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# Deep learning of brain magnetic resonance images: A brief review

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ABSTRACT

Magnetic resonance imaging (MRI) is one of the most popular techniques in brain science and is important for understanding brain function and neuropsychiatric disorders. However, the processing and analysis of MRI is not a trivial task with lots of challenges. Recently, deep learning has shown superior performance over traditional machine learning approaches in image analysis. In this survey, we give a brief review of the recent popular deep learning approaches and their applications in brain MRI analysis. Furthermore, popular brain MRI databases and deep learning tools are also introduced. The strength and weaknesses of different approaches are addressed, and challenges as well as future directions are also discussed.

## 1. Introduction

Magnetic resonance imaging (MRI) becomes one of the most popular techniques due to its non-invasive and painless advantage, and is widely used to obtain detailed information about anatomy and function for different organs of the body (Fig. 1b) [1]. Especially, the brain MRI is an excellent way to capture changes in the brain's internal structure and activity status, and have been used to explore the brain functional mechanisms and diagnose brain disorders, such as brain maturation [2,3], alteration of brain structures (e.g. GM) in neurodegenerative disorders [4], and abnormal functional connectivity in some psychiatric disorders [5].

Recently, deep learning has shown superior performance over traditional machine learning approaches in various tasks [6], e.g. object detection and image segmentation [7,8]. As shown in Fig. 1a, deep learning is becoming popular in the analysis of brain MR images, and is more widely used to MRI compared with other types of medical images (Fig. 1b). For example, deep learning has been used for preprocessing and analysis of MR images, including brain segmentation [9], registration [10], noise reduction [11], resolution enhancement [12], detection of lesions [13], and disease diagnosis [14]. Some popular deep learning approaches, e.g. U-net [15] and recurrent neural network (RNN), have been successfully employed in challenges of MRI analysis, such as the Multimodal Brain Tumor Segmentation Challenge (BraTs) [16] and the Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge [17].

In this review, we give a timely brief survey of recent popular deep learning approaches and their applications in brain MRI analysis. As shown in Fig. 2, we will focus on the preprocessing of MRIs with deep learning as well as the diagnosis of brain disorders based on deep learning and MRIs. Some popular brain MRI databases and deep learning tools are also introduced. The strength and weaknesses of different approaches are addressed, and challenges as well as future directions are also discussed.

## 2. Overview of deep learning methods

### 2.1. Convolutional neural network

Convolutional neural network (CNN) composed of a regularized

*Abbreviations:* T1, T1-weight MR image; T1c, T1 weight enhancing contrast MR image; T2, T2-weight brain image; T2-FLAIR, T2-weighted-Fluid-Attenuated Inversion Recovery MR images; ASL, Arterial spin labeling (ASL) MR perfusion image; GM, grey matter; WM, white matter; CSF, cerebro-spinal fluid; NLM, Optimized block-wise non-local means; WSM, Optimized block-wise non-local means.; ODCT3D, 3D oracle-based discrete cosine transforms (DCT) filter; PRINLM3D, 3D pre-filtered rotationally invariant nonlocal means filtering; rs-fMRI, resting-state functional MRI; sMRI, structural MRI; DTI, Diffusion tensor imaging; NN, Neural networks; BI, Bicubic interpolation.

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multilayer perceptron is an outstanding branch of deep learning and has been extensively used for object recognition and image segmentation [18]. CNN has shown excellent performance on feature extraction by conserving the local correlation and spatial invariance with convolutional filters, and has been widely used for feature extraction of brain images. As shown in Table 1, some new CNN based architectures have been proposed and shown excellent performance [15,19].

A typical CNN usually consists of multiple convolutional layers, max-pooling layers, and a full connection layer, where a local receptive field, weight sharing, and subsampling are employed to reduce the number of parameters to be optimized [20]. The convolution layer is often used to extract local features from different positions and shares the weights with sliding trainable convolutional kernels $k_{ij}^{(l)}$, which is the connection weight between the feature map $i$ from layer $l$-1 and feature map $j$ at layer $l$. The activation function $A_j^{(l)}$ of the $l$th layer is computed with only a spatially contiguous subset of $A_i^{(l-1)}$(the feature map $i$ of the preceding layer $l$-1) by convolving the kernels $k_{ij}^{(l)}$ as follows.

$$A_j^{(l)} = f\left(\sum_{i=1}^{M^{l-1}} A_i^{(l-1)} * k_{ij}^{(j)} + b_j^{(l)}\right) \tag{1}$$

where $M^{l-1}$ denotes the number of feature maps in the $(l-1)$th layer, the asterisk denotes a convolutional operator, $b_j^{(l)}$ is a bias parameter, and $f(\cdot)$ is a nonlinear activation function (e.g. Rectified linear units (ReLUs) [21–23]). The max-pooling layer follows the convolutional layer, and downsamples the feature map by selecting the maximum feature within overlapping or non-overlapping local neighborhoods [24]. For this layer, some variant methods have been proposed, e.g. deformation pooling [25] and the combination of max and average pooling [26]. The fully connected layer has full connections to all of the units in the previous layer, which transforms the previous feature maps into a one-dimensional feature vector. To avoid optimizing the large number of parameters in this process, ResNet [27] and GoogLeNet [28] using the global average pooling layer instead of the fully connected layer. This layer is generally used as the last layer of the deep neural networks and the output is used for classification or prediction [29].

### 2.2. Autoencoder

Autoencoder is an unsupervised learning approach that is widely adopted in feature extraction and feature representation of high-dimensional data, and it is often used together with other deep learning approaches for prediction or classification [38,39]. Autoencoder has been used in the analysis of brain MRIs, such as detection of brain lesions and identification of abnormal brain structural patterns in neuropsychiatric disorders [40–42]. Autoencoder is a symmetrical neural network that includes encoding and decoding, and the process can be computed as follows.

$$h = f_\theta(x) = s_e(Wx + b) \tag{2}$$

$$r = g_\theta(h) = s_d(W^{'}h + d) \tag{3}$$

where $h$ is a latent variable, $r$ is the output of reconstructed data from the latent space, $f_\theta$and$g_\theta$ are respectively the encoder and the decoder, $s_e$ and $s_d$ are non-linear activation functions. The objective of auto-encoder is to learn the latent or compressed representation of inputs by minimizing the reconstruction error between inputs and outputs. Because of the simple and shallow structure, the conventional auto-encoder has limited representational ability. Some deep auto-encoders have been proposed to improve the generalization and representation ability by increasing the hidden units or noise, such as the stack auto-encoder (SAE) and the denoising autoencoder (DAE) [43].

### 2.3. Recurrent neural network

Recurrent neural network (RNN) is a special feedforward neural network that conserves a state that can represent information from an arbitrarily long context window. RNN has been widely adopted with sequential data, such as video, text, and audio [44]. The functional magnetic resonance images (fMRIs) can be seen as a series of dynamic images, and RNN has been widely used for some brain functional analysis tasks based on fMRIs, e.g. decoding the brain signal and diagnosing disorders [45,46].

The architecture of RNNs contains some recurrent layers, where each recurrent layer consists of recurrent cells whose states are affected by both past states and current inputs with feedback connections. The recurrent cells can be organized into various architectures to form different RNNs, where the single standard recurrent sigma cell can be written as below.

$$h_t = \sigma(W_h h_{t-1} + W_x x_t + b) \tag{4}$$

$$y_t = W_{hy} h_t \tag{5}$$

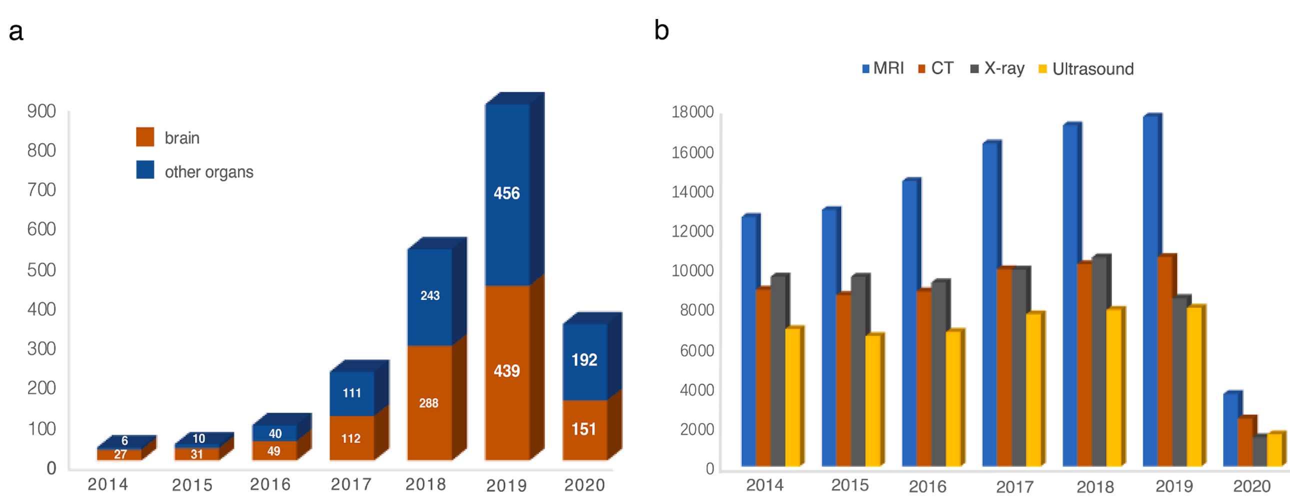


**Fig. 1. Statistics of papers published on MRI and deep learning for brain MRIs in the past 7 years.** a. The number of publications per year retrieved from the web of science with keywords of "deep learning" and "MRI" from 2014 to 2020. (Queried: May 16th, 2020), the color of orange denotes brain MRIs while blue denotes MRIs for other organs. b. The number of publications of different medical images (MRI, CT, X-ray, Ultrasound) from the web of science from 2014 to 2020 (Queried: May 16th, 2020). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

where $h_{t-1}$ is the previous layer output, and $x_t$ denote the input of the cell at time t, $y_t$ is the output of the cell at time t, $w_h$ is the weight of $h_{t-1}$, $W_x$ is the weights from the input x to the hidden layer, $W_{hy}$ is the weight from the hidden layer to output,$b$ is the bias, $\sigma(\cdot)$ is the activation function. The conventional recurrent neural network consists of the standard recurrent cell is unable to handle long-term dependencies, and then some new RNNs have appeared, such as the long short term memory networks (LSTM) and Bidirectional LSTM [47,48].

### 2.4. Generative adversarial network

Like the auto-encoder, the generative adversarial network (GAN) is also a generative model but is more complicated than auto-encoder [49]. GAN has been widely applied in image or video analysis, e.g. increase image resolution and generate realistic photographs [50,51]. For brain MRIs, GAN was often used for reconstruction, augmentation, or registration of brain images, e.g. MRI - CT deformable image registration [52] and synthetic multi-sequence brain MRIs [53].

GAN usually adopts two networks, i.e. generative (G) network and discriminative (D) network, to learn a representative distribution from the training data. The generative network generates candidates from the input noisy variables $p_z(z)$ while the discriminative network evaluates the difference between those candidates and the real data $p_{data}(x)$, and the objective function can be formulated as below.

$$\min_{G}\max_{D} V(D,G) = \mathrm{E}_{x\sim p_{data}(x)}[log(D(x))] + \mathrm{E}_{z\sim p_z(z)}[log(1-D(G(z)))] \quad (6)$$

where $G(z)$represents the data generated by G network and $D(x)$ is the probability that D network judges whether x is true. The training of the original GAN requires big data and generates data with the same distribution as the real data. Later, Wasserstein GAN (WGAN) [54] was developed to improve both stability and diversity of GAN, and Condition GAN [55] and CycleGANs [56] were developed that were able to convert one image from one domain to another domain (e.g. from 3 T MRI to 7 T MRI).

### 2.5. Optimizing the parameters and architectures of deep neural networks

In the deep neural networks, the parameters and architecture of the model determine how well your model performs on the task. Updating and optimizing model parameters have been an ongoing issue in the training of deep neural network models. The optimization process often consists of two steps, the first is to set the optimization problem and the second is to iteratively update the parameters to be optimized. For a certain task involving either classification or regression, the optimization problem can be represented by different cost functions (e.g. Mean Square error or Cross-entropy). The parameters can be updated with different gradient descent algorithm, e.g. the Nesterov accelerated gradient (NAG) method [57] and the Adaptive Gradient (Adagrad) method [58].

With deep learning getting popular for more challenging tasks, the architectures of neural networks have become more and more complicated, which makes it harder to design by hand. For this purpose, a few general principles and optimization ideas for scaling up convolution network in an efficient way have been proposed [59]. For example, Miikkulainen et al. [60] developed an approach for automatic designing deep neural networks based on the neuro evolution technique of NeuroEvolution of Augmenting Topologies (NEAT). Haber et al. [61] proposed a new forward propagation method inspired by the System of Ordinary Differential Equations (ODEs) that overcame the problem of stability for deep architectures. Some other approaches have been proposed for optimization of the network architectures inspired by brain physiological mechanisms, such as the mechanism of visual attention [62,63].

**Table 1**
Popular **CNN** architectures used in brain MR image analysis.

| Dimension | Architecture | Modalities | Method name, Application | Reference |
|---|---|---|---|---|
| 2D | 2D CNN | T1, T2-FLAIR | Segmentation of WM hyperintensities | [30] |
| | 2D FCN | MRI (BTFE sequence) | Automatic fetal brain extraction | [31] |
| | 2D U-Net | T1, T1c, T2, T2-FLAIR. | Brain tumor detection and segmentation | [16] |
| 3D | 3D CNN | T1, T2, proton density (PD) | Brain developmental age estimation (BDAE) | [32] |
| | 3D-CNN (VGGNet) | T1 | Alzheimer's disease classification | [33] |
| | 3D FCN | T1 | SLANT, whole-brain segmentation | [34] |
| | 3D U-net | T1, T2, T1c, T2-FLAIR. | S3D-Unet, Brain tumor segmentation | [35] |
| | 3D V-net | T1, T2, T1c, T2-FLAIR | Brain tumor segmentation | [36] |
| | Cascaded CNN | T1, T2, T1c, T2-FLAIR | ITCN, Segmentation of brain gliomas | [37] |

## 3. Open brain MRI datasets and deep learning models

With more and more deep learning methods developed for brain MR image analysis, it is becoming a challenge to choose the right model for

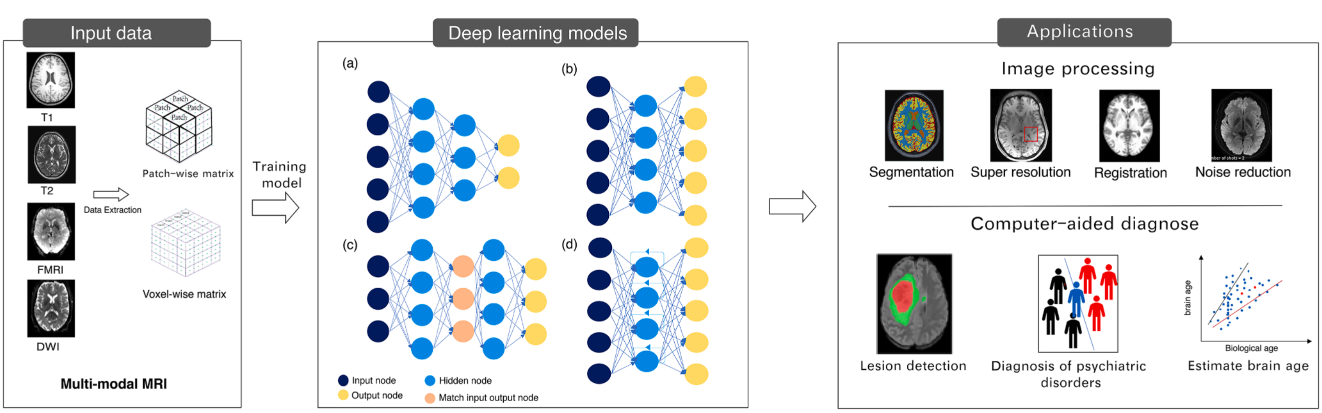


**Fig. 2.** The workflow of deep learning for brain MR images analysis. The input takes multi-modal brain MR images, and the voxel/patch wise matrices are extracted from the images, which are in turn used as the input of deep neural networks with the most four popular architectures, (a) Convolutional neural network, (b) Autoencoder, (c) Generative adversarial network, (d) Recurrent Neural Network. The output of the deep neural networks can achieve the brain MR image processing and analysis.

the right data. In this section, we summarize the popular open databases (see Table 2) and deep learning models or toolbox (see Table 3).

## 4. The application of deep learning in brain MRIs

When analyzing the brain MR images, the deep learning approaches were widely used for image pre-processing, e.g. image segmentation and registration, and computer-aided diagnosis. In the following parts, we will show how deep learning is used for the analysis of brain MRIs.

### *4.1. Image preprocessing*

#### *4.1.1. Restoration and reconstruction of brain MR images*

When analyzing brain MR images, the high quality and resolution images with sufficient details are generally preferred [75]. For this, image restoration (denoising and artifact removing) and reconstruction (super-resolution (SR)) are the two mostly used techniques. The image restoration technique reduces noise and artifacts using self-similarity and sparseness based methods, while image reconstruction improves the trade-off between resolution and signal-to-noise ratio (SNR) and reconstructs SR images from low-resolution images [76,77].

Recently, the deep learning approaches have been widely adopted in this area, where most of the approaches are based on three common deep learning architectures, including single/multi-scale CNN, autoencoder, and GAN. For brain MR image restoration, Jiang et al. [78] designed multi-channel denoising convolutional neural networks (MCDnCNNs) with 3D residual networks as the underlying framework and developed two training strategies to denoise MR images, and showed better robust denoising performance compared with four state-of-the-art denoising methods (NLM, WSM, ODCT3D, PRINLM3D). The single-CNN (SCNN) network was proposed for multiple sequences, such as T1w, T2w, and FLAIR [79]. Bermudez et al. developed an autoencoder with skip connections for T1-weighted (T1w) imaging denoising, and outperformed the FSL SUSAN denoising software based on the peak signal-to-noise ratio (PSNR) [42]. Muckley et al. [80] proposed a U-Net based method for artifact removal when analyzing diffusion-weighted imaging data, and suppressed the Gibbs-ringing artifacts with knowledge transferred from simulated MRI from ImageNet. Seo et al. [81] developed new artificial neural networks (ANNs) to suppress metal artifact of MR images by slice the encoding for metal artifact correction (SEMAC), and accelerated SEMAC MRI while suppressing the production of metal artifacts.

The SR MR images can be grouped into two categories, including single-contrast SR (no reference information) and multi-contrast SR (used another modality as reference information). For single-contrast SR, Chen et al. [82] designed a new network architecture, 3D densely connected super-resolution networks (DCSRN), to reconstruct high-resolution (HR) features of brain MR images inspired by the densely connected network (DenseNet) with skip connections. DCSRN outperforms other popular interpolation and deep learning methods, e.g. NN, BI, 2D FSRCNN, and 3DFSRCNN. With different up-sampling methods to improve the resolution of the input image, a 3D SRGAN model was proposed to get the brain SR MRIs [59]. For multi-contrast SR, Zeng et al. [60] trained a CNNs model that was able to generate single-contrast SR and multi-contrast SR brain MRI images simultaneously. A multi-scale training approach was proposed to learn multiple isotropic scale factors for SR MRIs based on CNNs, where the HR reference image of the same subject can guide the process of low resolution (LR) image reconstruction [12]. DeepVolume [83], a two-step deep learning architecture for SR MRI, contained a brain structure-aware network (based on 3D U-net) and spatial connection-aware network (based on LSTM), and got the brain structure from thick-section MR images and adjusted the reconstruction results layer by layer. The reconstruction of the brain MR image showed significantly structural similarity (GM, WM, CSF) with thin-section MR images.

**Table 2**
A list of open brain MRI datasets.

| Dataset name | Summary | URL |
|---|---|---|
| OpenNeuro | An open platform for sharing neuroimaging data under the public domain license. Contains brain images from 168 studies (4,718 participants) with various imaging modalities and acquisition protocols. | https://openneuro.org/ |
| UK Biobank | Health data from half a million participants. Contains MRI images (T1 and fMRI) from more than 40,000 participants. | http://www.ukbiobank.ac.uk/ |
| TCIA | The cancer imaging archive hosts a large archive of medical images of cancer accessible for public download. currently contains images from 14.355 patients across 77 collections. | http://www.cancerimagingarchive.net/ |
| ADNI | The Alzheimer's disease neuroimaging initiative. Contains many images in different modalities, such as T1, FLAIR, DTI, ASL, and fMRI data, about 2,000 participants. (controls, early MCI, MCI, late MCI, AD) | http://adni.loni.usc.edu/ |
| HCP | Healthy people data focus on the study the adulthood, lifespan, and human disease. | https://www.humanconnectome.org/ |
| ABCD | The largest long-term study of brain development and child health in the United States. consisting of a Coordinating Center, a Data Informatics and Analysis Center, that will recruit approximately 10,000 children ages 9–10 and following them into early adulthood | ABCDStudy.org |
| INDI | An international Neuroimaging data-share plan, include many projects, include 1000 functional connectome, autism related project of ABID and ADHD200(N = 900), some healthy data (SALD (N = 500), NKI-Rockland (N = 973)), and Parkinson's Disease Datasets (N = 27) | http://fcon_1000.projects.nitrc.org/ |
| IXI | A brain development dataset, includes 600 healthy subjects, age range from 19 to 87. | https://brain-development.org/ixi-dataset/ |
| PPMI | The Parkinson's Progression Markers Initiative (PPMI) is a | https://www.ppmi-info.org/ |

(*continued on next page*)

**Table 2** (*continued*)

| Dataset name | Summary | URL |
|---|---|---|
| | Parkinson's disease brain MR image (T1 and DTI) dataset, include 683 participants. | |
| BraTS | A dataset for brain tumor segmentation | http://braintumorsegmentation.org/ |
| IMAGEN | A database collected and processed by the Imagen consortium form 2000 adolescents and their parent, Include the neuropsychological assessments, medical questionnaires, MR neuroimaging (T1 and fMRI) and genomics data.. | https://imageneurope.com/resources/imagendataset/IMAGEN |

#### 4.1.2. Segmentation of brain MR images

The accurate segmentation of brain images is important for the quantitative assessment of many neurological diseases and conditions, and plays an important role in the downstream analyses, such as the mechanism of brain development, maturing, and aging [84–86]. The segmentation tasks can be generally divided into two categories, including brain extraction and segmentation of the brain tissue or whole brain structure.

There is much effort has been devoted to developing deep learning approaches for MRI segmentation. For example, Isensee et al.[87] proposed an algorithm named as HD-BET based on the 3D U-net architecture, which outperformed six commonly used tools (i.e. BET [88], BEaST [89], BSE [90], ROBEX [91], and MONSTR [92]) for multi-sequence MRIs (T1-weight, contrast-enhanced T1 weighted, FLAIR, and T2-weight), especially in the presence of pathology or treatment-induced tissue alterations. The input of this architecture is a large patch size ($128 \times 128 \times 128$), which makes it computational expensive due to the large size of MRIs. Therefore, the full convolutional layers or arbitrary-sized patches obtained by splitting the image with seed-based methods have been used as the input for the 3D neural network, and the prediction results of the network correspond to every patch rather than every subject [93–95]. To further improve the performance of patch-wise architecture, Moeskops et al.[96] developed a multi-scale 3D CNN architecture that makes full use of multi-scale information about each voxel by using multiple patch sizes and convolution kernels, and worked well in the segmentation of eight brain tissues with the Dice [97] ratio range from 0.82 to 0.91 on five different data sets (subject from preterm infants to elder). Wachinger et al. [98] proposed a 3D multi-task network architecture (DeepNAT) that adopted the multi-task learning method to predict the voxel label by integrating center label of the patch and labels in a small neighborhood. DeepNAT added spectral brain coordinates as the location information that improved the segmentation accuracy, and accomplishes brain extraction and segmentation of brain structures with two multi-task CNN hierarchically. DeepNAT showed promising segmentation results on 25 brain structures with a median Dice ratio of 0.90.

Since the single-modal imaging features might not fully encompass all structural information of the brain, the images of different modalities and multiple levels of contextual features can complement with each other and in turn enhance the discrimination capability of the generated features [99]. For this, Chen et al. [100] designed a deep voxel-wise residual network (VoxResNet) based on a residual block architecture with a shallower depth, which concatenated multi-modal images (T1, T1 contrast-enhanced, and T2-FLAIR MRI) as input for VoxResNet, and in the first layer combined the multi-modal information by concatenating the weights from each modality. VoxResNet uses the auto-context algorithm to integrate high-level context information to train a new classifier called Auto-context VoxResNet, and the model was used to segment the brain into three tissues with Dice ratios as 0.89(GM), 0.91 (WM) and 0.83(CSF), respectively.

#### 4.1.3. Registration of brain MR images

The registration of brain MR images seeks to find an optimal spatial transformation that achieves normalization of the input images or makes the output image contain more complementary and multiparametric tissue information. The registration of brain MR images can be used in many cases, such as aligning multiple individual MR images to a standard space (e.g. Montreal Neurological Institute (MNI) space) [20]. Among traditional registration methods, they can be divided into rigid (SPM [101]), affine (ANTs [102]) and deformable (optical flow [103], Demons [104]) categories from the perspective of deformation models. According to the input MR images, the registration methods can group into intra vs. inter-modality or intra vs. inter-subject.

Since deep learning was used for brain MR image registration, it has achieved state-of-the-art performances in many applications [105,106]. In general, most of the deep learning registration methods can divided into supervised and unsupervised methods depends on the training process. Chee et al. [107] proposed a self-supervised learning network

**Table 3**
A brief list of deep learning models or tools for brain MRIs.

| Reference | Summary | URL |
|---|---|---|
| [64] | A framework based on 3D-GAN for MR image super resolution | https://github.com/imatge-upc/3D-GAN-superresolution |
| [65] | DLTK, an open-source library that makes deep learning on medical images easier | https://github.com/DLTK/DLTK |
| [66] | DeepMedic, a software for brain lesion segmentation based on a multi-scale 3D Deep Convolutional Neural Network coupled with a 3D fully connected conditional random field | https://github.com/Kamnitsask/deepmedic |
| [67] | GANCS, a framework to compressed sensing MRI based on deep generative adversarial network | https://github.com/gongenhao/GANCS |
| [68] | H-CNN, the hierarchical fully convolutional network for structural MRI-based Brain disorder diagnosis | https://github.com/mxliu/HFCN_TPAMI |
| [69] | U-net++, a new general-purpose image segmentation architecture for more accurate MRI segmentation based on U-net | https://github.com/MrGiovanni/UNetPlusPlus |
| [70] | NiftyNet, an open-source convolutional neural networks platform for medical image analysis and image-guided therapy | https://niftynet.io/ |
| [71] | V-net, a fully convolutional network for brain MRI segmentation | https://github.com/mattmacy/vnet.pytorch |
| [72] | A 3D MRI brain tumor segmentation model that using autoencoder regularization | https://github.com/IAmSuyogJadhav/3d-mri-brain-tumor-segmentation-using-autoencoder-regularization |
| [73] | A novel feature extractor for multimodal data | https://github.com/simeon-spasov/MCI |
| [74] | A brain age prediction framework based on residual neural network | https://github.com/benniatli/BrainAgePredictionResNet |

architecture, named as affine image registration network (AIRNet), and achieved registration between different modalities of brain MRIs. AIRNet used the self-supervised learning method to generate a synthetic dataset from the abundance of cheap unlabelled data for training, and updated the transformation parameters (a twelve-dimensional vector) between the input image and reference image by back-propagation, then achieve the one-short registration by warping the input images used the transformation parameters. Cao et al. [108] used a deep regression network to learn the association and deformations between any pair of 3D representative patches, and utilized the local similarity between inputted image patches to guide the learning process. This method outperforms SyN [109] and Demons-based [104] registration methods on some brain MR image dataset (e.g. IXI, ADNI). Moreover, to fully learn the similarity metric features other than ground truth to enhance the performance of the model, some dual supervised methods were adopted. For example, Fu et al. [10] designed a hierarchical dual-supervised model, a U-Net [15] based regression model, to predict the deformation field for 3D brain MRI deformable registration. They trained the model by leveraging both the similarity of deformation field between the predicted images and ground truth and the difference between the fixed images and the deformable subject image, and modified the U-net architecture with gap-filling by inserting convolutional layers after the U-type ends.

The above supervised methods require ground truth as reference, whereas acquiring reliable ground truth remains a challenge. To overcome this problem, some generator-based models have been developed. Fan et al. [110] proposed an unsupervised adversarial similarity network that achieves mono-modal and multi-modal registration of brain MR Images. They designed the U-net based generator of registration network and the CNN based discriminator of discrimination network, and then trained the registration network to learn the deformation field by maximizing image similarity and used the discrimination network to judge whether the registration of two images as well.

### 4.2. Deep learning for computer-aided diagnosis

#### 4.2.1. Lesion detection

Lesion detection is the detection or localization of abnormal or suspicious areas in brain structural images, which is important in clinical practice. Accurately detecting the lesion is very important for the diagnosis and prognosis of diseases. For brain lesion detection, deep learning methods have been used for brain tumors, multiple sclerosis, and cerebral microbleeds (CMBs) detection, and most of the methods are based on the CNN architecture.

To detect the brain tumor, Chen et al. [86] proposed a novel deep convolutional symmetric neural network (DCSNN) to automatically segment brain gliomas, and extracted the features of the image and the left–right flip image with CNN. Then, those extracted features were used to calculate the asymmetrical location information with similarity metric as the spatially symmetric features inputted into the network. Furthermore, to improve the CNN performance, the 2D fully convolutional neural networks (FCNNs) and conditional random fields (CRFs) were integrated for brain tumor segmentation with multi-modal MRIs [111], and the FCNNs predicted result and image slice information (pixel's intensity and position information) were used as input to optimize appearance and spatial consistency of the segmentation results with Dice ratio over 0.85.

The white matter lesions are an important symptom for detecting changes in multiple sclerosis [112,113]. Mckinley et al. [114] presented a new CNN-based method to quickly and reliably segment multimodal MRIs (T1, T2, and FLAIR) into lesion categories and normal GM and WM structures. They labeled healthy appearance structures while predicting lesion structure, and improved the discriminative accuracy between positives and negatives. Later, they also proposed a U-net based method, named as DeepSCAN, for detecting lesion change in longitudinal MRIs in multiple sclerosis [115]. DeepSCAN trained the model with two loss functions, where one was a label-flip loss [116] that used the different probability between prediction label and ground truth to supervise label loss in regions of high uncertainty, and the other was a focal loss [117]. DeepSCAN shows good performance (AUC ranged from 0.75 to 0.91) on three datasets.

The CMBs are neuroimaging biomarkers of stroke risk and play an important role in diagnosing dementia and traumatic brain injury (TBI) [14,118–120]. To automatically detect the CMBs, Chen et al. developed a 3D residual network that reduces the false positives for CMB detection and uses 7 T susceptibility-weighted images (SWI) acquired as input, which led to the sensitivity of 0.95 and precision of 0.72 with the number of false positives (FPs) per scan was 11.6. Since a large number of parameters need to be optimized, Liu et al. [121] presented a CNN based model and applied it to SWI and phase images for automatic CMB detection with a 3D fast radial symmetry transform [122], and reduced false positives with the residual neural network and showed good performance with sensitivity of 0.96 and precision of 0.71 with 1.6 false positives per case for medium and large lesions detection.

#### 4.2.2. Diagnosis of psychiatric and neurodegenerative disorders

Accurate diagnosis of psychiatric and neurodegenerative disorders in clinical practice is still a big challenge [123], due to their complex clinical manifestations and uncertain pathogenesis. Brain MR images is an effective way to diagnose psychiatric and neurodegenerative disorders by detecting structure or connectivity alteration, such as the GM atrophy in Alzheimer's disease [124] and the abnormal connectivity of cortico-cerebellar-striatal-thalamic loop in schizophrenia [125]. The deep learning methods have been used for diagnosis or prediction tasks, e.g. patients classification [126] and prediction of disorders progression [127]. Here, we mainly show the application of deep learning to Schizophrenia, Alzheimer's disease (AD), and Parkinson's disease (PD).

*4.2.2.1. Schizophrenia.* Schizophrenia (SZ) is a serious psychiatric disorder that can cause impairments involved in thinking (cognition), behavior, and emotions. Qureshi et al. [128] designed a 3D-CNN based classifier for distinguishing schizophrenic patients from normal controls (NC) with an accuracy of 0.98 They utilized independent component analysis (ICA) to semi-automatically extract the more meaningful features from the rs-fMRI as the input to the network, and adopted 3D CNN for classification. To overcome the problem of insufficient samples from a single site for training, Zeng et al. [129] proposed a deep autoencoder network with sparsity constraint (DANS) that learned reliable connectomes patterns from functional MRI samples collected from multi-sites, where the multi-site data were used to pre-train the model to learn the discriminative features and sparse weights. Subsequently, a linear support vector machine (SVM) was trained with the learned features and weights for diagnosing schizophrenia with an accuracy of 0.81. By comparing deep learning models with traditional machine learning methods (e.g. SVM, logistic regression, random forest), it has been found that the deep learning models provided a higher accuracy in diagnosing schizophrenia [126], and used together with other algorithms (e.g. canonical correlation analysis (CCA) [130]) or rules (e.g. Bayes' rule [131]) may help improve the classification accuracy of schizophrenia.

*4.2.2.2. Alzheimer's disease.* Alzheimer's disease is an irreversible, progressive neurodegenerative disorder caused by brain degeneration, usually in older adults. The tasks for diagnosing Alzheimer's disease can divide into two steps, one is the diagnostic classification (normal vs AD) and the other is the prediction of mild cognitive impairment (MCI) to AD. Lian et al. [132] proposed a hierarchical fully convolutional network (H-FCN) that extracted spatial structural patch level, region level and subject level from the whole-brain structural MRI, and merged the multi-scale features with the convolution layers for AD diagnosis and showed promising results on AD vs NC (accuracy = 0.90) and progressive MCI (pMCI) vs stable MCI (sMCI, accuracy = 0.81). To improve the efficiency and precision of diagnosing AD, multi-modal data have also been explored. For example, Spasov et al. [73] developed a parameter efficient 3D separable CNN architecture for the accurate prediction of MCI-to-AD conversion within 3 years with AUC of 0.93 and accuracy of 0.86. They designed a multi-modal feature extractor (sub-networks) to extract the feature representations from multi-modal data (structural MRI images, standard cognitive tests, demographic information, APOe4 genetic status data) for distinguishing pMCIs from sMCIs. Lee et al. [133] trained a multi-modal recurrent neural network for predicting the conversion from MCI to AD by using sequential data, including neuroimaging biomarkers (sMRI), longitudinal CSF, and cognitive performance biomarkers. A pre-trained model has been used to extract different scales features by SAE and a DNN was used for classification in the last step, and good performance has been reported with classification accuracy of 0.85 between AD and NC and prediction accuracy of 0.83 between pMCI and sMCI [134].

*4.2.2.3. Parkinson's disease.* Parkinson's disease is also a progressive neurodegenerative disorder with the first symptom of the problem of movement. Deep learning has been widely applied to diagnose PD with brain MR images [135]. For example, Esmaeilzadeh et al.[136] developed a voxel-based 3D CNN architecture for classification of PD from NC based on brain MRIs and personal information (i.e. age, gender) with the accuracy of 1.00. Sivaranjini et al.[137] classified PD from NC with the pre-trained 2D CNN architecture AlexNet by fine-tuning the later layers with T2 weighted MR brain images from PPMI [138]. Li et al.[139] proposed a stacked sparse auto-encoder encoder (SSAE) based feature encoding algorithm that can encode the longitudinal and multi-modal features (GM, WM, mean diffusivity) into meaningful feature representations, which can distinguish PD from NC with an accuracy of 0.96. An RNN has been trained to extract latent information from MRI and Dopamine Transporters (DaT) Scan data for prediction of PD [140].

#### *4.2.3. Brain age estimation*

The brain aging process is complex, increasing the risk of mortality and some neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [141,142]. Recently, estimating brain age with MRIs provides new ways to explore the brain aging process. Traditional machine learning approaches, e.g. Gaussian process regression [143] and support vector regression [144], have been used for brain age prediction based on multi-modality brain MRI features, such as thickness, GM and WM. The performance was generally assessed with mean absolute error (MSE) and the correlation between predicted age and chronological age, and the brain prediction age difference (brain-PAD) has been found associated with many neuropsychiatric diseases [145], e.g. epilepsy [146] and major depressive disorders [147].

However, the traditional methods only consider some of the structural or functional features, and do not take advantage of the spatial features of 3D MR images. To make full use of the information from brain MR images to improve the accuracy of predictions, some studies are using CNN to extract the image features instead of morphological or functional features. For example, Jonsson et al. [148] used 3D CNNs based on residual architecture to predict brain age based on T1 MRIs, and trained four 3D CNNs with different image types (registered T1, Jacobian map, GM, WM) generated by preprocessing the T1 MR images. The majority voting principle was used to integrate the network outputs to determine the final predicted brain age with good performance (MAE = 3.58, $r^2$=0.85). To further make full use information of each voxel. Li et al. [149] developed a method that used CNNs to learn comprehensive features from the fine-grained (voxel-wise) whole-brain functional connectivity (FC) by taking into account the individual difference of each voxel. A novel complex network model has been proposed to get the network-based feature (e.g. the strength that computed by the sum of all weights) to train the CNNs for predicting the brain age, which created a network by calculating the Pearson's correlation coefficient between two patches, and the mean MAE of 4.75 has been reported on five independent datasets [150].

## 5. Challenges and future perspectives

The deep learning techniques have shown a big success in brain MRI analysis, especially the convolutional neural networks that showed good performance in brain feature extraction, segmentation, and disease diagnosis. The deep learning methods also demonstrate good generalization when dealing with different MR image data types compared with traditional machine learning methods [9]. Despite the success of deep learning, there are still many challenges when analyzing brain MRIs [151]. In the following parts, we discuss the challenges facing deep learning from both data and model perspectives.

In principle, the deep learning methods are data-driven, which makes the performance of most models relies on the training datasets available. As for brain MR images, most of the datasets have small size with imbalance between samples due to the privacy protection and acquisition cost [152], especially for some brain disorder related MRIs. Another issue is the significant difference among datasets generated with different types of equipment and parameters, which makes it hard to compare and combine multiple datasets. Although some techniques have been developed to increase data size, e.g. data augmentation and image synthesis [153], they can only be used to certain data types and may increase noise or even change the distribution of data. For the diagnosis of disorders, the labeled images play important roles in the training procedure. However, MRIs with accurate annotations are not commonly available due to the expensive annotation cost. The lack of large, balanced, and labeled brain MRIs make it challenging to develop efficient deep learning approaches. For this, there are four potential alternative ways. Firstly, a pre-trained network based on large datasets is fine-tuned for a task-specific small-scale dataset. Secondly, different types of data can be fused to augment the data size. Thirdly, the deep learning models can be integrated with traditional machine learning approaches to improve the learning ability based on small data. Fourthly, the unsupervised learning techniques should be developed to automatically learn the potential features and rules from the data.

On the other hand, most of the deep learning models are black boxes, and only the input and output are clearly known. The good performance sometimes is very difficult to interpret, which makes it difficult for clinical diagnosis. In the future, the deep learning models with better interpretability will be preferred for brain MR image analysis.

## 6. Conclusion

In this survey, we introduced popular deep learning models and their application in the analysis of brain MRIs in recent years. Specifically, the applications of deep learning to MRI preprocessing, including denoising, SR, segmentation and registration, and diagnosis of psychiatric and neurodegenerative disorders were introduced. Furthermore, public MRI databases and popular deep learning tools/models were also presented, which will be useful for newcomers to the field. In addition, the main challenges facing deep learning in the analysis of brain MRIs were addressed, and future directions were also discussed.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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