A study of automatic segmentation of White Matter Hyperintensity for detection of Alzheimer’s disease

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Abstract: Alzheimer’s disease is a type of neurodegenerative disorders involving a long-term and generally significant decrease in cognitive performance. Age is the main risk factor for neural disorder, and so it is the aged who are highly affected by this neural disorder. Because of the intensity of the spread of this disease on a global level, organizations and researchers are continuing to invest in the early detection and prevention of such disorders, with an emphasis on proper treatment and medication. Cost-efficient and scalable methods for detecting dementia from some of the most extreme ways are required, similar to the early stages of Subjective Memory Loss (SML), to more drastic stages like Mild Cognitive Impairment (MCI) and Alzheimer's Dementia (AD) itself. The focus of this work is to build a reliable Deep learning algorithm based on the OASIS, ADNI, and WMH challenge dataset for the identification of cognitive impairment (CI). In this paper an elaborate review has been made of the various methodologies and algorithms used in various frameworks to efficiently and automatically segment WMH (White Matter Hyperintensities) in the brain to detect lesions and areas related to various anomalies, Alzheimer’s being one of them.

KeyWords: Deep Learning, Alzheimer’s, Biomarker, Segmentation

1. Introduction

Alzheimer's disease (AD) is a rigorous neurological disorder that affects people around the world between the age group of 60 to 90 years. Machine learning models have recently been used to depict AD development, but they still do take advantage of the clinical and structural components related to multimodal medical information like MRI scans, PET models etc.

The brain being the quintessential part of the human body any disorders or anomalies in the brain will affect daily activities and functionalities badly for the whole human body. So early
diagnosis is an essential criterion for AD diagnosis; otherwise it can have a broad impact on brain and human behavior. An Alzheimer patient would be experiencing many issues within his brain function like a rigorous degeneration starting with issues like forgetting names, things to forgetting people and memories to finally resulting in hallucinations and finally death.

According to Ramzan's recent survey (2020), Alzheimer's disease (AD) is a disease affecting the nerves of the brain that accounts for 70 percent to 80 percent of cases of dementia around the world. The research on AD has taken a leap over the years, though apt methodologies are hard to find due to the complexity and heterogeneity of the anomalies. Resting-state functional magnetic resonance imaging (rs-fMRI) is a neuroimaging technology widely used for the study of neurodegenerative disease development and progression. Precise and early diagnosis of Alzheimer's disease increasingly plays a crucial role in providing suitable and effective care and treatment. Works by Shaik(2019) show that predicting AD from mild cognitive impairment (MCI) and normally cognitive impairment (NC) are becoming common even before it reaches the final stages. Recently, sophisticated machine learning approaches in diverse fields including brain image processing have successfully shown high efficiency. Such techniques are also used for the identification of infectious diseases.

Allioui et al (2020) did the job of automating the finding of the damaged brains and identifying Alzheimer's disease using a CAD (Computer assisted diagnosis) system with deep learning approaches. A PSO-FCM (particle swarm optimization-Fuzzy C means) classification was used for the automatic correction of the weight values. A U-NET architecture was utilized to segregate through various features and get a segmented output.

Medical Image Segmentation has a vital role to play in diagnosing brain anomalies as the pixels surrounding the ROI (Region of Interest) are labeled individually and later grouped and classified. Various factors which render the proper detection of the area of anomaly are factors like the levels of heterogeneity involved in the location and outside factors like noise caused from various modalities of input data.

Sepideh et al (2015) reviewed and summarized the popularly used segmentation algorithms, with increasing focus on their features, benefits and drawbacks of these methods. The literature contained numerous segmentation techniques which segmented brain MRI into White matter (WM), Gray matter (GM), and Cerebrospinal fluid (CSF), a common and important evaluation of the state of the MRI segmentation techniques was used.

Machine Learning methods with predictive and statistical approach have given hand to many biomedical problems, algorithms like Ada Boost used for learning of region characteristics and k-means clustering of feature spaces have aided in the process. But the disadvantage with these methods is they are time consuming when it comes to the precise feature detection.

Deep learning is a powerful classification algorithm which extracts features with the availability of deep layers for feature detection. With the availability of many layers for feature selection it enables the ROI to be specifically identified and in a quicker manner. Though the training process is time consuming, with the available GPU’s, execution time can be carried out fast.

**State-of-the-Art Review**

Alzheimer's disease is one of the most commonly found neuro development disorders these days. Over the past decade, research on AD diagnosis has directly linked significant impact to artificial intelligence-focused diagnostic algorithms. Alzheimer's disease affects the person and their families in a tremendous way with noteworthy emotional and financial implication.

Anbeek (2004) suggested a structure for fully automatic white matter lesion segmentation (WMLs) in Brain MR imaging. The method collected data from multimodal inputs, scans of T1-weighted (T1-w), inversion recovery (IR), proton density-weighted (PD), T2-weighted (T2-w) and reversal of fluid attenuation (FLAIR). The system was created based on the supervised classification K-Nearest Neighbor (KNN), which constructed a feature map making use of two predominantly important features the voxel intensities and spatial information /location.
The method generates images that reflect the probability of a WML being included per voxel. Voxels closest to the class with similar features are clubbed together. Binary segmentations can be obtained by applying limits on certain probability charts. For further quantitative analysis the similarity index (SI), the overlap fraction (OF) and the extra fraction (EF) are calculated. The SI helps in the correct fortitude of the optimal threshold value. This approach for automated segmentation of WML is appropriate for diagnosis of WMLs in large legion and links to various serious anomalies like stroke too.

Brand et al (2020) came up with a new method using the multi-block alternating multiplier path approach to enhance and incorporate a novel objective that receives multi-modal clinical data from different modalities to concurrently estimate the formulative scores and assessments in Alzheimer's disease Neuroimaging. The methodology was built to exploit the clinical research structure that targeted a single kind of input data. T1-weighted MR and FDG-PET were among the various imaging data inputs used to serve the purpose of image segmentation of a heterogenous kind of input. To take this kind of a multi-modality input in the detection of AD, Huang et al (2019) developed a Convolutionary Neural Network (CNN) to include all the multi-modality knowledge found in both T1-MR and FDG-PET showcasing the hippocampal area of the brain. Unlike the traditional ML (Machine Learning) algorithms, where the features had to be selected manually, here the CNN was given the choice of selecting the features automatically.

Segmentation of an image into regions has been one of the greatest challenges for many decades in the field of computer vision Felzenszwalb et al (2004) carried this out using the help of graph edges. The technique requires a graph based features of the image, where each pixel is treated as a node and connected to another node via an edge. The weights assigned to each edge varies according to the similarity or dissimilarity of the next node. Khagi et al (2018) discussed Brain MRI segmentation using conventional clustering techniques that rely on Simple Linear Iterative Clustering Based on the Superpixel approaches.

Biju (2017) calculated the ratio between the grey and white matter to calculate the amount of damage caused to the brain of an AD affected person. The Discrete wavelet concept was used to denoise the image, the image was later reconstructed using the 3D construction so that each slice could be depicted. But the method failed to showcase the level of the AD progression.

Segmentation refers to the detection of pixels of various regions, labeling each pixel and grouping them to a particular class based on a particular feature. Shanthi (2013) proposed an approach for segmenting the brain without human aid and for correctly identifying differences in the total volume or scale of the brain. The aim of this study was to detect any significant differences in brain volumes like enlargement or shrinkage.

In brain connectivity studies, Song (2019) has implemented Graph Convolution Neural Networks (GCNNs) as a classifier which makes use of a structural connectivity graph that diagnosis the various levels of disease progression from normal to late mild cognitive disorders in the AD spectrum. The classifier takes in input from the DTI-Diffusion Tensor Imaging and generates a class label as output. Four corresponding class labels are suggested depending on the severity of the impairment. Gnana Jebadas (2016) research described accurate segmentation of WM from structural Magnetic Resonance (MR) images is essential in identification and quantification of atrophy in WM.

Hans et al (2019) proposed a novel technique to WMH segmentation using an unsupervised trained CNN auto encoder which detected cerebral small diseases. As supervised CNN's need lot of time to manually outline lesion labels for training, an unsupervised CNN comes to the aid. An auto encoder with fully convolutional layers and a leaky rectified activation function was used with an N4 bias correction method to remove all kinds of inhomogeneities. Jeong et al (2019) suggested the use of Saliency U-Net and Irregularity Map (IAM) to lessen the architectural complexity of the U-Net without loss of effectiveness.

The work proposed by Oh (2019) used deep-learning methods for the classification of Alzheimer's disease related neuroimaging results, making substantial progress. However, due to the
widespread challenge of neuroimaging associated with data shortages, end-to-end knowledge which is able to maximize the impact of deep learning yet. A gradient-based visualization method was applied to detect the most significant biomarkers related to AD and pMCI which approximates the spatial impact of the decision of the CNN model. Sarraf et al (2016) used the Convolutionary Neural Network (CNN) and the popular LeNet-5 architecture to sort functional MRI data.

Methods of pattern recognition using neuroimaging data for Alzheimer's disease diagnosis have been the focus of comprehensive studies. Payan et al (2015) developed deep learning methods, particularly sparse auto-encoders and 3D convolutional neural networks, to construct an application that could determine a patient's disease status based on a brain MRI scan.

Sandhya et al (2017) proposed a study describing an pioneering and precise method of segmentation of brain MRIs. The classification of the MR brain image is to know the internal intricate structure of the brain, identify the anomalies and determine various area of interest that help in the decision making of the diagnosis before treatment. This suggested technique was a Multilevel Thresholding (MT) approach based on the Electromagnetism theory and it categorizes the image into three tissues such as White Matter (WM), Gray Matter (GM), and CSF. First the image is preprocessed to remove any kind of dissimilarities ,a technique called Skull Stripping was incorporated to remove the Area of the brain from the skull.A filtering technique involving an anisotropic diffusion filter is used to remove any kind of noise elements present.The Multi level Thresholding has the basics from Otsu’s and Kapur’s thresholding technique along with an Attraction and Repulsion technique.

In the research work done by Hongwei et al (2018) a study using fully convolutional deep network and ensemble models were used to routinely detect WMH using fluid attenuation inversion recovery (FLAIR) and T1 magnetic resonance (MR) scans. Hongwei brought in ideas were base models were put together to form a predictive model. The current work aims in developing automatic segmentation of white matter intensity using a Deep Learning model.

2. Methodology:

When selecting WMH as a biomarker things get a little critical because in most elderly people the presence of white areas in an increase is felt through the research. Thus effectively analyzing the load of WMH, its volume of deposition and areas of occurrence is what the crux of any good model is. And damaged white matter has a longer T2 relaxation time due to its higher content of water. Automatic segmentation is a challenging problem because of its high dimensionality, imaging noise, artifacts and other factors associated. Thus a preprocessing stage always helps.

3. Preprocessing:

The image preprocessing usually consists of brain extraction, skull stripping, Bias field correction and Image registration.

**Brain extraction:**

This process is done to the dataset to remove the skull region from the anatomical region, because the ROI-region of interest is not the skull or any other non brain areas. This process also aids or improves registration and normalization. Here the ROI can be given a label of 1 and the background as 0. For example in a brain MRI scan, the eyes, lips and other fat tissue area can be labeled as 0 and the hippocampus and frontal area of the brain as 1.
**Bias field correction:**

MRI scans often showcase discrepancies in image intensities which are caused as an underlying fact of magnetic field differences rather than anatomical differences. To correct these dissimilarities a bias field corrector can be used in the preprocessing phase. The disrupted MRI image can be retrieved by isolating it by an approximate bias field signal.

**Image registration:**

Is the process that aids transforming different sets of data into one co-ordinate system. It aids in finding spatial/temporal correspondence between the image data and models.

**Fig 1: Processes involved in segmenting a biomarker and classifying stages of AD.**

4. **Segmentation**

Segmentation algorithms are generally divided by two methods of learning: supervised and unsupervised. Semi-automated and fully automated methods can be used. Numerous segmentation methods are based on FLAIR images and can overrate WMH in cortical areas due to their typical high intensity appearance and, where a significant proportion of false positives (FP) are identified. FP adjustment can be made in the preprocessing stages.
5. Implementation: -Exploring the Medical image packages

**Dataset:** OASIS, ADNI dataset, WMH segmentation challenge dataset are available.

Data was gathered from Kuiji et al (2019) initial result of WMH Segmentation Challenge MICCAI 20172017 (https://wmh.isi.uu.nl/data/) and data has a collection of 60 sets of brain MR images (T1 and FLAIR) with manual observations of WMH (binary masks) from three different institutes / scanners. For each patient, a 3D T1-weighted image and a 2D multi-slice FLAIR image are given. Manual explanation has been made by expertise in WMH scoring.

![Figure 2 Plot one slice of the MRI of a subject](image1)

Figure 2 Plot one slice of the MRI of a subject

![Figure 3 Segmentation and superpose the histogram Histogram Visualization- CSF(blue), white matter(green), Grey matter(red)](image2)

Figure 3 Segmentation and superpose the histogram Histogram Visualization- CSF(blue), white matter(green), Grey matter(red)
6. Evaluation

Segmentation objective or automated evaluation is very simple and requires doing a check on the segmented pixels with a defined set of pixels. For any segmentation process, there are mostly three piece of parameters, such as sensitivity, specificity, and precision in segmentation.

**Sensitivity:**
Indicates true positivity and it is the likelihood that a detected or segmented pixel/label belongs to the particular tissue from the ROI.

\[
\text{Sensitivity} = \frac{TP}{TP + FN}
\]

**Specificity:**
It refers to the true negativity and it is the probability that a detected or segmented pixel value does not belong to particular tissue but is more related to the background area. Here TN is the true negativity, FP stands for false positivity and TN stands for true negativity.

\[
\text{Specificity} = \frac{TN}{FP + TN}
\]

**Segmentation Accuracy:**
It indicates the degree to which the segmentation algorithm outcomes are more likely to coordinate with the ground truths. Taking the True positive and the true negative and dividing it with the sum of all the positives and negative values.

True Positive: Occurrence of a pixel which belongs to the ROI.
True Negative: Occurrence of a pixel which does not belong to the ROI.
False Positive: Non-Occurrence of a pixel which belongs to the ROI.
False Negative: Non-Occurrence of a pixel which does not belong to the ROI.

\[
\text{Segmentation Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}
\]

7. Conclusion:

This research work has elaborately collected the various methodologies used in segmenting White Matter Hyperintensities in detecting the various stages in AD. Various techniques like GCNN, CNN,
UNET were used, and compared to ML methods have found a better reception due to its automatic feature extraction techniques. But ML methods like Linear regression and clustering techniques aided in the detection of independent associations between WMH volume and cognitive impairments. But the detection and segmenting of small lesions compared to large ones is still a problem, better methods which could detect false positives and be less location sensitive should be developed.

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