ABSTRACT The rapid advancements in machine learning, graphics processing technologies and availability of medical imaging data has led to a rapid increase in use of machine learning models in the medical domain. This was exacerbated by the rapid advancements in convolutional neural network (CNN) based architectures, which were adopted by the medical imaging community to assist clinicians in disease diagnosis. Since the grand success of AlexNet in 2012, CNNs have been increasingly used in medical image analysis to improve the efficiency of human clinicians. In recent years, three-dimensional (3D) CNNs have been employed for analysis of medical images. In this paper, we trace the history of how the 3D CNN was developed from its machine learning roots, brief mathematical description of 3D CNN and the preprocessing steps required for medical images before feeding them to 3D CNNs. We review the significant research in the field of 3D medical imaging analysis using 3D CNNs (and its variants) in different medical areas such as classification, segmentation, detection, and localization. We conclude by discussing the challenges associated with the use of 3D CNNs in the medical imaging domain (and the use of deep learning models, in general) and possible future trends in the field.

INDEX TERMS CNN, Machine learning, 3D Deep Learning, 3D Medical Imaging, 3D Convolutional Neural Networks.
can be used to detect infection, cancers, traumatic injuries, and abnormalities in blood vessels and organs.

II. DEEP LEARNING BACKGROUND

Deep learning refers to artificial neural networks containing multiple interconnected layers of artificial neurons [18]. An artificial neuron by analogy to a biological neuron is something that takes multiple inputs, performs a simple computation, and produces an output. This simple computation has the form of a linear function of the inputs followed by a activation function (usually non-linear) denoted by \( f(.) \). Examples of some commonly used non-linear activation functions are the hyperbolic tangent (Tanh), sigmoid transformation and the rectified linear unit (ReLU) (gives a max of 0 and the input) [19]. Deep learning is essentially a reincarnation of the artificial neural network where we stack layer upon layer of artificial neurons. Using the outputs of the terminal layers built on the outputs of previous layers, one can start to describe arbitrarily complex patterns.

In a very short span of time, deep learning has become an alternative to several machine learning algorithms traditionally used in medical imaging. In order to understand the reasons behind the wide usage and success of deep learning in medical imaging applications, we searched for machine learning + medical in the title and abstract in PubMed publication database (As on 20th March 2020). We come across a quite predictable nice trend of using more and more similar data to different approaches (Fig. 1). On the other hand, if we do a similar query for deep learning + medical, and 3D deep learning + medical in the title and abstract, we see a different scenario. This basically signifies that there was not much work in the domain a few years ago and eventually there is fast rise in the number of publications related to deep learning. An exponential increase is being seen for deep learning in medical after the year 2015. In a very similar manner 3D deep learning is showing an exponential increase in the study for medical applications from year 2017.

The historical evidence and development phases of deep learning might be traced back to Walter Pitts and Warren McCulloch (1943). Further, this journey can be traced with some of the most important development phases such as continuous Back Propagation Model (1960), convolutional neural networks (1979), LSTM (long short-term memory) (1997), ImageNet (2009), AlexNet (2011) [20], [21]. In 2014, Google presented GoogleNet (Winner of ILSVRC 2014 challenge) [22] which uses the concept of inception in CNN. GoogleNet contains inception modules (Fig. 2) which surprisingly reduces the computational complexity of the network. Indeed, the new deal with deep learning is the strategy to generate the features within the network using convolutional operations at each individual layer inside the deep network. This network is referred to as a convolutional neural network [23]. Essentially, in CNN, features are generated within the network by convolving a kernel with the

input images. These features are generally in the form of shapes, curves, edges, etc.

A complete CNN comprises four basic components: 1) Local receptive field, 2) Sharing weights, 3) Pooling, and 4) Fully connected (FC) layers. Deep CNN architecture is constructed by stacking several convolutional layers and pooling layers and one or so fully connected layers at the end of the network. Suppose we have a layer of \( M \times M \) neurons followed by the convolutional layer \( \omega \) with filter size \( a \times b \). In order to compute the per-linearity input to \((i,j)\)'th unit in layer \( 'f' \), \( x_{i,j}^{f} \), we add up the weight contribution from the previous layer as follows:

\[
x_{i,j}^{f} = \sum_{a=0}^{n_{f}-1} \sum_{b=0}^{n_{f}-1} \omega_{a,b} x_{i+(a+b)}^{f'} + b_{i,j}
\] (1)
III. 3D CONVOLUTIONAL NEURAL NETWORK

1-D CNN extracts spectral features while 2-D CNN can extract only spatial features from the input data. On the other hand, 3D CNN can take advantages of both 1-D and 2-D CNN by extracting both spectral and spatial features simultaneously from input volume. These 3D CNN features could be very useful in analyzing the volumetric data in medical imaging. The mathematical formulation of 3D CNN is very similar to 2D CNN with one extra dimension added. A basic architecture of 3D CNN is shown in Fig. 3. Following sections will briefly discuss the mathematical background of 3D CNN.

**Convolutional Layer:** The basic definition, principle, and working equation of 3D CNN same as 1-D or 2-D CNN. We only add an extra dimension (depth) to the working equation of 2-D CNN. Suppose we have a layer of $M \times M \times D$ neurons followed by the convolutional layer $\omega$ with filter size $a \times b \times c$. In order to compute the per-nonlinearity input to $(i, j, k)^{th}$ unit in layer $\ell'$, $x_{i,j,k}^{\ell'}$, we add up the weight contribution from the previous layer as follows:

$$x_{i,j,k}^{\ell'} = \sum_{a=0}^{n_a-1} \sum_{b=0}^{n_b-1} \sum_{c=0}^{n_c-1} \omega_{a,b,c} x_{(i+a)(j+b)(k+c)}^{\ell} + b_{i,j,k}$$

**Pooling Layer:** Each convolutional layer in 3D CNN may contain a pooling layer. Pooling layer simply takes small voxels (rectangular boxes in case of 2-D CNN) and produces a single output to the input of the next layer using taking the average or maximum of the input sample.

In backward pass, the CNN adjusted its weights and parameters according to the output by calculating the error by means of some loss functions, $e$ (other names are cost function and error function) and back-propagating the error with some rules towards the input. The loss is calculated by taking the partial derivative of $e$ w.r.t. the output of each neuron in that layer such as $\frac{\partial e}{\partial y_{i,j,k}^{\ell'}}$ for the output, $y_{i,j,k}^{\ell'}$ of $(i,j,k)^{th}$ unit in layer $'\ell'$. Chain rule allow us to write the add up the contribution of each variable as follows:

$$\frac{\partial e}{\partial x_{i,j,k}^{\ell'}} = \frac{\partial e}{\partial y_{i,j,k}^{\ell'}} \frac{\partial f(x_{i,j,k}^{\ell'})}{\partial x_{i,j,k}^{\ell'}} = \frac{\partial e}{\partial y_{i,j,k}^{\ell'}} f'(x_{i,j,k}^{\ell'})$$

Weights in the previous convolutional layer can be updated by backpropagating the error to the previous layer according to the following equation:

$$\frac{\partial e}{\partial y_{i,j,k}^{\ell-1}} = \sum_{a=0}^{n_a-1} \sum_{b=0}^{n_b-1} \sum_{c=0}^{n_c-1} \frac{\partial e}{\partial y_{i,j,k}^{\ell'}} \frac{\partial x_{i,j,k}^{\ell}}{\partial y_{i,j,k}^{\ell'}}$$

$$= \sum_{a=0}^{n_a-1} \sum_{b=0}^{n_b-1} \sum_{c=0}^{n_c-1} \omega_{a,b,c}$$

Eq. (6) simply allow us to calculate the error for the previous layer. Also, above eq. makes sense for the only those points which are $m$ times away from each side of the input data. This situation can be avoided by simply adding the zero padding to the end of each side of the input volume.

IV. 3D MEDICAL IMAGING PRE-PROCESSING

The preprocessing of the image dataset before feeding the CNN or other classifiers is important for all types of imaging modalities. However, in particular, it is much more crucial for 3D medical imaging as the whole volume has to be fed to the 3D CNN. Several necessary preprocessing steps for the medical imaging scans are necessary before feeding the data to the deep neural network model, such as 1) artifacts removing, 2) normalization, 3) slice timing correction (STC), 4) Image registration, and 5) bias field correction. Although all the steps through 1) to 5) are necessary for reliable results, it becomes extremely important to perform STC and image registration in the case of 3D medical images. The performance of the classifier is highly dependent on these two steps in 3D CNN. We briefly discuss the above pre-processing steps.

A. REMOVING ARTIFACTS

The first part of any preprocessing pipeline is the removal of artifacts. Removal of extra-cerebral tissues is highly recommended before analyzing the T1 or T2 weighted MRI, and DTI modalities for brain images. fMRI data often contains transient spikes artifacts or is slowed over drift time. Thus, the principal component analysis technique can be used to look at
these spike related artifacts [3], [24], [25]. Before feeding the data for preprocessing to an automated pipeline, a manual check is also advisable. For example, if the input T1 anatomical data is large in size, FSL BET command will not perform proper brain region extraction (Fig. 4) and if we use images with artifacts for the popular fMRI preprocessing tool fMRIPrep [26], it fails as well. Therefore, to remove these extra neck tissue, we should perform other necessary steps for proper preprocessing.

B. NORMALIZATION

The brain and other body parts for imaging of every person can vary in shape and size. Hence it is advisable to normalize brain scans before further processing. [4], [27]–[30]. Due to the characteristics of MRI, essentially, the same scanning device can have different intensities even in the same medical patient's images. Since scanning of the patient may be performed in different light conditioning, intensity normalization also plays an important role in the performance of 3D CNN. Additionally, typically with CNN, each input channel (i.e. sequence) is normalized to have zero mean and unit variance within the training set. Parameter normalization within the CNN also affects the CNN performance.

C. SLICE TIME CORRECTION

In creating the volumetric representation of the brain, we often sample several slices in the brain during each individual repetition time (TR). However, each slice is typically sampled at slightly different time points as we acquire them sequentially [31], [32]. Hence, even though the 3D brain volume is being scanned at a single time point, it also may be possible that the top of the brain volume might be sampled later (e.g. one or two seconds) than the bottom. This is the key problem which needs correction before any other analysis like classification, or segmentation.

In this regard, STC is frequently employed for adjusting the temporal misalignment and is widely utilized by a range of software such as SPM and FSL [33]. Several types of techniques have been proposed based on data interpolation methods for STC, including cubic spline, linear, and CNC interpolation [34]. In general, the STC methods based on interpolation techniques can be grouped as scene-based and object-based. In the scene-based approach, the interpolated pixel intensity is revealed by the pixel intensity of a slice. Although the interpolation techniques are sub-standard, they are relatively simple, intuitive, and easy to implement. On the other hand, the object-based methods have much better accuracy and are reliable but are computationally expensive. Subsequently, cubic spline and other polynomials were also found in medical image interpolation. Essentially, all these strategies perform strength averaging of the neighboring pixels without forming any feature deformation. Therefore, the resultant in-between pieces have blurring negative effects within the object boundary. Cubic interpolation is the standard technique selected in BrainVoyager [35] software.

D. IMAGE REGISTRATION

Medical imaging is increasingly multimodal. For instance, when the images of the same patient from CT, MRI-T1, and T2 are considered, each of the modalities detects different features. In medical imaging, a situation may be expected where multiple images are acquired with a different
orientation. Here, it becomes necessary to match the images by visual comparison [36]. This gives us an analytical problem where we can automate the alignment or registration in the dataset in which abnormalities are present. This allows us to identify prominent parts of the images for further review. T-1 and T-2 MRI show different structure of the same brain data. Also, for different image acquisition resolution, two images will have different sampling grids. Therefore, if there is a need to overlay and feeding these images to 3D CNN, alignment [37]–[39] of these images is a must.

E. BIAS FIELD CORRECTION

MRI images are influenced through bias field distortion, which usually causes the intensity to fluctuate [40], [41]. Bias field is an unwanted artifact which usually appears due to improper image acquisition practice as well as certain properties of the subject under imaging. These artifacts are characterized by smooth variations of intensities all over the image.

V. APPLICATIONS IN 3D MEDICAL IMAGING

A. SEGMENTATION

For several years, machine learning and artificial algorithms have been facilitating radiologists in the segmentation and assessment of medical images such as breast cancer mammograms, brain tumor, lesion, brain hemorrhage, etc. The segmentation operation greatly helps expert radiologists in quantitative assessment and further planning of treatment methods as necessary. Several researchers have contributed to the use of 3D CNN in medical image segmentation. Here, we focus on the most important related work of medical image segmentation using 3D CNN.

Brain tumor/lesion/substructures: Lesion segmentation is probably the most challenging task in medical imaging because lesions are rather small in most of the cases. Also, there are considerable variations in their sizes in different scans which can create data imbalance issue. In this regard, recognizable work is Deep Medic [42], which was also the winner of the ISLES 2015 competition. In DeepMedic, a 3D CNN architecture has been introduced for automatic brain lesion segmentation, which gives a state-of-the-art performance on 3D volumetric brain scans. The multiresolution approach has been utilized to include the local as well as the spatial contextual information. The network gives a very attractive 3D map of where the network believes the lesions are located. It was implemented on datasets where patients suffered from traumatic brain injuries due to accidents. DeepMedic was also shown to work well for classification and detection problems in cases of brain tumor. After this, the work has been extended by Kamnitsas et al. [43] for BRATS 2016 challenge, where the authors exploit the advantages of residual connections in 3D CNN. The results were impressive and were in the top 20 teams with median Dice scores of 0.898 (whole tumor, WT), 0.75 (tumor core, TC) and 0.72 (enhancing core, EC). Medical imaging field often suffers from the class imbalance problem. In this context, Zhou et al. [44] proposed 3D CNN (3D variant of FusionNet) for brain tumor segmentation on BRATS 2018 challenge. The authors split the multiclass tumor segmentation problem into three separate segmentation tasks for the deep 3D CNN model i.e. i) Coarse segmentation for whole tumor, ii) Refined segmentation for Wavelet transform(WT) and intra class tumor, and iii) precise segmentation for brain tumour. Their model was ranked first for BRATS 2015 dataset and third (among 64 teams) on BRATS 2017 validation dataset. Some important developments in 3D CNN for Brain tumor/Lesion segmentation applications on BRAST Challenges are summarized in Table I.

U-Net Shows very good performance in the segmentation of 2D biomedical images [45]. In accordance with DeepMedic, Casamitjana et al. [46] proposed a 3D CNN to process the entire 3D volume in a single pass in making predictions. They make use of up-sampling layers which in turn increase the effective batch size without any increase in memory space or any extra burden of computational complexity. However, this network was not too deep as there was a single pooling after the convolution layer. Therefore, this network was not able to analyze the network at multiscale.

As we know that 2D convolution does not fully exploit the spatial information of medical volumetric data while 3D CNN suffers from computational complexity and computational memory issues. To solve these issues, Chen et al. [47] proposed a separable 3D U-Net for brain tumor segmentation. On BRATS 2018 challenge dataset, they achieved Dice scores of 0.749 (EC), 0.893 (WT) and 0.830 (TC). Kayalıbay et al. [48] presented 3D U-Net like architecture for brain tumor segmentation using the 2017 challenge. The authors introduce some nonlinearity in traditional U-Net architecture by inserting residual blocks during up-sampling, hence, it facilitates gradients to flow easily. The proposed architecture also intrinsically handles the class imbalance problem due to use of Jaccard loss function. However, the proposed architecture was quite computational complex as they used large receptive field. Isensee et al. [49] Proposed a 3D U-Net architecture which consists of a perspective collection pathway for brain tumor segmentation. The strategy encodes progressively abstract interpretations of the input as we move deeper, subsequently a localization pathway that recombine these interpretations with lower features. By hypothesizing that semantic features are easy to learn and process, in [50] Peng et al. presented a multi scale 3D U-Nets for brain tumor segmentation. Their model consists of several 3D U-Net blocks for capturing long distance spatial resolutions. The upsampling was done at different resolutions in order to capture meaningful features. On BRATS 2015 challenge dataset they achieved 0.893 (WT), 0.830 (TC), 0.742 (EC). CNNs are also frequently being tested for segmentation of deep brain regions. Milletari et al. [51] combined a Hough voting approach with 2D, 2.5D, and 3D CNN to segment
Table I: Important developments in 3D CNN for Brain tumor/Lesion segmentation on BRAST Challenges.

| Ref.          | Methods                                                                 | Data     | Task                      | Performance evaluation                                  |
|---------------|-------------------------------------------------------------------------|----------|---------------------------|--------------------------------------------------------|
| Zhou et al. [44] | 3D variant of FusionNet (One-pass Multi-task Network (OM-Net))          | BRATS 2018 | brain tumor segmentation | 91.59 (WT), 82.74 (TC), 80.73(E)                        |
| Chen et al. [47] | Separable 3D U-Net                                                       | BRATS 2018 | --do--                    | 0.93(WT), 0.83(TC), 0.75(EC)                            |
| Peng et al. [50] | Multi-Scale 3D U-Nets                                                   | BRATS 2015 | --do--                    | 0.95(WT), 0.72(TC), 0.61(EC)                            |
| Kayalbay et al. [48] | 3D U-Nets                                                                 | BRATS 2015 | --do--                    | 0.95 (WT), 0.872(TC), 0.61(EC)                          |
| Kamnitsas et al. [43] | 11 layers deep 3D CNN                                                   | BRATS 2015 and ISLES 2015 | --do--                    | 0.989 (WT), 0.75 (TC), 0.72(EC)                         |
| Kamnitsas et al. 2016 [42] | 3D CNN in which features extracted by 2D CNNs                          | BRATS 2017 | --do--                    | 0.918 (WT), 0.883(TC), 0.854 (EC)                      |
| Casamitjana et al. [46] | 3D U-Net followed by fully connected 3D CRF                           | BRATS 2015 | --do--                    | 0.974(WT), 83.61(TC), 76.82(EC)                        |
| Isensee et al. 53 [49] | 3D U-Nets                                                                | BRATS 2017 | --do--                    | 0.985(WT), 0.74(TC), 0.64(EC)                          |

volumetric data of MRI scans. However, these networks still suffer from the class imbalance problem. In [52], a 3D CNN was implemented for subcortical brain structure segmentation in MRI and this study was basically based on the effect of the size of kernels in a network. In [53], the author applied 3D U-Net for a dense volume segmentation. However, this network was not entirely 3D CNN because they used 2D annotated slices for the training of the network. Sato et al. [54] proposed 3D CNN for segmentation of head CT volume. 3D CNNs are also being used in segmentation of knee structures. In [55], Ambellan et al. proposed a technique with 3D Statistical Shape Models along with 2D in addition to 3D CNNs to accomplish an effective and precise segmentation of knee structures. In [56], the authors suggest a 3D CNN to segment cervical tumors on 3D PET images. Their architecture uses prior information constraint spatial information for segmentation purpose. Authors claim highly precise results for segmenting cervical tumors on the 3D PET. In [57], authors propose a 3D convolution kernels for learning filter coefficients and spatial filter offsets simultaneously for 3D CT multi-organ segmentation work. The outcomes were compared with U-Net architectures. Authors claim that their architecture needs less trainable parameters and storage while obtaining high quality.

Liver and Heart: Liver cancer is certainly one of the major causes of cancer deaths. Therefore, a reliable and computerized liver and tumor segmentation technique are strongly needed to assist the expert radiologist and doctors in hepatocellular carcinoma identification and management. Duo et al. [58] presented a fully connected 3D CNN for liver segmentation from 3D CT scans. The same network was also tested on whole heart and vessel segmentation. 3D U-Net was applied in liver segmentation problems [59]. In [60], 3D ResNet was used for liver segmentation using the coarse to fine approach. Some other similar approaches for segmentation of the liver can be found in [32], [61]–[63]. In this sequence, another work based on 2D DenseUnet and hierarchical diagnosis approach (H-DensNet) for segmentation of liver lesions were presented in [64]. This network secured the first position in the LiTS 2017 Leaderboard. The network was tested on 3DIRCADs database and achieved state-of-the-art outcomes compared to other very well established liver segmentation approaches. They achieved 98.2% and 93.7% accuracy on Dice for liver and tumor segmentation respectively.

B. CLASSIFICATION

Alzheimer’s Disease (AD) is certainly the most general category of dementia, usually linked with the pathological amyloid depositions, structural-atrophy and metabolic variations in the chemistry of the brain. The timely diagnosis of AD plays an important role in slowing, avoiding, and preventing the incidence of dementia. In recent years, many researchers applied machine learning techniques to predict AD. However, very few attempts have been made to use 3D CNN to classify AD [65], [66]. In Yang et al. [28] nicely visualized the 3D CNN for classification problem in AD. The author proposed three types of visual inspection approaches; 1) based on sensitivity analysis, 2) 3D class activation mapping, and 3) 3D weighted gradient weighted mapping. Authors explains how the visual inspection can improve the accuracy and the possible improvements in deciding the 3D CNN architecture. Experiments were conducted on 3D deep VGGNet and 3D ResNet for classification of AD using MRI dataset. In [67] the author trained an auto-encoder to select the appropriate features from 3D patches extracted from the preprocessed MRI scans downloaded from ADNi dataset and showed some improved results than the 2D CNN available in the literature. The author showed a remarkable improvement in terms of accuracy. In [68], authors stacked LSTM with
3D CNN for AD classifications using PET and MRI data. Firstly, deep feature representations were derived from 3D fully connected CNN and the LSTM was applied on these features for performance improvement. We summarized some important developments in 3D CNN for classification task in medical imaging in Table II.

In [28], the author nicely visualizes the 3D CNN in terms of AD features which can be a very good step in understanding the behavior of each layer of 3D CNN. In this work, some well-known baseline 2D CNN have been converted to 3D CNN such as VGGNet, ResNet, and the results were compared with data on the ADNI. In [69], quite a deep 3D CNN has been researched on a sizeable dataset for classification of the AD. 91x109x91 voxels were used for training and testing of the network. On the other hand, Nie et al. [70] take advantage of the 3D aspect of MRI through training a 3D CNN to evaluate the survival in patients going through high-grade gliomas. Zhou et al. [71] proposed a weakly supervised 3D CNN for breast cancer detection. However, there were several limitations with the study: 1) the data was selective in nature, 2) The proposed architecture was only able to detect the tumor with high probability, and 3) only structural features were used for the experiments. Ha et al. [72] modify 2D U-Net into 3D CNN to quantify the breast MRI fibro-glandular tissue (FGT) and background parenchymal enhancement (BPE). In [58], Nie et al. proposed a multi-channel structure of 3D CNN for Survival Time Prediction of Brain Tumor Sufferers using Multi-Modal Neuroimages (T1 weighted MRI and diffusion tensor imaging, DTI). Recently, in [73], the authors presented a hybrid model for classification and prediction of LNM in head and neck cancer. They combined the outputs of MaO-radiomics and 3D-CNN architecture by using an ER fusion strategy. In [74], the authors presented a 3D CNN for predicting the maximum standardized uptake value of lymph nodes in patients suffering from cancer using CT images from a PET/CT examination.

CT brain hemorrhage: Recently Jnawali et al. [30] have demonstrated the performance of 3D CNN in the classification of CT brain hemorrhage scans. Through this study, the author constructed three versions of 3D CNN. Among them, two architectures ended up being the modest 3D CNN packages of VggNet and GoogleNet. This unique research was done on a large private dataset and about 87.8% accuracy was demonstrated. Gao et al. [75] show 87.7% accuracy in classification of AD, lesion, and normal aging by implementing 7 layers deep 3D CNN on 285 volumetric CT head scans from Navy General hospital, China. In this study, the authors also compared their results from 3D CNN with hand crafted features of 3D scale invariant Fourier transform (SIFT) and show that the proposed 3D CNN approach performs around four percent better performance in terms of overall accuracy. In [76] Ker et al. developed a 3D layer shallow 3D CNN for brain hemorrhage classification. The proposed network was giving state-of-the-art results with small training time compared to 3D VGGNet and 3D GoogleNet.

### C. DETECTION

**Cerebral Microbleeds (CMBs)** are small foci of chronic blood products in the normal brain along with the slightly abnormal brain. There have been a few studies in the detection of CMBs using 3D CNN. Dou et al. [77] proposed a two-stage fully connected 3D CNN architecture to detect CMBs from the dataset of SWI images. This network helps in reducing a large number of false positive candidates. For training purpose, several 3D blocks were extracted from the preprocessed dataset. This study also examines the effect of the size of 3D patches on network performance. Overall, this study presents the high performance of 3D CNN in the classification of CMB in compare to 2D techniques in similar studies such as Random Forest and 2D-CNN-SVM. Dou et. al. employed a fully 3D CNN to detect microscopic areas of a brain hemorrhage on MRI brain scans [78]. The described method

| Ref.     | Task               | Model                  | Data                                          | Performance measures                      |
|---------|--------------------|------------------------|-----------------------------------------------|-------------------------------------------|
| Yang et al. [28] | AD classification | 3D VggNet, 3D ResNet  | MRI scans from ADNI dataset (47 AD, 56 NC) | 0.863 AUC using 3D VggNet and 0.854 AUC using 3D ResNet |
| Kruthika et al. [67] | --do-- | 3D capsule network, 3D CNN | MRI scans from ADNI dataset (545 AD, NC, 605, and 991MCI) | Acc. for AD/MCI/NC 89.1% |
| Feng et al. [68] | --do-- | 3D CNN + LSTM        | PET + MRI scans from ADNI dataset (93 AD, 100 NC) | Acc. 65.5% (sMCI/NC), 86.4% (pMCI/NC), and 94.8% (AD/NC) |
| Wegmayr et al. [69] | --do-- | 3D CNN                | ADNI and AIBL data sets, 20000 T1 scans       | Acc. 72% (MCI/AD), 86% (AD/NC), and 67% (MCI/NC) |
| Oh et al. [66]   | --do-- | 3D CNN + transfer learning | MRI scans from ADNI dataset (AD 198, NC 230, pMCI 166, and sMCI 101) at baseline. | 74% (pMCI/sMCI), 86% (AD/NC), 77% (pMCI/NC) |
| Parmar et al. [70] | --do-- | 3D CNN                | fMRI scans from ADNI dataset (30 AD, 30 NC) | Classification acc. 94.85% (AD/NC) |
| Nie et al. [70] | Brain tumor        | 3D CNN with learning supervised features | Private adat 69 patient (T1 MRI, IMRI and DTI) | Classification acc. 89.85% (AD/NC) |
| Amidiri et al. [103] | Protein shape | 2-layer 3D CNN         | 63,558 enzymes from PDB data sets | Classification acc. 78% |
| Zhou et al. [71] | Breast cancer      | Weakly supervised 3D CNN | Private, 1537 female | Classification acc. 78% 83.7% |

**Table II Important developments in 3D CNN for classification task in medical imaging.**
had a sensitivity of 93% and outperformed prior methods of detection. Detecting cerebral micro-hemorrhages in brain tissue is a difficult and time-consuming task for radiologists, and their work is an example of how 3D CNN can help radiologists in a clinically meaningful application.

Standvoss et al. [79] detected CMS's in Traumatic brain injury (TBI). In their study, the authors prepared three types of architectures of 3D CNN with varying depth i.e. 3, 5 and 8 layers. These models were quite simple and straight forward, with the overall best accuracy of 87%. The drawback of these studies was that they utilized a small dataset for training the network. In [80], the author presented a 3D CNN to forecast route and radius of an artery at any given point in a cardiac CT angiography (CCTA) image which depends on the local image patch. This approach has the capacity to precisely and effectively figure out the path and radius of coronary arteries according to details extracted through the image files.

D. LOCALIZATION
Localization of biological architectures is a basic requirement for various initiatives in medical image investigation. Localization might be a hassle-free process for the radiologist, but it is usually a hard task for NNs that are vulnerable to variation in medical images induced by dissimilarities in the image acquisition process, structures, and pathological differences among patients. Generally, a 3D volume is required for the localization in medical images. Several techniques have been suggested which usually begin to treat the 3D space as an arrangement of 2D orthogonal planes. Wolterink et al. [81] detected coronary artery calcium scoring in coronary CT angiography by working with standard CNN's. De Vos et al. [82] introduced localization technique using a solitary CNN, and 2D CT image slices (chest CT, cardiac CT, and abdomen CT) as input. Although, this work was related to 3D localization approach, but they didn't make use of 3D CNN in a real sense. In addition, the approach depends heavily on the accurate recognition of biological structures. Huo et al. [83] utilized the properties of a 3D fully connected CNN and presented a spatially localized atlas network tiles (SLANT) model for whole brain segmentation on high-resolution multi-site images.

Intervertebral discs (IVDs) are modest joint parts that are located in between surrounding vertebrae and the localization of IVDs, are usually important for spine disease analysis and measurement. In [84], the authors presented a 3D detection of multiple brain structures in fetal neuro-sonography using fully connected CNN and named it VP-Nets. They explained that the proposed strategy requires a comparatively less amount of data for training and learns from coarsely annotated 3D data. Recently, a 3D CNN based on regression has been introduced in [31] to assess the degree of Enlarged perivascular spaces (EPVS) through 2000 basal ganglia scans from 3D head MRI. In [85], the authors reported the human level efficiency of 3D CNN in landmark detection in clinical 3D CT data. In [86], Saleh et al. proposed a 3D CNN regression models for 3D pose estimation of anatomy using T2 weighted imaging. They showed that 3D deep CNN offers fine initialization for optimization-based techniques to increase the capture range of slice-to-volume registration. Also, 3D CNN are volume-to-volume rigid registration in real-time. Xiaomeng et al. [87] presented fully connected, accurate and automatic 3D CNN for localization and segmentation of IVD using multimodal MR images. The work shows state-of-the-art performance in MICCAI-2016 challenge for IVD localization and segmentation section with dice score 91.2% for IVD segmentation.

VI. CHALLENGING PROSPECTS AND CONCLUSIONS
Usually, it is presumed that it takes a large number of training samples to train deep learning models [42], [88], [89]. This is further strengthened by the recent successes of deep learning models trained on large datasets like the ImageNet. However, it is still ambiguous whether deep learning models can work with smaller datasets in the case of medical images. For example, the images from the ImageNet dataset possess large variations in their appearance (e.g. light, intensity, edges, color, etc.) [23], [25], [90]–[92] since the images were taken at different angles and distances and have several different features that are completely different from medical images. Therefore, networks needed to learn meaningful representations of these images require huge training parameters and thus training samples. However, in case of medical images, there is much less variation in comparison to traditional image datasets [93]. In this regard, the process of fine-tuning of 3D CNN models which are already trained on natural image dataset can be applied to medical image [23], [25], [90]–[92], [94], [95]. This process is called transfer learning and has been successfully applied to many areas of medical imaging.

Regardless of high computational complexity, 3D CNNs are showing incredible performance in many areas of AI machine learning. 3D CNNs require large number of parameters to be trained which becomes more severe in the case of 3D medical images where the depth of the image volume varies roughly from 20 to 400 scans per volume [9], [25], [70], [96] with each scan volume containing very fine and important information about the patient. Usually, high-resolution scan volumes are of the size of 512x512 and need to be downsampled before being fed to the 3D CNN architecture in order to reduce the computational cost. Researchers generally use interpolation techniques to reduce the overall size of these medical image volumes but on the cost of significant information loss. There are also restrictions on the resizing of the medical image volume without loss of significant information. This is still an unexplored area and there is further research scope.

Although the number of trainable parameters of convolution layers are independent of the input size, but the number of trainable parameters in the subsequent fully connected layers depend on the output of the convolution
layers. This often leads to intractable models due to large number of trainable weights in the case when input images are fed into 3D CNN models without any downsampling. However, this issue is not the case with 2D images, that have smaller latent representations learnt by convolution filters. This makes it harder (and GPU intensive) to train 3D CNNs. The inception module by GoogleNet can be further explored in the concern of computational complexity in 3D medical image analysis.

As mentioned earlier, the depth of medical image volumes approximately varies between 20 and 400. For 3D CNN, we put the whole volume as the input to the 3D CNN. In most of the cases, only a few slices show abnormalities and therefore a lot of unnecessary volumes are fed to the model for most of the cases. However, for most cases we have labels for the entire image volume only and not for each image slice. Therefore, methods which choose what data to feed into a model can be investigated.

Indeed, in the deep learning context, learning the right features might sound unconventional because we cannot be sure if ANNs would learn features that are indeed discriminating for the condition or just overfit on some dataset specific features. CNNs can handle raw image data and they do not need handcrafted and designing the features [18], [90]. It is the responsibility of CNN to discover the right features from the data. While CNNs have made encoding the raw features in a latent space very convenient, it is very important to understand whether the CNN learnt features that are generalizable across datasets. Machine learning models often overfit on train samples, whereby they only perform well on the test samples from the training dataset. This issue is acute in case of medical imaging applications where there are issues with scanner variability, scan acquisition settings, et cetera. Therefore, it is important to decode the trained network using model interpretability approaches and validate the important features learnt by the network [97]. It also becomes important to report testing results with an external dataset whose samples were not used for training. However, this may not always be possible because of paucity of datasets for training and testing.

Finally, the ultimate challenge is to go beyond a human-level performance. It has already been discussed in several talks and literature. Researchers are working on reaching human-level performance for many tasks (known as Artificial General Intelligence) [24], [42], [98], [99]. However, the lack of labelled images, the high costs involved in labeling the datasets, the lack of consensus among experts in the assigned labels [27], [100], [101] are some present challenges that face the field. These issues force us to consider using reliable data augmentation methods and generate samples with known ground-truths. In this regard, generative adversarial networks (GAN) [102], especially CycleGANs for cross-modal image synthesis, offer a viable approach for synthesizing data and have been used to produce pseudo images that are highly similar to the original dataset.

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