International Journal of Engineering Sciences Paradigms and Researches (IJESPR)
(Vol. 32, Issue 01) and (Publishing Month: July 2016)
(An Indexed, Referred and Impact Factor Journal)
ISSN: 2319-6564
www.ijesonline.com

REVIEW OF MRI-BASED BRAIN TUMOR IMAGE SEGMENTATION USING DEEPLEARNING METHODS

Amiya Kumar Sahoo[1]
Aryan Institute of Engineering & Technology, Bhubaneswar, Odisha
Tanmaya Kumar Pattnaik[2]
NM Institute of Engineering and Technology, Bhubaneswar, Odisha
Subrat Dash[3]
Capital Engineering College, Bhubaneswar, Odisha
Premananda Sahu[4]
Raajdhani Engineering College, Bhubaneswar, Odisha

Abstract

Brain tumor segmentation is an important task in medical image processing. Early diagnosis of brain tumors plays an important role in improving treatment possibilities and increases the survival rate of the patients. Manual segmentation of the brain tumors for cancer diagnosis, from large amount of MRI images generated in clinical routine, is a difficult and time consuming task. There is a need for automatic brain tumor image segmentation. The purpose of this paper is to provide a review of MRI-based brain tumor segmentation methods. Recently, automatic segmentation using deep learning methods proved popular since these methods achieve the state-of-the-art results and can address this problem better than other methods. Deep learning methods can also enable efficient processing and objective evaluation of the large amounts of MRI-based image data. There are number of existing review papers, focusing on traditional methods for MRI-based brain tumor image segmentation. Different than others, in this paper, we focus on the recent trend of deep learning methods in this field. First, an introduction to brain tumors and methods for brain tumor segmentation is given. Then, the state-of-the-art algorithms with a focus on recent trend of deep learning methods are discussed. Finally, an assessment of the current state is presented and future developments to standardize MRI-based brain tumor segmentation methods into daily clinical routine are addressed.

1. Introduction

Cancer can be defined as the uncontrolled, unnatural growth and division of the cells in the body. Occurrence, as a mass, of these unnatural cell growth and division in the brain tissue is called a brain tumor. While brain tumors are not very common, they are one of the most lethal cancers[1].

Depending on their initial origin, brain tumors can be considered as either primary brain tumors or metastatic brain tumors. In primary ones, the origin of the cells are brain tissue cells, where in metastatic ones cells become cancerous at any other part of the body and spread into the brain. Gliomas are type of brain tumors that originate from glial cells. They are the main type of brain tumors that current brain tumor segmentation research focuses on. The term glioma is a general term that is used to describe different types of gliomas ranging from low-grade gliomas like astrocytomas and oligodendrogliomas to the high grade (grade IV) glioblastoma multiform (GBM), which is the most aggressive and the most common primary malignant brain tumor[2]. Surgery, chemotherapy and radiotherapy are the techniques used, usually in combination, to treat gliomas[3].

Early diagnosis of gliomas plays an important role in improving treatment possibilities. Medical Imaging techniques such as Computed Tomography (CT), Single-Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Magnetic Resonance Spectroscopy (MRS) and Magnetic Resonance

Imaging (MRI) are all used to provide valuable information about shape, size, location and metabolism of brain tumors assisting in diagnosis. While these modalities are used in combination to provide the highest detailed information about the brain tumors, due to its good soft tissue contrast and widely availability MRI is considered as the standard technique. MRI is a non-invasive in vivo imaging technique that uses radio frequency signals to excite target tissues to produce their internal images under the influence of a very powerful magnetic field. Images of different MRI sequences are generated by altering excitation and repetition times during image acquisition. These different MRI modalities produce different types of tissue contrast images, thus providing valuable structural information and enabling diagnosis and segmentation of tumors along with their subregions[4]. Four standard MRI modalities used for glioma diagnosis include T1-weighted MRI (T1), T2-weighted MRI (T2), T1-weighted MRI with gadolinium contrast enhancement (T1-Gd) and Fluid Attenuated Inversion Recovery (FLAIR) (see Fig. 1). During MRI acquisition, although can vary from device to device, around one hundred and fifty slices of 2D images are produced to represent the 3D brain volume. Furthermore, when the slices from the required standard modalities are combined for diagnosis the data becomes very populated and complicated.

Generally, T1 images are used for distinguishing healthy tissues, whereas T2 images are used to delineate the edema region which produces bright signal on the image. In T1-Gd images, the tumor border can easily be distinguished by the bright signal of the accumulated contrast agent (gadolinium ions) in the active cell region of the tumor tissue. Since necrotic cells do not interact with the contrast agent, they can be observed by hypo intense part of the tumor core making it possible to easily segment them from the active cell region on the same sequence. In FLAIR images, signal of water molecules are suppressed which helps in distinguishing edema region from the Cerebrospinal Fluid (CSF).

Before applying any therapy, it is crucial to segment the tumor in order to protect healthy tissues while damaging and destroying tumor cells during the therapy. Brain tumor segmentation involves diagnosing, delineating and separating tumor tissues, such as active cells, necrotic core and edema (Fig. 2) from normal brain tissues including Gray Matter (GM), White Matter (WM) and CSF. In current clinical routine, this task involves manual annotation and segmentation of large amount of multimodal MRI images. However, since manual segmentation is a very time consuming procedure, development of robust automatic segmentation methods, to provide efficient and objective segmentation, became an interesting and popular research area in recent years[5]. Current high segmentation performances obtained by deep learning methods make them good candidates for achieving this task.

The rest of the paper is organized as follows: First we briefly review methods for brain tumor image segmentation in section 2. Then, in section 3, we especially focus on methods based on deep learning algorithms, which provide the state-of-the-art results in recent years. In particular, we compare designs of different deep learning methods and their performances. Finally, in conclusions, we assess the current state-of-the-art and provide future directions for development.

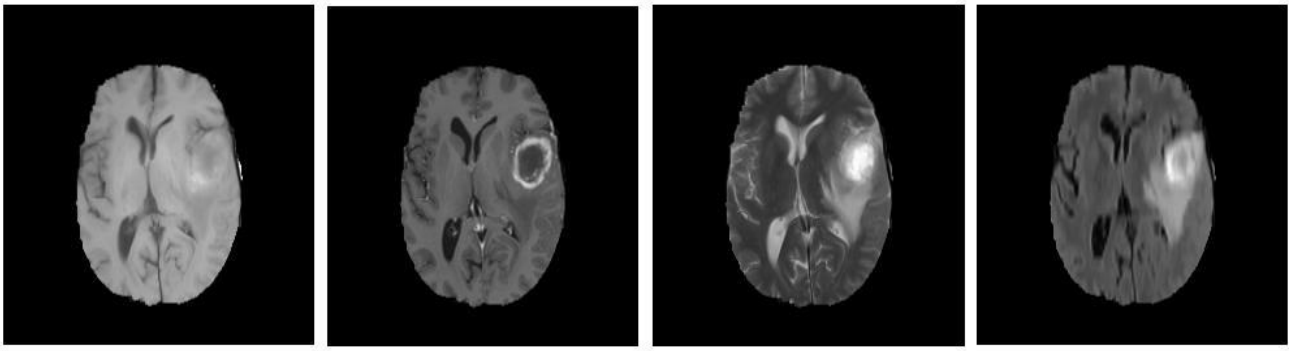

Fig. 1. Four different MRI modalities showing a high grade glioma, each enhancing different subregions of the tumor. From left; T1, T1-Gd, T2, and FLAIR. Images are generated by using BRATS 2013 data[5].

2. Methods for Brain Tumor Image Segmentation

Brain tumor segmentation methods can be classified as manual methods, semi-automatic methods and fully automatic methods based on the level of user interaction required[6].

Manual Segmentation Methods

Manual segmentation requires the radiologist to use the multi-modality information presented by the MRI images along with anatomical and physiological knowledge gained through training and experience. Procedure involves the radiologist going through multiple slices of images slice by slice, diagnosing the tumor and manually drawing the tumor regions carefully. Apart from being a time consuming task, manual segmentation is also radiologist dependent and segmentation results are subject to large intra and inter rater variability[7]. However, manual segmentations are widely used to evaluate the results of semi-automatic and fully automatic methods.

Semi-Automatic Segmentation Methods

Semi-automatic methods require interaction of the user for three main purposes; initialization, intervention or feedback response and evaluation[8]. Initialization is generally performed by defining a region of interest (ROI), containing the approximate tumor region, for the automatic algorithm to process. Parameters of pre-processing methods can also be adjusted to suit the input images. In addition to initialization, automated algorithms can be steered towards a desired result during the process by receiving feedbacks and providing adjustments in response. Furthermore, user can evaluate the results and modify or repeat the process if not satisfied.

Hamamci et al. proposed the "Tumor Cut" method[9]. This semi-automatic segmentation method requires the user to draw the maximum diameter of the tumor on input MRI images. After initialization a cellular automata (CA) based seeded tumor segmentation method run twice, once for tumor seeds provided by the user and once for the background seeds to obtain a tumor probability map. This approach includes separately applying the algorithm to each MRI modality (e.g. T1, T2, T1-Gd and FLAIR), then combining the results to obtain the final tumor volume.

A recent semi-automatic method employed a novel classification approach[10]. In this approach segmentation problem was transformed into a classification problem and a brain tumor is segmented by training and classifying within that same brain only. Generally, machine learning classification methods, for brain tumor segmentation, requires large amounts of brain MRI scans (with known ground truth) from different cases to train on. This results in a need to deal with intensity bias correction and other noises. However in this method, user initializes the process by selecting a subset of voxels belonging to each tissue type, from a single case. For these subsets of voxels, algorithm extracts the intensity values along with spatial coordinates as features and train a support vector machine (SVM) that is used to classify all the voxels of the same image to their corresponding tissue type.

Despite semi-automatic brain tumor segmentation methods are less time consuming than manual methods and can obtain efficient results, they are still prone to intra and inter rater/user variability. Thus, current brain tumor segmentation research is mainly focused on fully automatic methods.

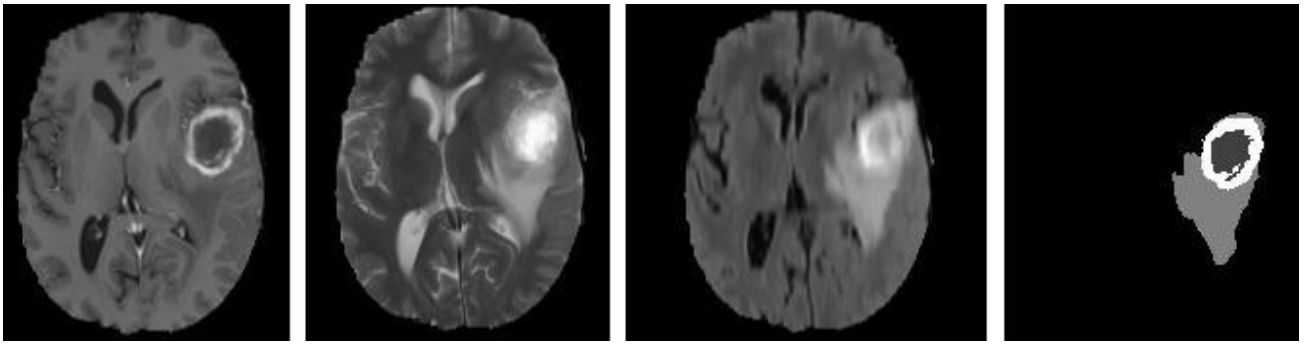

Fig. 2. Brain tumor segmentation. From left: T1-Gd, T2, FLAIR and Segmented Tumor. In segmented image; bright signal is active region, dark signal is necrotic core and medium level signal is edema. Images are generated by using BRATS 2013 data[5].

Fully Automatic Segmentation Methods

In fully automatic brain tumor segmentation methods no user interaction is required. Mainly, artificial intelligence and prior knowledge are combined to solve the segmentation problem.

Challenges

Automatic segmentation of gliomas is a very challenging problem. Tumor bearing brain MRI data is a 3D data where tumor shapes, size and location can vary greatly from patient to patient. Also tumor boundaries are usually unclear and irregular with discontinuities, posing great challenge especially against traditional edge-based methods. In addition to these, brain tumor MRI data obtained from clinical scans or synthetic databases[11] are inherently complex. MRI devices and protocols used for acquisition can vary dramatically from scan to scan imposing intensity biases and other variations for each different slice of image in the dataset. The need for several modalities to effectively segment tumor sub-regions even adds to this complexity.

BRATS Dataset

Objective evaluation of the results of various brain tumor image segmentation methods with the state-of-the-art is a difficult task. However, with the development of a widely accepted benchmark, the BRATS benchmark[5], for automatic brain tumor segmentation, now it is possible to objectively compare various glioma segmentation methods using this common dataset. Current version (2015) of the BRATS training dataset contains 274 multi-modality MRI scans of patients with gliomas (both high and low grades) along with their ground truth segmentations for evaluation. As for testing data, 110 scans are available with unknown grades and unknown ground truths. Evaluation on the testing data is only possible with the online evaluation tool. Results are presented by the tool mainly in the form of well-known Dice Score, Sensitivity (true positive rate) and Specificity (true negative rate) for three main tumor regions; whole tumor (all tumor components), core tumor (all tumor components except edema) and active tumor (only active cells). We only report dice scores as performance measures. For each tumor region, P_1 represents the segmented tumor area by the proposed method, and T_1 is the actual tumor area in the ground truth. Then, dice score is calculated by the online tool for each region as;

$$\mathbf{Dice(P,T)} = \frac{|\mathbf{P_1} \curlywedge \mathbf{T_1}|}{(|\mathbf{P_1}| + |\mathbf{T_1}|)/2}$$

where ر is the logical AND operator and $|.|$ is the size of the set (the number of voxels belonging to it).

Types of Automatic Brain Tumor Segmentation Methods

Automatic brain tumor segmentation methods can be classified as; discriminative and generative methods. Detailed reviews of these methods were previously presented[6, 12, 13, 14].

Earlier reported results indicate that, methods based on discriminative classification techniques were the top performing in general among other automatic methods[5]. Discriminative methods try to learn the relationship between the input image and the ground truth. Mainly they rely on choice of features and feature extraction. In most cases they use supervised learning techniques requiring large data set with valid ground truth. On the other hand, generative methods generate probabilistic models by using prior knowledge like location and spatial extent of

healthy tissues. Previously obtained atlases of healthy tissues are used to extract the unknown tumor compartments. However, converting prior knowledge into suitable probabilistic models is a complicated task. Although a semi-automatic method, Kuwon et al. proposed the best performing generative model[15].

Processing Pipelines of Automatic Methods

Most of the proposed discriminative methods implement a similar processing pipeline, involving pre-processing, feature extraction, classification and post-processing steps. Pre-processing step usually include noise removal operations[16], skull-stripping[17] and intensity bias correction[18]. After pre-processing step, image processing techniques are employed to extract features that represent each distinct tissue type effectively. Features like, asymmetry-related features[19], discrete wavelet transforms[20] (DWT), textons[21], multifractal Brownian motion features[22], first order statistical features[19], raw intensities, local image textures, intensity gradients and edge based features[12] are some examples. By using these features different types of classifiers; neural networks (NN), support vector machines (SVM)[10,23], AdaBoost[22], k-nearest neighbor classifier (kNN)[20], self-organizing maps (SOM)[20], random forests (RFs)[19, 24] are implemented all producing viable segmentation results. In some cases results of the segmentation are refined to increase performance. Conditional random fields (CRF) [23, 24] and connected components (CC) [27, 29] are among the popular choices. As the best performing traditional discriminative method[5], Tustison et al. used asymmetry and first order statistical features to train concatenated RFs by introducing the output of the first RF as an input to the another[19]. Although these traditional classification methods reported high performances, new trend of fully automatic brain tumor segmentation techniques based on deep learning methods are also emerging with the state-of- the-art results.

3. Deep Learning Methods

Recent performances of deep learning methods, specifically Convolutional Neural Networks (CNNs), in several object recognition[25] and biological image segmentation[26] challenges increased their popularity among researches. In contrast to traditional classification methods, where hand crafted features are fed into, CNNs automatically learn representative complex features directly from the data itself. Due to this property, research on CNN based brain tumor segmentation mainly focuses on network architecture design rather than image processing to extract features. CNNs take patches extracted from the images as inputs and use trainable convolutional filters and local subsampling to extract a hierarchy of increasingly complex features. Although currently very few in number compared to other traditional brain tumor segmentation methods, due to state-of-the-art results obtained by CNN based brain tumor segmentation methods, we will focus the review on these methods in this section. Comparison of the reviewed deep learning and traditional glioma segmentation methods is presented in Table 1.

Urban et al. proposed a 3D CNN architecture for the multi-modal MRI glioma segmentation task[27]. Multi-modality 3D patches, basically cubes of voxels, extracted from the different brain MRI modalities are used as inputs to a CNN to predict the tissue label of the center voxel of the cube. Input has 3D spatial intensity information and one additional dimension for MRI modalities. Thus 4D input data is handled effectively by the CNN. While high dimensional processing can better represent 3D nature of biological structures, it also increases processing load of the network. As for the architecture, two different networks are designed. The first one is a four layer CNN with the input layer containing 15 3D filters that have 5^3 spatial dimensions with an additional 4^{th} dimension accounting for the corresponding MRI modality resulting in a filter shape of 5 x 5 x 5 x 4. Two of the hidden layer filters also have 5^3 spatial dimensions plus one dimension which corresponds to the number of filters in the preceding layer. Number of filters in each hidden layer is 25. The last layer, the softmax layer contains 6 filters one for each tissue type to be classified allowing the interpretation of the output as probabilities (see Fig.3. for example architecture). The second network is almost identical with the exception of an additional hidden layer with 40 filters of size 5^3. Connected components are used to post-process the results. Reported average results of the two proposed networks are promising with BRATS dice scores of 87% for the whole tumor region, 77% for the core tumor region and 73% for the active tumor region.

In contrast to the high dimensional method of Urban et al., Zikic et al. developed an interpretation method to transform the 4D data, so that standard 2D-CNN architectures can be used to solve the brain tumor segmentation task[28]. This can remove the burden of high dimensional CNN design while increasing computational efficiency. Interpretation is done by transforming each 4-modalitiy 3D input patch of size (d_1 x d_2 x d_3 x 4) into 4.d_3-channel of 2D patches of size (d_1 x d_2 x 4d_3). With this method, input patches of size 19x19x4 (single slice is used for each

modalitiy) are fed into a 2D-CNN containing two convolutional layers with 64 filters with size 5 x 5 x 4 and 3 x 3 x 4 respectively, separated by a max-pooling layer, followed by one fully-connected (FC) layer and a soft-max layer.

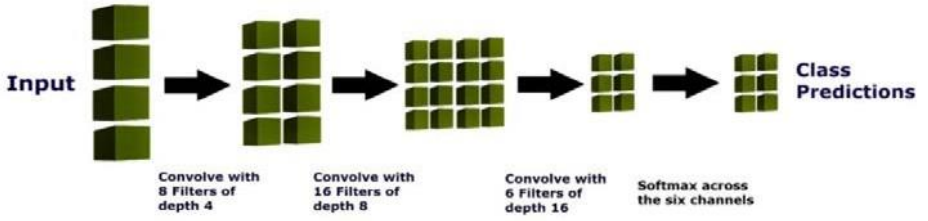

Fig. 3. Example illustration of 3D-CNN architecture for brain tumor segmentation[27].

While Urban et al. used hyperbolic tangent function, this method applied rectified linear unit (ReLU) as a non-linearity term. No post-processing is applied. Reported results indicate BRATS dice scores of 83.7% for the whole tumor region, 73.6% for core tumor region and 69% for active tumor region. It is important to note that, these results are obtained with a limited dataset which might affect the performance.

Another novel approach implemented a cascaded two-pathway CNN architecture[29]. By extracting smaller sized patches and larger sized patches at the same time, a cascaded CNN that process local details of the brain MRI along with larger context of brain tissue is realized. Centred at the same location of the image, patches sized 33 x 33 pixels are extracted from each different MRI modality for local pathway and patches sized 65 x 65 are extracted for global pathway to classify the label of the central pixel. 2D multi-modality global input patches of size 65 x 65 x 4 are first processed by a CNN to output patches of size 33 x 33 x 5. Those output patches are then concatenated with the local patches of size 33x33x4 and fed as an input to a two-pathway CNN with convolutional layers containing 7 x 7 sized filters in one path and 13 x 13 sized filters in the other one. Thus, creating cascaded two-pathway CNN architecture. Several modified architectures of this cascaded CNN method are also proposed. Along with this novel architectural approach, two phase training is also implemented to avoid class imbalances. In first phase, cascaded CNN is trained with balanced distribution of classes and later in the second phase CNN is retrained with a more representative distribution of the original images. Furthermore, Maxout non-linearity is used and connected components method is implemented as a post-processing step. High BRATS dice scores of 88% for whole tumor region, 79% for core tumor region and 73% for active tumor region are reported. A similar two-pathway approach with only one CNN is also proposed[30].

One of the recent CNN approaches[31] evaluated the brain tumor segmentation performance of using deeper CNN architectures. This approach is realized by implementing small 3 x 3 sized filters in the convolutional layers. In this way, more convolutional layers can be added to the architecture without reducing the effective receptive field of the traditional bigger filters. Furthermore, deeper architectures apply more non-linearities and have less filter weights, due to the use of smaller filters, reducing the chance of overfitting. Modified version of ReLU, leaky rectifier linear unit (LReLU) is used as non-linearity activation function. Proposed CNN that has 11 layers of depth (6 convolutional layers followed by 3 fully-connected layers with 2 max-pooling layers dividing them into blocks of three) obtained BRATS dice scores of 88%, 83% and 77% for whole tumor, core tumor and active tumor regions respectively. Implementation of intensity normalization, intensity bias correction and input patch augmentation as pre-processing operations along with threshold based unwanted cluster removal as post- processing contributed to the state of the art results.

Some of the glioma segmentation methods combined CNN application with other classification or clustering techniques. In one method a local structured prediction with CNN is proposed[32]. Instead of using CNNs to classify central voxels of input image patches into brain tissue classes, first patches of labels are extracted from ground truth images and then clustered by k-means algorithm into N groups to form a label patch dictionary of size N. Later, a 2D CNN is used to classify multimodal input image patches into one of these clusters. As for the segmentation performance of the method, BRATS dice scores of 83%, 75% and 77% for whole tumor, core tumor and active tumor regions are reported respectively. On the other hand Rao et al.[33] extracted multi plane patches around each pixel and trained four different CNNs each taking input patches from a separate MRI modality image. Outputs of the last hidden layers of those CNNs are then concatenated and used as feature maps to train a RF classifier.

Implementations of pre/post-processing steps are not reported and only an accuracy level of 67% is provided as a result.

Table 1. Comparison of the reviewed brain tumor segmentation methods (results are obtained using challenge dataset of BRATS 2013 benchmark[5]. Note that, we only considered dice scores as the performance measure. Refer to the benchmark for further evaluation metrics)

Author	Method	Level of user interaction	Performance (Dice Scores)		
			Whole Tumor	Core Tumor	Active Tumor
Human Rater[5]	Medical training and experience	Manual	0.88	0.93	0.74
Pereira et al.[31]	CNN with small (3x3) filters for deeper architecture	Fully automatic	0.88	0.83	0.77
Kwon et al.[15]	Generative model that performs joint segmentation and registration	Semi-automatic	0.88	0.83	0.72
Havaei et al.[29]	Cascaded Two-pathway CNNs for simultaneous local and global processing	Fully automatic	0.88	0.79	0.73
Tustison et al.[19]	Concatenated RFs, trained using asymmetry and first order statistical features	Fully automatic	0.87	0.78	0.74
Urban et al.[27]	3D CNN architecture using 3D convolutional filters	Fully automatic	0.87	0.77	0.73
Havaei et al.[10]	Uses SVM; training and segmentation implemented within the same brain	Semi-automatic	0.86	0.77	0.73
Dvorak and Menze[32]	Local structured prediction with CNN and k-means	Fully automatic	0.83	0.75	0.77
Davy et al.[30]	Two-pathway CNN for simultaneous local and global processing	Fully automatic	0.85	0.74	0.68
Zikic et al. [28]	3D input patches are interpreted into 2D input patches to train a CNN	Fully automatic	0.837	0.736	0.69
Hamamci et al.[9]	Generative model, uses cellular automata to obtain tumor probability map	Semi-automatic	0.72	0.57	0.59
Rao et al.[33]	Four CNNs, one for each modality, with their outputs concatenated as an input into a RF	Fully automatic	Not reported	Not reported	Not reported

4. Conclusions

Automatic segmentation of the brain tumors for cancer diagnosis is a challenging task. Recently, availability of public datasets and the well-accepted BRATS benchmark provided a common medium for the researchers to develop and objectively evaluate their methods with the existing techniques. In this paper, we provided a review of the state-of-the-art methods based on deep learning, and a brief overview of traditional techniques. With the reported high performances, deep learning methods can be considered as the current state-of-the-art for glioma segmentation. In traditional automatic glioma segmentation methods, translating prior knowledge into probabilistic maps or selecting highly representative features for classifiers is challenging task. However, convolutional neural networks (CNN) have the advantage of automatically learning representative complex features for both healthy brain tissues and tumor tissues directly from the multi-modal MRI images. Future improvements and modifications in CNN architectures and addition of complementary information from other imaging modalities such as Positron Emission Tomography (PET), Magnetic Resonance Spectroscopy (MRS) and Diffusion Tensor Imaging (DTI) may improve the current methods, eventually leading to the development of clinically acceptable automatic glioma segmentation methods for better diagnosis.

References

1. De Angelis L M. Brain Tumors. *N. Engl. J. Med*. 2001; **344**:114-23.
2. Deimling A. Gliomas. *Recent Results in Cancer Research vol 171*. Berlin: Springer; 2009.
3. Stupp R. Malignant glioma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2007; **18**(Suppl 2):69-70.
4. Drevelegas A and Papanikolou N. *Imaging modalities in brain tumors Imaging of Brain Tumors with Histological Correlations*. Berlin: Springer; 2011; chapter 2:13-34.
5. Menze B, et al. The Multimodal brain tumor image segmentation benchmark (brats). *IEEE Trans Med Imaging 2015*; **34(10):**1993-2024.
6. Gordillo N, Montseny E, Sobrevilla P. State of the art survey on MRI brain tumor segmentation. *Magn Reson Imaging* 2013; **31(8):**1426–38.
7.White D, Houston A, Sampson W, Wilkins G. *Intra and interoperator variations in region-of-interest drawing and their effect on the measurement of glomerular filtration rates* 1999; **24**:177–81.
8. Foo JL. *A survey of user interaction and automation in medical image segmentation methods.* Tech rep ISUHCI20062, Human Computer Interaction Department, Iowa State Univ; 2006.
9. Hamamci A, et al. Tumor-Cut: segmentation of brain tumors on contrast enhanced MR images for radiosurgery applications. *IEEE Trans Med Imaging* 2012; 31(3):790–804.
10. Havaei M, Larochelle H, Poulin P, Jadoin P M. Within-brain classification for brain tumor segmentation. *Int J Cars* 2016; 11:777-788.
11. Prastawa M, Bullitt E, Gerig G. Simulation of brain tumors in mr images for evaluation of segmentation efficacy. *Medical Image Analysis* 2009;13(2):297- 311.
12. Bauer S, Wiest R, Nolte L, Reyes M. A survey of MRI-based medical image analysis for brain tumor studies. *Phys Med Biol*.2013;58:97-129.
13. Liu J, Wang J, Wu F, Liu T, Pan Y. A survey of MRI-based brain tumor segmentation methods. *Tsinghua Science and Technology* 2014;19(6):578-595.
14. Angelini E D, Clatz O, Mandonnet E,Konukoglu E,Capelle L, Duffau H. Glioma dynamics and computational models: a review of segmentation, registration, and in silico growth algorithms and their clinical applications. *Curr. Med. Imaging* 2007; 3: 262–76.
15. D. Kwon et al. Combining generative models for multifocal glioma segmentation and registration. *Medical Image Computing and Computer-Assisted Intervention–MICCAI 2014*. Springer, 2014:763–770.
16. Nowak R D, Wavelet-based rician noise removal for magnetic resonance imaging. *IEEE Trans Image Processing 1999*; 8(10):1408-1419.
17. Zhuang AH, Valentino DJ, Toga AW. *Skull stripping magnetic resonance brain images using a model based level set. NeuroImage* 2006;32(1):79-92.
18. Shah M, Xiao Y, Subbanna N, Francis S, Arnold D. L, Collins D. L, Arbel T. Evaluating intensity normalization on mris of human brain with multiple sclerosis. *Medical Image Analysis* 2011;15(2): 267-282.
19. Tustison N. et al. Optimal symmetric multimodal templates and concatenated random forests for supervised brain tumor segmentation (simplified) with antsr. *Neuroinformatics* 2015;13(2): 209–225.
20. Anitha V, Murugavalli S. Brain tumor classification using two-tier classifier with adaptive segmentation technique. *IET Comput.Vis*. 2016;10(1):9-17.
21. Leung T, Malik J. Representing and recognizing the visual appearance of materials using three-dimensional textons. *Int. J. Comput. Vision* 2001 43(1)29–44.
22. Islam A, Reza S, Iftekharuddin K. Multifractal texture estimation for detection and segmentation of brain tumors. *IEEE Trans Med Imaging* 2013;60(11):3204–3215.
23. Bauer S, Nolte LP, Reyes M. Fully automatic segmentation of brain tumor images using support vector machine classification in combination with hierarchical conditional random field regularization. *In Medical Image Computing and Computer-Assisted Intervention-MICCAI 2011*. Springer; 2011: 354-361.
24. Zikic D, et al. Decision forests for tissue-specific segmentation of high-grade gliomas in multi-channel MR. *Med Image Comput Comput Assist Interv 2012;*15(3):369–76.
25. Krizhevsky A, Sutskever I, Hinton G E. Imagenet classification with deep convolutional neural networks. *Advances in neural information processing* systems 2012:1097–1105.
26. Ciresan D. et al. Deep neural networks segment neuronal membranes in electron microscopy images. *Advances in neural information processing systems* 2012: 2843–2851.
27. Urban G. et al. Multi-modal brain tumor segmentation using deep convolutional neural networks. *MICCAI Multimodal Brain Tumor Segmentation Challenge (BraTS)* 2014:31–35.
28. Zikic D. et al. Segmentation of brain tumor tissues with convolutional neural networks. *MICCAI Multimodal Brain Tumor Segmentation Challenge (BraTS)* 2014:36–39.
29. Havaei M, Davy A, Farley W D, Biard A, Courville A, Bengio Y, Pal C, Jadoin P M, Larochelle H. Brain tumor segmentation with deep neural networks. *Medical Image Analysis 2016*, doi:10.1016/j.media.2016.05.004.
30. Davy A. et al. Brain tumor segmentation with deep neural networks. *MICCAI Multimodal Brain Tumor Segmentation Challenge (BraTS)* 2014:1–5.
31. Pereira S, Pinto A, Alves V, Silva C A. Brain tumor segmentation using convolutional neural networks in MRI images. *IEEE Trans Med Imaging* 2016;35(5):1240–1251.
32. Dvorak P, Menze B. Structured prediction with convolutional neural networks for multimodal brain tumor segmentation. *MICCAI Multimodal Brain Tumor Segmentation Challenge (BraTS)* 2015:13–24.
33. Rao V, Sarabi M S, Jaiswal A. Brain tumor segmentation with deep learning. *MICCAI Multimodal Brain Tumor Segmentation Challenge (BraTS)* 2015:56–59.