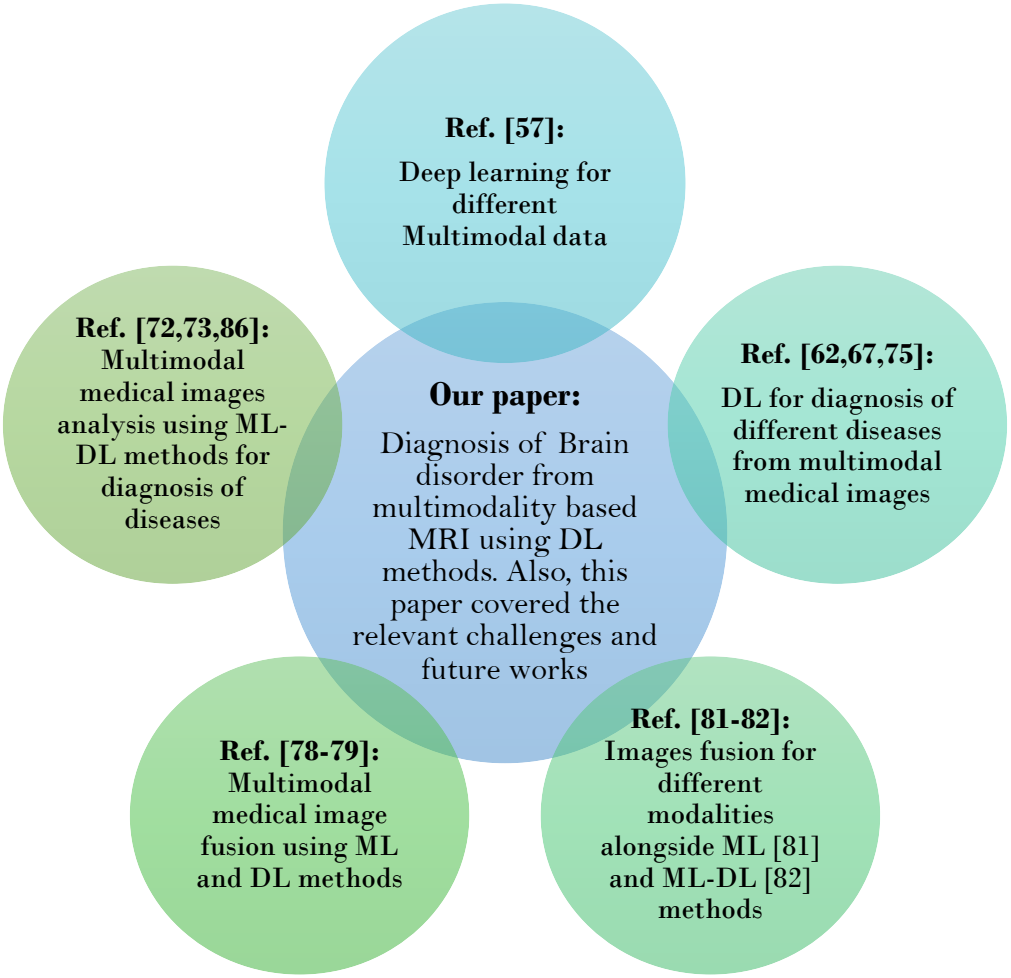

Fig. 12. Comparison of current review paper with other related works.

Table 7. Review papers published on the diagnosis of brain diseases in neuroimaging multimodalities using DL methods

Works	Year	Publisher	Methods	Application	Paper modalities
[57]	2017	IEEE	DL	Deep Multimodal Learning	Different Modalities
[62]	2019	Elsevier	DL	Medical Image Segmentation	PET, MRI, CT
[67]	2019	Springer	DL	Multimodal Medical Image Analysis	CT, MRI, PET
[72]	2020	Hindawi	ML and DL	Multimodal Medical Image Fusion	MRI, PET, CT, SPECT
[73]	2020	MDPI	ML and DL	Liver Cancer	CT, MRI, PET, Ultrasound
[75]	2020	Nature	DL	Medical Imaging Fusion and Electronic Health Records	Medical Imaging With EHR
[78]	2021	Elsevier	ML and DL	Multimodal Medical Image Fusion	CT, PET, MRI, SPECT
[79]	2021	IEEE	ML and DL	Multimodal Medical Image Fusion	MRI, SPECT, PET, CT, Ultrasound, X-Rays
[81]	2021	Elsevier	DL	Image Fusion	Different Modalities
[82]	2021	Springer	ML and DL	Image Fusion	Different Modalities
[86]	2022	ArXiv	ML and DL	Fusion of Image and Non-image Data in Disease Diagnosis and Prognosis	Image and Non-Image Data

8.2. Fusion Level

As noted in previous sections, fusion levels include the pixel, feature, and decision [91-93]. However, more recently, researchers have used a combination of fusion levels for brain disease detection, which is called

the hybrid level, in this study [219]. In pixel-level fusion, the images are fused in their original domain. This fusion level maintains the information in the images very well; hence, it is considered the popular fusion approach [91]. In feature-level fusion, the fusion process occurs inside the DL architecture, requiring high hardware resources [92]. In decision-level fusion, the outputs of various DL methods are fused [93]. The final fusion level is the hybrid approach that has recently attracted more attention from researchers [218]. Figure 13 depicts the fusion levels in studies focusing on brain disease detection. It can be seen that the hybrid fusion approach has been extensively used in the diagnosis of brain diseases. This is because, in hybrid scenarios, high-level fusions can ensure the model's training and convergence. In contrast, low-level fusions help the information from various modalities to be integrated at low levels.

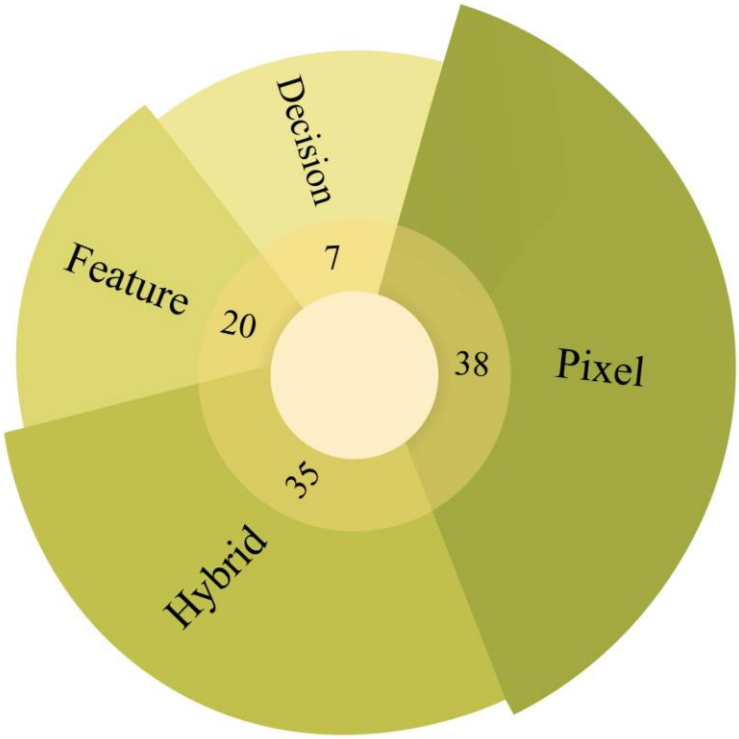

Fig. 13. Number of fusion levels for brain diseases detection using fusion of neuroimaging modalities based on MRI with DL methods.

8.3. Fusion Levels in Years

Tables 3 to 6 presented the studies on the diagnosis of brain diseases using neuroimaging multimodalities based on various levels of fusion. The number of fusion levels for diagnosis of brain diseases using neuroimaging multimodalities is depicted in Figure 13. An annual presentation of a comprehensive discussion on research in the diagnosis of brain diseases based on fusion levels is included in this section. Accordingly, Figure 14 illustrates the yearly assessment of fusion levels for diagnosing brain diseases utilizing DL methods. In recent years, additional hybrid fusion approaches have been employed for the diagnosis of brain diseases, as illustrated in Figure 14. Researchers have employed the combination of some levels of fusion to the diagnosis of brain diseases in these papers. This research increases the efficacy and precision of diagnosing brain diseases utilizing multimodal neuroimaging and DL approaches. Using neuroimaging multimodalities and DL models, researchers anticipate that hybrid fusion will enable the development of software to diagnose brain diseases in the near future with more accuracy .

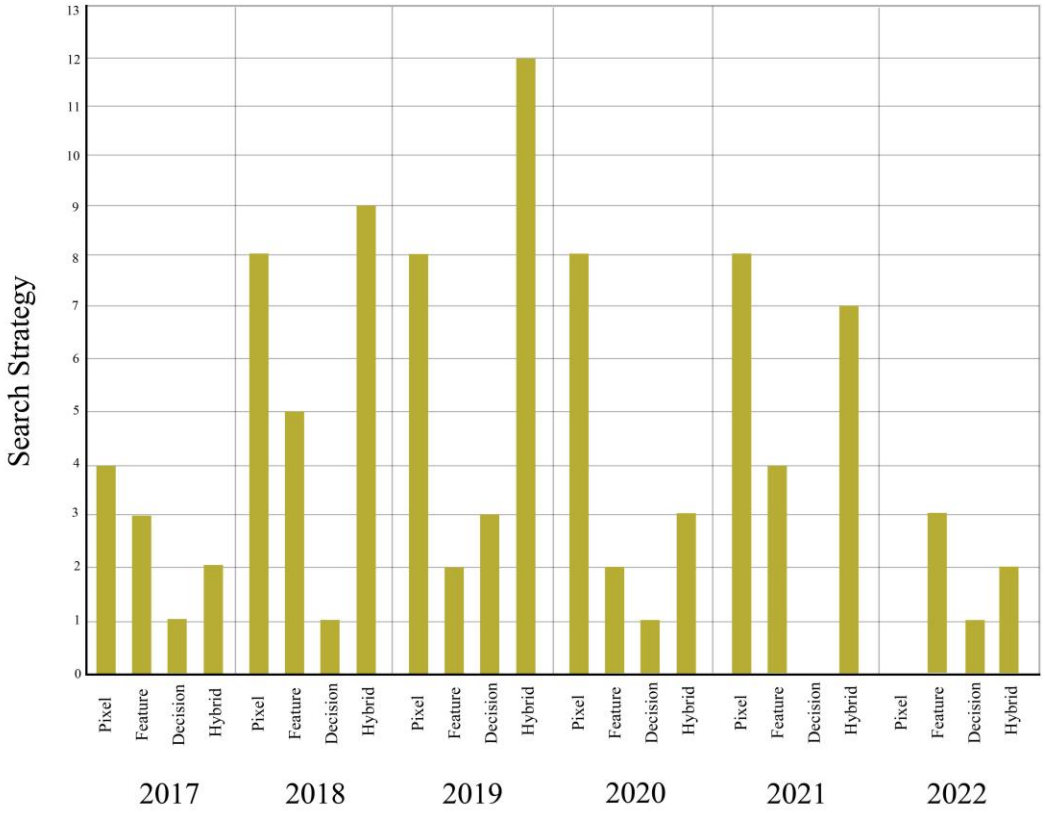

Table 14. The number of fusion-level papers accepted each year for diagnosis of brain diseases using DL models.

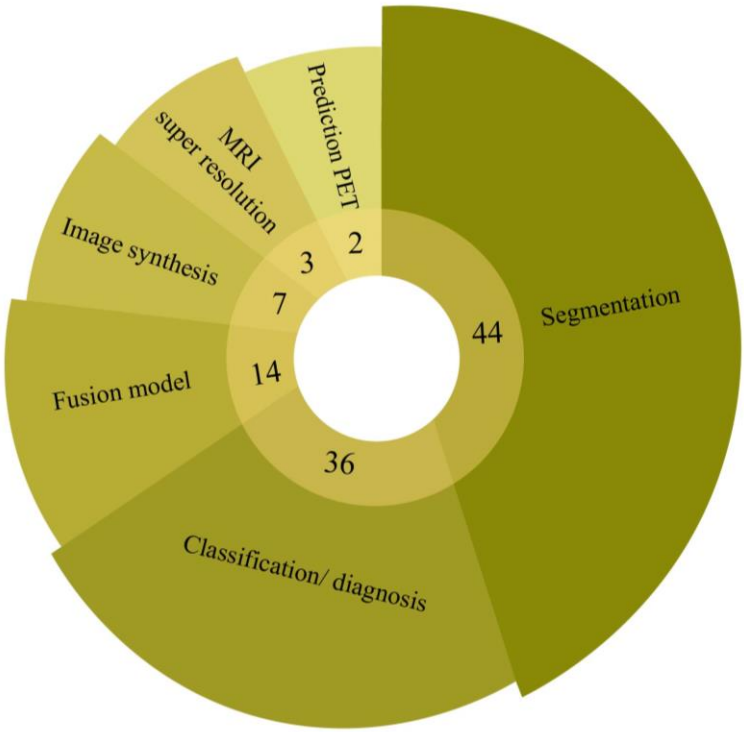

Fig. 15. Number of papers published on various applications related to brain diseases detection using neuroimaging multimodalities based on MRI with DL methods.

8.4. Types of Application

Fusion of neuroimaging modalities which have been used in various applications are shown in Tables 3 to 6. Figure 15 depicts various applications based on the fusion of neuroimaging modalities and DL models. It can be noted from Figure 15 that the segmentation of brain images using DL techniques is the most popular application, as it is the focus of many of the selected papers. In these studies, the segmentation of neuroimaging multimodalities has been done for the diagnosis of various brain tumors. Another common fusion application involves identifying or classifying various brain diseases. Diagnosis of brain diseases using the fusion of neuroimaging modalities and DL models has resulted in successful results.

8.5. Diagnosis of Brain Diseases using Fusion of Neuroimaging Modalities

As indicated previously, physicians' primary objective is to apply fusion neuroimaging modalities to improve the precision of brain disease diagnosis. The diagnosis of cerebral diseases such as ADHD, SZ, Brain Tumors, Ischemic Strokes, Glioma, Glioblastoma, Acute Bilirubin Encephalopathy, Migraineurs, Mild Cognitive Impairment, Isointense Infant Brain, and Dementia has been conducted using multimodality neuroimaging, as shown in Tables 3 to 6. The number of brain diseases diagnosed utilizing multimodal neuroimaging, and DL approaches are depicted in Figure 16. Most researchers have concentrated on diagnosing Alzheimer's disease using DL methods based on fusion neuroimaging modalities. This has paved the way for multimodality datasets for Alzheimer's disease diagnosis.

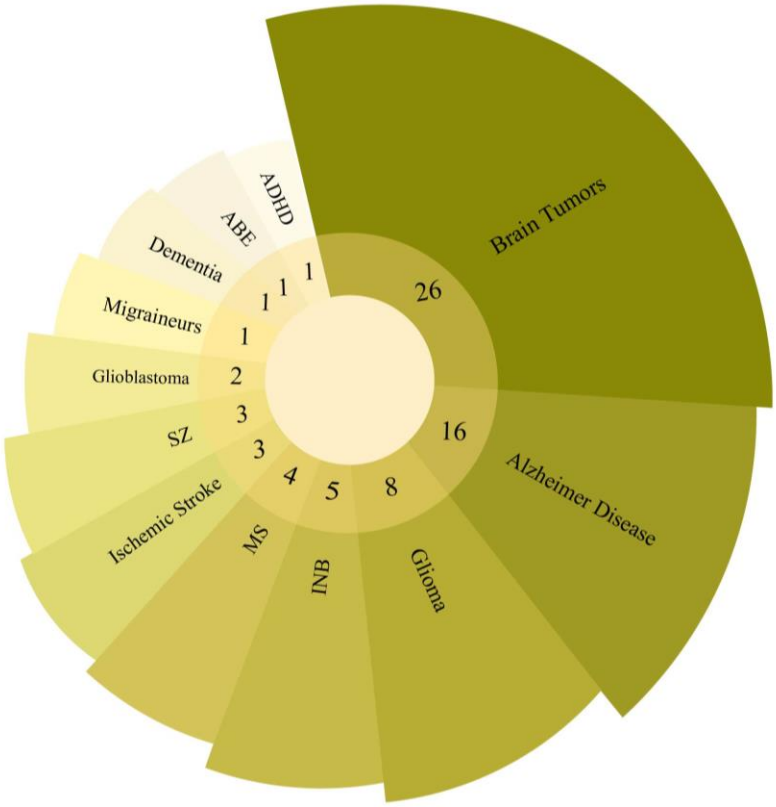

Fig. 16. Number of papers published on the diagnosis of brain diseases using fusion of neuroimaging modalities.

8.6. Types of neuroimaging modalities

Table 3 and 6 summarize the studies on fusion neuroimaging modalities using DL techniques. The main objective of this study is to explore research studies focusing on fusion neuroimaging modalities based on MRI and DL methods. Figure 17 presents the number of neuroimaging modalities based on MRI in various neuroscientific applications, including the diagnosis of brain diseases. As seen in Figure 17, MRI multimodality is the most commonly used method in research studies on fusion neuroimaging modalities using DL techniques. Compared to other fusion techniques, it is easier for researchers to analyze MRI multimodality; hence, this domain accounts for the highest number of studies. On the other hand, various MRI multimodality datasets are available to researchers. Based on the above-mentioned reasons, most studies have used MRI multimodality.

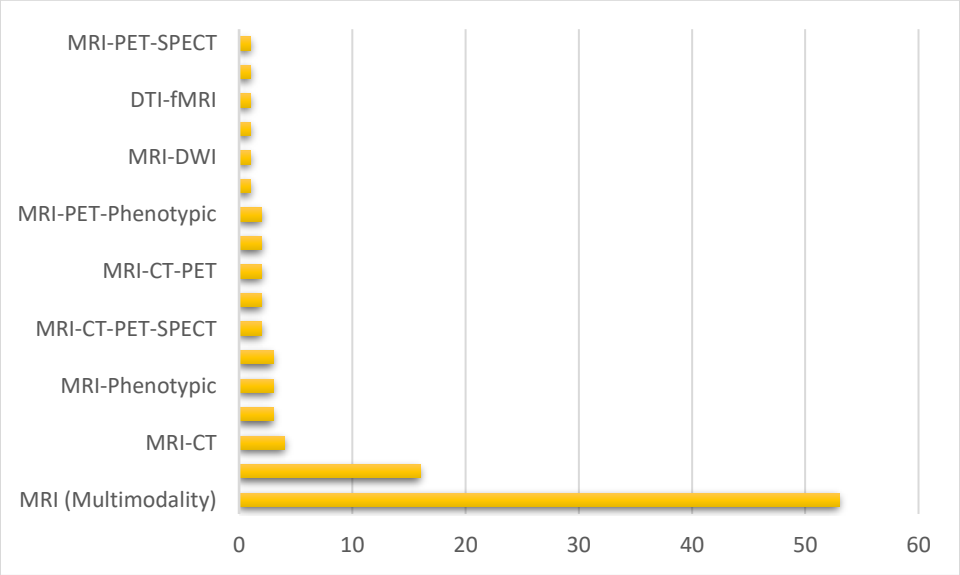

Fig. 17. Number of neuroimaging multimodalities for diagnosis of brain diseases.

8.7. Deep Learning Models

This section discusses the fusion of neuroimaging modalities based on DL methods. Tables 3 to 6 present various DL models for neuroimaging modalities applications. Different DL models used for the fusion of neuroimaging modalities are shown in Figure 18. According to Figure 18, most studies have used CNN-based models. Another group of DL models used for the segmentation of medical images consists of models based on U-Net.

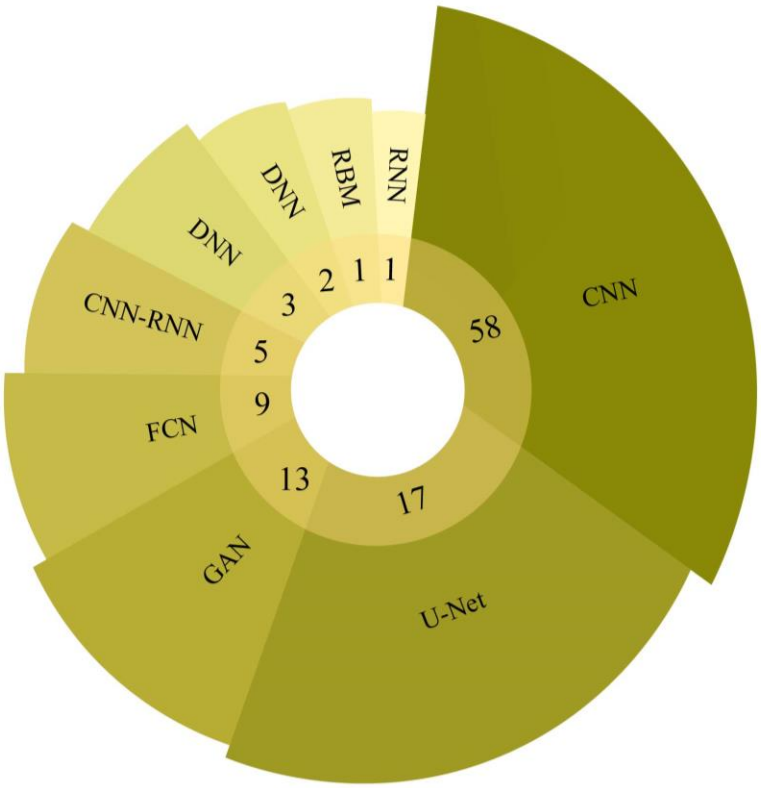

Fig. 18. Number of DL models for brain diseases detection using neuroimaging multimodalities based on MRI.

8.8. Classifiers

This section discusses and compares various classification algorithms used in DL architectures. Some parts of Tables 3 and 6 report classification methods for fusion neuroimaging modalities applications. Figure 19 displays the number of classifier algorithms used in DL models to diagnose brain diseases from fusion neuroimaging modalities. As can be observed, the SoftMax method is extensively used in DL architectures.

9. Future work

Previous sections briefly discussed the challenges related to the fusion of neuroimaging modalities using DL techniques. Mitigating these challenges will help to improve the efficiency and accuracy of brain disease detection using the fusion of neuroimaging modalities. This section introduces several future directions in fusion neuroimaging modalities using DL techniques. Importantly, these future directions align with the challenges stated in Section 6. Datasets, DA, imbalanced data, DL models, explainable AI, fuzzy deep learning (FuDL), and hardware resources are the main focuses of future work. These future works are briefly discussed below.

9.1. Datasets

The lack of access to many subjects are one of the most important challenges facing the diagnosis of brain diseases using DL techniques [20-21]. In the diagnosis of brain diseases, usually multimodal datasets from sMRI-fMRI [230], MRI-PET [45], MRI-CT [231], and MRI-SPECT [232] data are not freely available to researchers. Moreover, such datasets are not available for the diagnosis of ASD, PD, ADHD, etc. [233-236]. Hence in the future, providing freely available datasets from sMRI-fMRI, MRI-PET, MRI-CT, and MRI-SPECT modalities for the diagnosis of brain diseases will be important. MRI neuroimaging modalities include sMRI, DTI, DWI, rs-fMRI, and T-fMRI. However, multimodality datasets containing all MRI

modalities have not yet become available for diagnosing brain diseases. Therefore, providing neuroimaging multimodality datasets containing several types of MRI data can be another future work in this field.

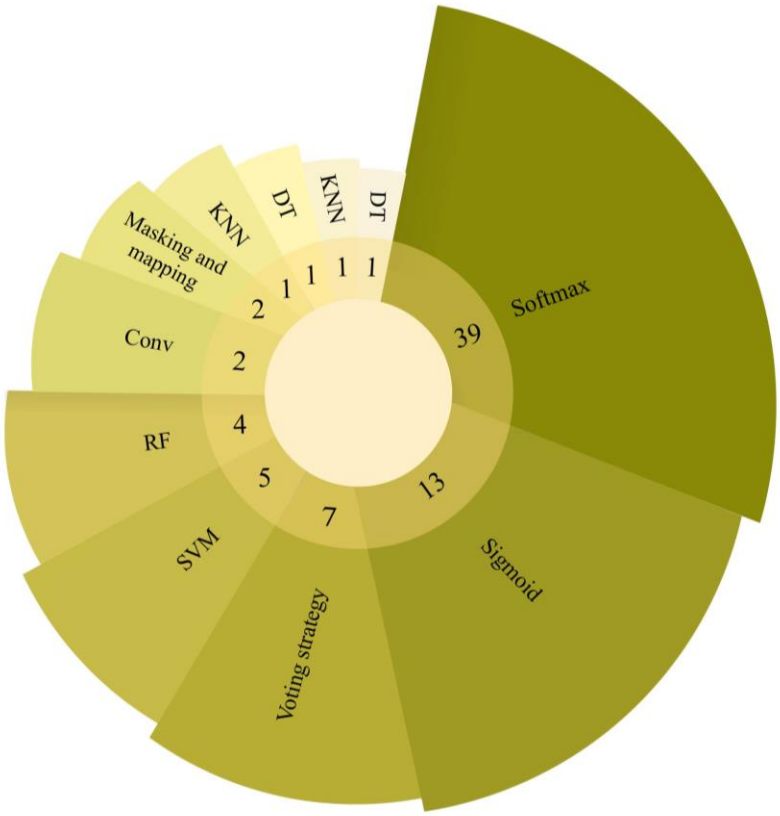

Fig. 19. Number of classifier algorithms in DL models for diagnosing brain diseases from neuroimaging multimodalities based on MRI.

9.2. Data augmentation methods

In DL models, insufficient data at the network input will result in overfitting. Their structure and parameters determine the extent of the complexity of DL models. Therefore, selecting an appropriate number of layers and accurately adjusting the parameters of DL models can significantly reduce the complexity of the network. On the other hand, instead of changing the architecture of a DL model, various methods can be used to augment the amount of training data artificially. Data augmentation (DA) techniques are common in DL research [237-238]. DA methods involve various transformations, including rotation, translation, scaling, flipping, distortion, and adding noise, applied to the images during the training stage to create new images [237-238]. Afterward, the original and artificial images are given to the DL network as training data GAN [105-106] and simple copy-paste [239] models are new DL-based methods extensively used in DA applications. Various medical research studies have shown that DA models can significantly mitigate insufficient data problems. These methods have different variations, e.g., the most important GAN models include DCGAN [240], Laplacian GAN (LAPGAN) [241], boundary equilibrium GAN (BEGAN) [242], information GAN (InFoGAN) [243], and Wasserstein GAN with gradient penalty (WGAN-GP) [244]. Future works can analyze the effect of using GAN and Simple Copy-Paste models for diagnosing brain diseases from neuroimaging multimodalities.

9.3. Data imbalance

The problem of imbalanced data results in the network's bias toward the class that contains the higher number of data records [245]. There are various solutions to this challenge, but few are discussed in this section. One of the solutions is to resample the data space [246]. To perform this process, three different approaches, i.e., under-sampling the negative class, up-sampling the negative class, and synthetic minority over-sampling technique (SMOTE), can be used to generate artificial samples [247-250]. These approaches increase the number of samples in the minority class. These methods are easy to use; however, some important data may be eliminated, or redundant data may be added to the training set. The method based on patch sampling can also mitigate the imbalanced data problem.

9.4. DL models

It can be noted from the papers presented in Tables 3 to 6 that the authors have opted to use standard DL techniques in various applications. More recently, a new family of DL models has been proposed by researchers, the most important of which include the attention mechanism [251-252], transformers [253-254], graph [255-256], and self-supervised learning [257-258]. On the other hand, some other uncertainty-based techniques have also been suggested [259-260]. Future works can use these methods along with neuroimaging multimodalities for the diagnosis of brain diseases to obtain better and more accurate results. More details regarding these methods are presented in the following subsections.

A) Deep attention mechanism

Recently, AI researchers have introduced methods based on the attention mechanism [251-252], and these methods have rapidly been utilized in different disciplines, including medicine [261-262]. In attention models, the model only processes part of the input that contains relevant information [251-252] to predict the output. Some popular models include Attention CNNs [263], attention auto-encoders [264], graph attention [265], and attention RNNs [266]. Attention models allow researchers and physicians to obtain real tools for diagnosing brain diseases and neuroimaging multimodalities. As a result, future works can use attention models to improve their performances.

B) Transformer models

Transformers are a new group of DL techniques that have provided valuable results in medical research, such as in segmenting medical images [253-254]. Authors in [267] proposed a transformer model based on self-attention and encoder and decoder sections. Vision Transformer (ViT) models are among the most well-known transformer architectures that can be utilized in future works [268]. Furthermore, graph transformers [269], recurrent spatial transformers [270], polar transformers [271], and dense transformers [272] have been suggested as new methods in this field. Also, in the future, new transformer models along with neuroimaging multimodalities will be proposed to improve the performance for the diagnosis of brain diseases.

C) Graph CNN models

Nowadays, graph techniques are extensively used in various medical fields [255-256]. GNNs are a group of DL methods designed for processing graph data and provide a simple solution for prediction tasks at the node, edge, and graph levels [255-256]. One of the benefits of GNN is the possibility of combining it with other DL methods, such as CNN [273]. Research has shown that using GCNN models will significantly improve the accuracy of diagnosis of brain diseases based on several types of medical data [274-277]. Future works can make use of GCNN methods along with neuroimaging multimodalities.

D) Semi-Supervised Learning (SSL)

One of the challenges related to medical data is that labeling them by physicians is highly time-consuming. Moreover, datasets for different patients may include unlabeled data. The semi-supervised learning (SSL) techniques can be used to overcome the challenges mentioned above [257-258]. So far, several studies have used SSL techniques for brain disease detection [278-279]. Some of the most recent models in this field include contrastive SSL [280], SSL attention [281], SSL graph [282], and on-contrastive SSL [283]. Therefore, future works can make use of SSL models for the diagnosis of brain diseases based on neuroimaging multimodalities

E) Deep models with uncertainty

Another challenge related to DL is the appropriate allocation and accurate learning of uncertainty in the model's decision-making [259-260]. The best model is the one that, in addition to accurate decision-making, provides a calibrated probability assignment and has a lower level of uncertainty in decision-making when facing data different from the training data [259-260]. These challenges are mostly observed when implementing the model in real-world scenarios and when the closed-world assumption is violated. Moreover, approaches such as calibration and open-set recognition have been used to mitigate these challenges in an attempt to create a fair and trustworthy AI [259-260].

9.5. Explainability and Interpretability

Creating black box models is usually not appreciated, as they cannot be trusted easily. No matter how strictly tested, black box models might fail when an unknown and unaccounted factor changes. Therefore the current trend of AI is switching toward more explainable models and interpretation of models' decisions. Many works are done on the model interpretation, and some of the introduced methods usually work on any network out of the box (such as Grad-CAM). However, one of interpretability's challenges is translating the results into humanly understandable outputs. Regarding information fusion, many works need to be done before having plug-and-play methods for model explain ability. Also, publishing protocols for evaluating model interpretability and trustworthiness is another direction for future research.

9.6. Fuzzy Deep Learning

Fuzzy methods are an important group of AI techniques that are widely used in various medical applications, such as the segmentation of medical images and the diagnosis and prediction of diseases [324-325]. Type 1 fuzzy sets were first introduced by Lotfi-Zadeh and were quickly applied in various fields after that [326-328]. After that, fuzzy type-2 was introduced, which, compared to type-1, would generally lead to higher performances in solving various problems [329-330]. Recently, fuzzy models have been utilized as a part of DL architectures, and researchers have utilized them to reach successful results in classification applications or image segmentation. These architectures are known as FuDL, and some of their most influential models include Pythagorean Fuzzy Deep Boltzmann Machine (PFDBM) [331], deep fuzzy CNN (DFCNN) [332], stacked AE trained using fuzzy logic (SAETFL) [333], and Takagi Sugeno deep fuzzy network (TSDFN) [334]. In future, FuDL methods can be used to diagnose brain diseases based on neuroimaging multimodalities.

9.7. Hardware Resources

As noted in the previous section, the lack of access to appropriate hardware for implementing DL models is a serious challenge. Various ideas, including providing available hardware resources and proposing new DL models, have been suggested to overcome this challenge. Using cloud computing to simulate DL models can mitigate the challenges faced by researchers. Implementing DL models based on deep compact-size

CNNs can also be a potential solution for researchers. Compared to other DL methods, deep compact-size CNNs require fewer hardware resources in the training stage. Furthermore, these models can be implemented on computers with average hardware and/or cellphones. Some of the more popular methods based on deep compact-size CNNs include FBNetV3 [284], MnasNet [285], TinyNet [286], and MobileNet [287]. Future works can use methods based on deep compact-size CNNs to perform research on the diagnosis of brain diseases using neuroimaging multimodalities.

10. Conclusion and Findings

Many people around the world suffer from brain diseases that seriously threaten their health. Early diagnosis of brain diseases is vital for specialists in this field. Hence, various screening methods have been proposed for identifying brain diseases. The main objective of these screening methods is the early diagnosis of various brain diseases by specialists accurately [288-289]. Among the different proposed diagnosis methods, specialists prefer more neuroimaging modalities; hence, these methods are extensively used for diagnosing brain diseases.

Neuroimaging modalities provide essential information to physicians about the structure and function of the brain; therefore, they are popular among researchers and physicians for brain disease diagnosis [313-316]. Compared to other screening methods, structural neuroimaging modalities have performed better in diagnosing brain diseases like brain tumors. sMRI and DTI are the most significant structural modalities that provide details of the brain structure with high contrast for accurate diagnosis of brain tumors [313-316]. Functional neuroimaging modalities, including fMRI, PET, EEG, and EMG, are the most important methods used for diagnosing neurological and mental disorders. These methods have the ability to show how the brain functions during various brain disorders, which are very useful for physicians [317-318]. Meanwhile, methods such as DSM-5 are less effective in diagnosing brain disorders compared to functional neuroimaging modalities [319-320].

Structural and functional MR imaging modalities have provided successful results for the diagnosis of brain diseases [21-22]. Using these data, physicians can accurately assess various brain diseases [19-20]. To diagnose brain diseases, physicians usually use several types of functional and/or structural MRI modalities [19-22]. More recently, clinical studies have shown that fusing MRI modalities with other neuroimaging modalities, such as CT, PET, and SPECT increase the accuracy of disease diagnosis [38-44]. However, alongside the advantages of neuroimaging multimodalities, challenges such as creating new images and the complexity of analysis are increased for physicians. The authors of this study have reviewed most of the research papers published on neuroimaging multimodalities using DL techniques.

The introduction provided an extensive review of various neuroimaging modalities, the benefits and disadvantages of the modalities, the importance of fusing the images, and different fusion methods. In addition, the importance of DL techniques in brain disease diagnosis using neuroimaging multimodalities for brain disease diagnosis was discussed.

Section 2 discussed the search strategy used for identifying the relevant papers based on the PRISMA guidelines. In this review study, the PRISMA guidelines with three analysis levels were used for the selection and evaluation of the papers. Moreover, the inclusion and exclusion criteria for selecting the papers were summarized in a table.

Section 3 presented the review papers focusing on the diagnosis of brain diseases using the fusion of neuroimaging modalities and AI models. This section reviewed papers published from 2016 to 2022 and summarized in Table 1. The reason for selecting this timeframe was that research on DL for the diagnosis of brain diseases using neuroimaging multimodalities started in 2016. The results of this section show that AI research studies focusing on neuroimaging multimodalities are becoming more common. Moreover, the

results show that in recent years, researchers have been interested in using neuroimaging multimodalities alongside DL models for the diagnosis of brain diseases.

Section 4 deals with brain disease detection from multimodal neuroimaging-based MRI using DL models. In this section, brain diseases are diagnosed using the fusion of neuroimaging modalities using DL models. Figure 2 shows the neuroimaging modalities used to diagnose brain diseases such as ADHD, SZ, brain tumors, ischemic stroke, glioma, glioblastoma, ABE, Migraineurs, MS, isointense infant brain, Alzheimer's disease, and dementia.

Section 5 presents the most common DL models used to diagnose brain diseases from neuroimaging multimodalities based on MRI. This section presents CNNs, pre-trained, AEs, RNNs, U-Net, FCN, and GANs models. Furthermore, some improved DL models used in research studies on diagnosing brain diseases based on the fusion of neuroimaging modalities were briefly discussed.

Section 6 discussed the fusion levels for the diagnosis of brain diseases from neuroimaging multimodalities. As noted earlier, the fusion levels in medical images include the input, layer, and decision. First, detailed descriptions of each fusion level were presented, and the research studies using each level were summarized in Table 6. This table (Table 6) presents the research studies focusing on the diagnosis of brain diseases that have used various fusion levels simultaneously. It also showed that most papers had used two or more fusion levels simultaneously to diagnose brain diseases.

The challenges in the field of neuroimaging multimodalities for the diagnosis of brain diseases were discussed in Section 7. The challenges in this field include limited datasets, class imbalance, DL methods, and a lack of appropriate hardware resources. Each of these challenges was explored in more detail. Overcoming these challenges will help researchers obtain a valuable and working tool for diagnosing brain diseases based on neuroimaging multimodalities using DL models.

Section 8 focused on the discussion and details to explore and explain the paper's important parts, including comparing this work with related works, fusion levels, applications, brain diseases, neuroimaging modalities, DL models, and classifier algorithms. This section will help the researchers provide useful results on various research on the diagnosis of brain diseases based on neuroimaging multimodalities using DL techniques.

Section 9 discusses potential future directions such as datasets, DA, imbalanced data, DL models, explainable AI, and hardware resources. This section will help the researchers provide novel information related to datasets, DL models, and hardware resources.

The research trend in the field of neuroimaging multimodalities based on DL for diagnosing various brain diseases is growing exponentially. Researchers are trying to overcome the challenges in this field to perform better. Soon, this will help specialist physicians use software and hardware platforms based on neuroimaging multimodalities to diagnose brain diseases.

Appendix A

A
Accuracy (Acc)
Adaptive Dual-Channel Spiking Cortical Model (ADCSCM)
Alzheimer's Disease Neuroimaging Initiative (ADNI)
Amplitude of Low-Frequency Fluctuations (ALFF)
Anterior Commissure _ Posterior Commissure (AC_PC)
Apparent Diffusion Coefficient (ADC)
Attention Deficit Hyperactivity Disorder (ADHD)
AUC
Automated Anatomical Atlas (AAL)
Average Gradient (AG)
Average Symmetric Surface Distance (ASD)
B
Baseline Convolutional Network (BCN)
Brain Tumor Segmentation (BraTS)
C
Canonical Correlation Analysis (CCA)
Cascaded Anisotropic Convolutional Neural Network (CA-CNN)
Cerebrospinal Fluid (CSF)
Channel and Spatial Attention Dense Network (CSpA-DN)
Computerized Tomography (CT) Scan
Convolutional Neural Network (CNN)
Correlation Factor (CF)
Cycle Consistent GAN (3D-cGAN)
D
Data Augmentation (DA)
Deep Fuzzy CNN (DFCNN)
Deep Neural Network (DNN)
Dice
Diffusion Magnetic Resonance Imaging (dMRI)
Diffusion Tensor Imaging (DTI)
Diffusion-Weighted Imaging (DWI)
DTI Structural Connectivity Network (DTISCN)
E
Edge Intensity (EI)
Edge Quality (EQ)
Enhanced Monarch Butterfly Optimization (EMBO)
Enhancing Tumor (ET)
Entropy
F
False Negative (FN)
False Positive (FP)
Feature Mutual Information (FMI)
Fluid-Attenuated Inversion Recovery (FLAIR)
Fluorodeoxyglucose_ Positron Emission Tomography (FDG_PET)
Fractional Anisotropy (FA)
F-Score
Full-Image Fully-Convolutional Network (FIFCN)
Fully Convolutional Neural Network (FCN)
Fully Stacked Bidirectional Long Short-Term Memory (FSBi-LSTM)
Functional Connectivity Network (FCN)
Fusion Factor (FF)
G
Gated Multimodal Unit (GMU)
Gated Recurrent Unit (GRU)
Generative Adversarial Network (GAN)
Gradient Class Activation Mapping (Grad-CAM)
Gray Matter (GM)
Green Fluorescent Protein (GFP)
H
Hausdorff Distance (HD)
I
Infant Brain MRI Segmentation (iSeg)
Institute of Mental Health (IMH)

Intervertebral Disc Localization and Segmentation from 3D Multi-Modality MRI (IVDM3Seg)
Intratumor Classification Network (ITCN)
J
Jaccard Coefficient (JAC)
K
L
Landmark Based Multi Modal Multi Instance Learning Method (LM3IL)
Latent Representation Conditional GAN (LR-cGAN)
Least the Absolute Shrinkage and Selection Operator (LASSO)
Locality Adaptive GAN (LA-GAN)
Logical Memory (LM)
M
Magnetic Resonance Imaging (MRI)
Mask Region-Based Convolutional Neural Network (MASK R-CNN)
Matthews Correlation Coefficient (MCC)
Mean Average Precision (MAP)
Mean Dice Overlap Coefficients (MDOC)
Mean Diffusivity (MD)
Mean Intersection over Union (Mean IoU)
Mean Square Error (MSE)
Mean Structural Similarity (MSSIM)
Mean Surface Distance (MSD)
Mild Cognitive Impairment (MCI)
Mini-Mental State Examination (MMSE)
Modified Hausdorff Distance (MHD)
Multi-Generator Multi-Discriminator Conditional GAN (MGMDcGAN)
Multi-Layer Perceptron (MLP)
Multimodal and Multiscale Deep Neural Network (MMDNN)
Multi-Modal Stacked Deep Polynomial Networks (MM-SDPN)
Multi-Modality MRI Fusion Network (MMFNet)
Multi-Modality Transfer Learning Network (MMTLNet)
Multi-Modality Whole Heart Segmentation Challenge (MM-WHS)
Multiparametric MRI (mpMRI)
Multiple Sclerosis (MS)
Multi-Scale Fully Convolutional Network (MsFCN)
Multi-Scale Local Extreme Scheme (MSLES)
Multi-Scale Multi-Modal Convolutional Neural Network with Long Short-Term Memory (MSMCNN–LSTM)
Multi-Task Deep Learning (MTDL)
Mutual Information (MI)
N
National Alzheimer Coordinating Center (NACC)
Naturalness Image Quality Evaluator (NIQE)
Neuromorphic Attention-Based Learner (NABL)
Non-Contrast Magnetic Resonance Imaging (NCMRI)
Non-Subsampled Contourlet Transform (NSCT)
Normalized Mean Absolute Error (NMAE)
Normalized Mean Squared Error (NMSE)
Normalized Root-Mean-Square Error (NRMSE)
Northwestern University Schizophrenia Data and Software Tool (NUSDAST)
Pythagorean Fuzzy Deep Boltzmann Machine (PFDBM)
O
P
Peak Signal to Noise Ratio (PSNR)
Phase Contrast (PC)
Positive Predictive Value (PPV)
Positron Emission Tomography (PET)
Precision (Prec)
Prostate Imaging Reporting and Data System (PI-RADS)
Q
R
Random Forests (RF)
Recall
Region of Interest (ROI)
Region to Image Matching Net (RIMNet)

Regional Functional Correlation Strength (RFCS)
Regional Homogeneity (ReHo)
Resting-State Functional Magnetic Resonance Imaging (rs-fMRI)
Restricted Boltzmann Machine (RBM)
Reversible GAN (RevGAN)
S
Self-Attention Conditional GAN (SC-GAN)
Sensitivity (Sen)
Signal to Noise Ratio (SNR)
Single Image Super-Resolution (SISR)
Single-Photon Emission Computerized Tomography (SPECT)
Soft Tissue Sarcoma Dataset from The Cancer Imaging Archive (STS_TCIA)
Spatial Frequency (SF)
Specificity (Spec)
Stacked Autoencoder (SAE)
Standard Deviation (SD)
Stacked AE Trained using Fuzzy Logic (SAETFL)
Stroke Penumbra Estimation of Ischemic Stroke Lesion Segmentation 2015 Challenge (SPES_ISLES 2015)
Structural Similarity Index Measurement (SSIM)
Structured and Sparse Canonical Correlation Analysis (ssCCA)
Support Vector Machine (SVM)
T
Takagi Sugeno Deep Fuzzy Network (TSDFN)
T2-Weighted (T2W)
Task Functional Magnetic Resonance Imaging (T-fMRI)
The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA)
The Cancer Genome Atlas Glioblastoma Multiforme (TCGA-GBM)
True Negative (TN)
True Positive (TP)
Tumor Core (TC)
Tumor Localization Network (TLN)
U
United Adversarial Learning Framework (UAL)
V
Visual Geometry Group (VGG)
Visual Information Fidelity (VIF)
W
Whole Tumor (WT)
Wide Residual Network and Pyramid Pool Network (WRN-PPNet)
Withe Matter (WT)
X
Xydeas and Petrovic Metric (Qabf)
Y
Z

Appendix B

Acc [290]	$Acc = \frac{TP + TN}{FP + FN + TP + TN}$
Sen [290]	$Sen = \frac{TP}{FP + TP}$
Spec [290]	$Spec = \frac{TN}{FP + TN}$
Prec [290]	$Prec = \frac{TP}{TP + FP}$
F-Score [290]	$F - Score = \frac{2\,TP}{2\,TP + FP + FN}$
Dice [291]	$Dice = \frac{2\,TP}{2\,TP + FP + FN}$
SD [292]	$SD = \sqrt{\frac{1}{MN}\sum_{i=1}^{M}\sum_{j=1}^{n}(I_F(i,j) - \mu_{I_F})^2}$
HD [293]	$HD(A_s, B_s) = max\left\{\max_{a\in A_s}\min_{b\in B_s} d(a,b), \max_{b\in B_s}\min_{a\in A_s} d(b,a)\right\}$
MHD [294]	$MHD(C,D) = \max\left(d(C,D), d(D,C)\right)$
SF [292]	$SF = \sqrt{RF^2 + CF^2}$ $RF = \sqrt{\frac{1}{M(N-1)}\sum_{i=1}^{M}\sum_{j=2}^{N}(X(i,j-1) - X(i,j))^2}$ $CF = \sqrt{\frac{1}{(M-1)N}\sum_{i=2}^{M}\sum_{j=1}^{N}(X(i,j) - X(i-1,j))^2}$
FF [295]	$FF = I_{AF} + I_{BF}$
MI [292]	$MI = \sum_{i=1}^{M}\sum_{j=1}^{N} h_{I_R I_F}(i,j) \times \log_2\left(\frac{h_{I_R I_F}(i,j)}{h_{I_R}(i,j)h_{I_F}(i,j)}\right)$
Entropy [292]	$EN = -\sum_{i=0}^{L-1} p(i)\log_2 p(i)$
MSE [296]	$MSE = \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}(A_{ij} - B_{ij})^2$
SNR [297]	$SNR = 10\log_{10}\left\{\frac{\sum_{x=1}^{P}\sum_{y=1}^{Q}(I_r(x,y))^2}{\sum_{x=1}^{P}\sum_{y=1}^{Q}(I_r(x,y) - I_f(x,y))^2}\right\}$
PSNR [292]	$PSNR = 10\log_{10}\left(\frac{L^2}{RMSE^2}\right)$

MSSIM [298]	$MSSIM\ (X,Y) = \frac{1}{M}\sum_{j=1}^{M} SSIM(x_j, y_j)$
AG [297]	$AG = \frac{1}{MN}\sum_{i=1}^{M}\sum_{j=1}^{N}\sqrt{\frac{\nabla F_x^2(i,j) + \nabla F_y^2(i,j)}{2}}$
JAC [299]	$JAC(R,G) = \frac{\lvert R \cap G \rvert}{\lvert R \cup G \rvert}$
MDOC [299]	$MDOC = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n} Dice_{ij}}{m.n}$
NMSE [300]	$NMSE = \frac{\left\lVert X - \hat{X} \right\rVert_2^2}{\lVert X \rVert^2}$
NRMSE [301]	$NRMSE\left(\hat{Y}, Y\right) = \sqrt{\frac{\sum_{x=1}^{N}(\hat{Y}(x) - Y(x))^2}{\sum_{x=1}^{N} Y(x)^2}}$
Mean IoU [302]	$Mean\ IoU = \frac{TP}{TP + TN + FP + FN}$
ASD [299]	$ASD = \frac{1}{\lvert SS \rvert \lvert GT \rvert} \times \left(\sum_{x \in SS} d(x, GT) + \sum_{y \in GT} d(y, SS)\right)$
NMAE [303]	$NMAE = \frac{1}{n_x n_y n_z}\sum_{x,y,z}^{n_x n_y n_z} \frac{\lvert s(x,y,z) - r(x,y,z) \rvert}{\max_{x,y,z}\{r(x,y,z)\} - \min_{x,y,z}\{r(x,y,z)\}}$
SSIM [292]	$SSIM = \frac{(2\mu_{I_R}\mu_{I_F} + C_1)(2\sigma_{I_R I_F} + C_2)}{(\mu_{I_R}^2 + \mu_{I_F}^2 + C_1)(\sigma_{I_R}^2 + \sigma_{I_F}^2 + C_2)}$
MCC [290]	$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$
Xydeas and Petrovic Metric ($Q^{AB/F}$) [304]	$Q^{AB/F} = \frac{\sum_{n=1}^{N}\sum_{m=1}^{M}(Q^A(n,m)W^A(n,m) + Q^B(n,m)W^B(n,m))}{\sum_{n=1}^{N}\sum_{m=1}^{M}(W^A(i,j) + W^B(i,j))}$
FMI [297]	$FMI = MI_{A,F} + MI_{B,F}$

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