# AUTOMATED FEATURE EXTRACTION ON BRAIN MRI IMAGES FOR PREDICTING MULTIPLE SCLEROSIS PATIENT DISABILITY

By

ALI M. MUSLIM

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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## DEDICATION

***I would like to dedicate my thesis to***

***My late father, My dear mother***
***&***
***My brother Mr. Safaa***
***&***
***All my family members***

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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**September 2022**

**Chairman : Associate Professor Syamsiah Mashohor, PhD**
**Faculty : Engineering**

Many past studies had used multiple MRI scans and protocols to automate the prediction of MS patients' disability. They focused on using non-raw MRI data including clinical, radiological, and general patient information with different study durations. Furthermore, they were using manual and semi-automated features extraction. Unlike previous studies, this study aims to predict MS patients' disability by using automated feature extraction, single MRI scan, and single MRI protocol, without patient follow up. Since each part of the brain controls a specific human body function, the location of brain abnormalities in which lobes would help to identify the type of dysfunction, and at which part of the human body. Different brain abnormality's location may result in different values of MS patient disability scores. Thus, segmenting the brain abnormalities that have a high correlation to the patient's disability and classifying them according to their locations would be significant for disability prediction. This study uses data extracted from 65 MS patients who were from multiple centers in Iraq and Saudi Arabia. The Dynamic Image Thresholding (DIT) method was proposed to segment areas of brain abnormalities on brain MRI. This is followed by an estimation method to segments the brain lobes and brain periventricular region segmentation (BLBPRS). The performance of DIT and BLBPRS methods were evaluated by two experts, radiologists, for each method with an overall performance evaluation of 80% and 79% respectively. A large-scale statistical, volumetric, texture, location, radiological, clinical and ratio-based features were extracted using clinical, radiological, general patient information, and raw-imaging data. From the large-scale features, a correlation analysis is performed to select the highly correlated features used for predicting patients' disability. This was based on machine learning and regression algorithms at the first phase. The proposed methodology is divided into two phases. The first phase aims to investigate the best types of required data, features and algorithms to be used in the final proposed methodology to predict exact EDSS, and different ranges of EDSS. A 5-fold cross-validation has been used to evaluate the performance. In the first phase, all dataset is combined and weak performance was found. In the second phase, the dataset was divided into four groups according to the MRI-Tesla and the condition of a lesion in the spinal cord or not. The division of dataset into four groups produced good performance in EDSS prediction and classification. The best machine learning performance, after the grouping, came from SVM, with an average accuracy, sensitivity, and specificity of 82%, 77%, and 79%, respectively. The best performance from the linear regression had an average RMSE of 0.6 for EDSS step of 2. These results showed the possibility of using fully automated feature extraction, single MRI scan, and single MRI protocols without patient follow-up to predict MS patients' disability.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**PERAHAN CIRI-CIRI BERAUTOMASI BAGI RAMALAN KETAKUPAYAAN PESAKIT SKLEROSIS BERBILANG MENGGUNAKAN IMEJ MRI OTAK**

Oleh

**ALI M. MUSLIM**

**September 2022**

**Pengerusi : Profesor Madya Syamsiah Mashohor, PhD**
**Fakulti : Kejuruteraan**

Kebanyakan kajian terdahulu telah memfokuskan ramalan ketakupayaan pesakit menggunakan imbasan dan protokol MRI berbilang untuk mengautomasi ramalan ketakupayaan pesakit MS dengan tempoh kajian yang berbeza dan menyokong data bukan MRI termasuk klinikal, radiologikal dan maklumat am pesakit menggunakan penyarian ciri-ciri manual atau separa automatik. Kajian ini bertujuan untuk meramal ketakupayaan pesakit MS menggunakan penyarian ciri-ciri berautomasi, imbasan MRI tunggal dan protokol MRI tunggal dan tanpa rawatan susulan pesakit. Setiap bahagian otak mengawal fungsi tubuh manusia spesifik. Lokasi keabnormalan otak, iaitu lobus mengenal pasti jenis ketakfungsian bahagian tubuh manusia yang terkesan yang mengakibatkan nilai yang berbeza bagi skor ketakupayaan pesakit. Oleh sebab itu, pembahagian keabnormalan otak yang mempunyai korelasi yang tinggi ke atas ketakupayaan pesakit dan mengklasifikasikan mereka berdasarkan lokasi adalah signifikan bagi peramalan ketakupayaan. Oleh itu, penyarian ciri-ciri berautomasi merupakan peraturan penting bagi ramalan ketakupayaan MS. Data daripada 65 pesakit MS telah digunakan dalam kajian ini dan telah dikumpul dari pelbagai pusat perubatan di Iraq dan di Arab Saudi. Kaedah ambang imej dinamik (DIT) telah disyorkan dalam kajian ini bagi membahagikan kawasan keabnormalan ke atas MRI otak. Kemudian, kaedah anggaran bagi membahagikan lobus otak dan kawasan di sekeliling periventrikular otak juga telah disyor bagi membahagikan lobus otak mengikut lobus frontal, parietal, temporal dan occipital, di samping kawasan di sekitar kawasan periventrikular otak. Dari ciri berskala besar, analisis korelasi telah dijalankan bagi membahagikan ciri berkorelasi tinggi sebagai input bagi kerangka ramalan berdasarkan pembelajaran mesin dan algoritma regresi. Metodologi yang disyor dibahagikan kepada dua fasa, fasa pertama bertujuan untuk menyelidiki jenis terbaik bagi data yang diperlukan dan algoritma ramalan yang digunakan dalam fasa kedua dalam mengutarakan metodologi cadangan akhir. Dalam fasa pertama, jenis data input yang berbeza termasuk data klinikal, data radiologikal dan maklumat am pesakit dan pelbagai algoritma ramalan telah digunakan bagi meramal EDSS yang tepat dan julat EDSS yang berbeza. Latihan dan pengujian telah dijalankan dengan 5 lipatan pengesahsahihan silang bagi memilih kaedah peramalan terbaik. Pengesahan silang 5 kali ganda telah

digunakan untuk menilai prestasi. Dalam fasa pertama, semua dataset adalah digabungkan dan prestasi lemah diperolehi. Dalam fasa kedua, dataset dibahagikan kepada empat kumpulan mengikut jenis MRI-Tesla dan keadaan lesion pada saraf tunjang atau tidak. Pembahagian dataset kepada empat kumpulan menghasilkan pencapaian yang baik dalam ramalan EDSS dan pengkelasan. Prestasi pembelajaran mesin terbaik selepas pengelompokan adalah daripada SVM dengan masing-masing ketepatan, sensitiviti dan spesifisiti iaitu 82%, 77% dan 79% manakala prestasi terbaik dari regresi linear adalah dengan purata RMSE 0.6. Dapatan tersebut memperlihatkan kewajaran ramalan ketakupayaan pesakit MS menggunakan penyarian ciri-ciri berautomasi sepenuhnya, imbasan MRI tunggal, protokol MRI tunggal dan tanpa rawatan susulan pesakit.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Date: 9 March 2023

**Declaration by Members of Supervisory Committee**

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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| | |
|---|---|
| 3D | Three Dimension |
| 9HPT | 9-Hole Peg Test |
| AUC | Area Under the Curve |
| BET | Brain Extraction Tool |
| BLBPRS | Brain Lobes and Brain Periventricular Region Segmentation |
| BPF, | Brain Parenchymal Fraction |
| CIS | Clinically Isolated Syndrome |
| CNN | Convolutional Neural Network |
| CNS | Central Nervous System |
| CPH | Cox Proportional Hazards |
| CPU | Central Processing Unit |
| CSF | Cerebrospinal Fluid |
| DT | Decision Trees |
| DTI | Diffusion Tensor Imaging |
| DWI | Diffusion-Weighted Imaging |
| EDSS | Expanded Disability Status Scale |
| EN | Elastic Net Regression |
| FA | Fractional Anisotropy |
| FLAIR | Fluid Attenuated Inversion Recovery |
| FN | False Negative |
| FP | False Positive |
| FS | Functional Systems |
| GM | Gray Matter |
| JC | Juxtacortical |

| | |
|---|---|
| KNN | K-Nearest Neighbour |
| LASSO | Least Absolute Shrinkage and Selection Operator |
| LK | Linear Kernel |
| LR | Linear Regression |
| MAE | Mean Absolute Error |
| MD | Mean Diffusivity |
| ML | Machine Learning |
| MRI | Magnetic Resonance Imaging |
| MS | Multiple Sclerosis |
| MSE | Mean Squared Error |
| MSFC | Multiple Sclerosis Functional Composite |
| PPMS | Primary-Progressive Multiple Sclerosis |
| RAM | Random Access Memory |
| RF | Random Forests |
| RMSE | Root Mean Square Error |
| RRMS | Relapsing-Remitting Multiple Sclerosis |
| SDMT | Symbol Digit Modalities Test |
| SP | Spinal Cord |
| SPMS | Secondary-Progressive Multiple Sclerosis |
| SPSS | Statistical Package for The Social Sciences |
| SVM | Support Vector Machines |
| T25W | Timed 25-Foot Walk |
| T2LL | T2-Weighted Lesion Load |
| T2WI | T2 Weighted Image |
| TN | True Negative |

| | |
|---|---|
| TP | True Positive |
| WM | White Matter |
| 3D | Three Dimension |
| 9HPT | 9-Hole Peg Test |
| AUC | Area Under the Curve |
| BET | Brain Extraction Tool |
| BLBPRS | Brain Lobes and Brain Periventricular Region Segmentation |
| BPF, | Brain Parenchymal Fraction |
| CIS | Clinically Isolated Syndrome |
| CNN | Convolutional Neural Network |
| CNS | Central Nervous System |
| CPH | Cox Proportional Hazards |
| CPU | Central Processing Unit |
| CSF | Cerebrospinal Fluid |

# CHAPTER 1

# INTRODUCTION

## 1.1 Overview

This chapter introduces the study by focusing on what Multiple Sclerosis (MS) is. It then delves into the background of the study, problem statement, motivation for this study, the research objectives, scope of this study, and the contributions. It ends with an organization of this thesis.

Multiple Sclerosis (MS) is a chronic, progressive autoimmune condition. It affects the central nervous system (brain and spinal cord). MS occurs when the immune system attacks the myelin that protects the nerve fibers in the brain and the spinal cord (Altermatt et al., 2018; Colato et al., 2021; Ghribi et al., 2018; Pinto et al., 2020) MS is considered a rare disease in Asia (Ruggieri et al., 2021) (Colato et al., 2021; Kaunzner & Gauthier, 2017). The exact cause of MS is still unknown. However, several risk factors have been suggested as possible causes of MS. They include one's race, genes, being female, the climate, the lack of sunlight, a lack of vitamin D, smoking, teenage obesity, or even viral infections (Altermatt et al., 2018; Colato et al., 2021; Pinto et al., 2020). Magnetic Resonance Imaging (MRI) has been increasingly used for diagnosing MS. MRI findings of the brain and spinal cord serve as the most helpful information which helps in the diagnosis of MS. It can also substitute as clinical findings. MRI has a crucial feature for making diagnosis, treatment decisions, monitoring treatment responses, and monitoring MS disease progression (Altermatt et al., 2018; Colato et al., 2021; Ghribi et al., 2018; Pinto et al., 2020).

McDonald's MS diagnostic criteria state that the most significant areas of findings in MRI are location, type, size, and number of MS-lesions (Ridler, 2018). Several MRI protocols have been used to evaluate MS abnormalities, for instance, fluid-attenuated inversion recovery (FLAIR), T2-weighted, and T1-weighted with, and without contrast. FLAIR MRI has a vital role in diagnosing MS (Filippi et al., 2016, 2019b; Trip & Miller, 2005). The MS-lesions in FLAIR MRI are typically hyperintense. Nonetheless, MS is a rare disease in Iraq and other Middle Eastern countries, with a prevalence of between 0 and 20 per 100,000 (Nguengang Wakap et al., 2020). As a result of this, there is a lack of sample size thereby causing difficulty in the extraction of data for studies conducted in Middle Eastern countries.

The Expanded Disability Status Scale (EDSS) is considered a golden standard when aiming to score MS patients' disabilities (Bonomi et al., 2021). The EDSS is a clinician-administered assessment scale. It is used as a tool to evaluate the eight functional systems of the patient's central nervous system. The EDSS scores range between 0 (no disability) to 10 (death due to MS), with an increment interval of 0.5 (Carass, Roy, Jog, Cuzzocreo, Magrath, Gherman, Button, Nguyen, Bazin, et al., 2017; Danelakis et al., 2018; Dewey et al., 2017; Doyle et al., 2018; Gonzalez et al., 2017; Rummel et al., 2018). Figure 1.1, shows the EDSS scores' range, with its corresponding disability level, and the progression of the disease. To assist the EDSS, eight neurological Functional Systems (FS) need to be scored by an expert. The scoring range for these eight neurological FS examinations is between 0-4 and 0-15 (Gonçalves et al., 2018). The lowest score means normal FS, while the highest score means complete loss of function in a particular neurological FS. Scoring MS patients' disability level through the EDSS is time-consuming. It also requires expert knowledge and inter-and intra-subject variations.

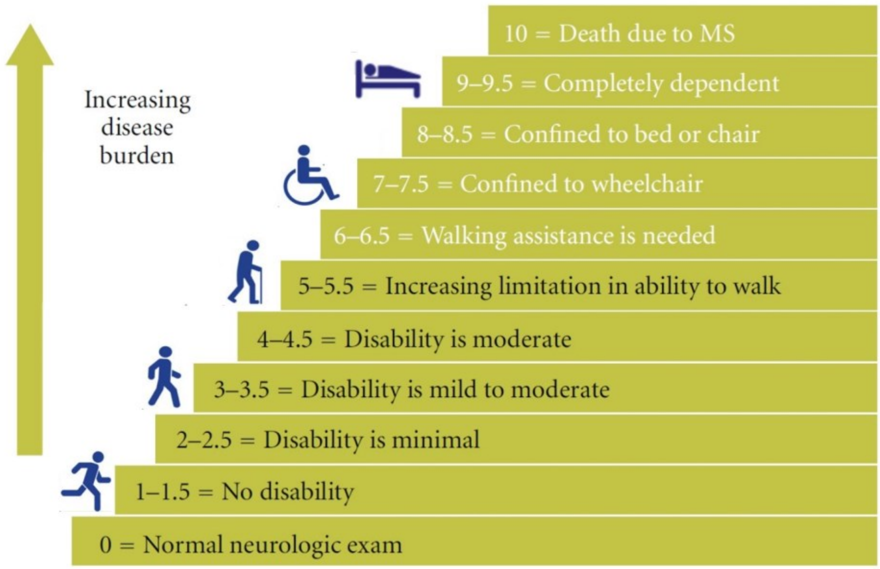


**Figure 1.1 : EDSS scores range with their corresponding disability level as well as the progression of the disease**

Identifying the central nervous system's abnormalities is crucial because it significantly predicts patients' disability levels. MS lesions within the brain and the spinal cord are considered as the key features in identifying the central nervous system's abnormalities. Each location within the central nervous system is responsible for controlling a specific function in the human body. Thus, the abnormality of any part of the central nervous system would directly affect a specific function of the human body corresponding to that location (Filippi et al., 2019a). In that regard, identifying the central nervous system abnormality's location is considered a key feature in predicting patients' disabilities.

The traditional method for evaluating the central nervous system's abnormalities is done by a specialist who uses manual MS-lesion detection. It considers any seen lesions or abnormalities by using one or several MRI protocols, such as T2-FLAIR, T2-weighted and T1-weighted with or without contrast.

There are several challenges in using the automated method to predict MS disability when using MRI. First, Multiple Sclerosis is a clinically heterogeneous disease with different symptoms, behaviour, and CNS abnormalities among patients. Second, the MRI is inhomogeneous due to different image sizes, brain sizes, image intensity range, and MRI Tesla. This makes the automated system, which detects and quantifies MS abnormalities, a difficult task. As a result of this, most studies focusing on disability prediction tend to use supporting non-raw MRI data, such as radiological, clinical, and general patient information, which requires human interactions and expert knowledge. Furthermore, they require patient follow-up.

## 1.2 Problem statement

Multiple Sclerosis (MS) patients' disability predictions is significant for diagnosis, treatment decisions, and monitoring the disease's progression. The traditional method to score MS patient disability is the Expanded Disability Status Scale (EDSS), which is scored by eight neurological physical examinations done by an expert. Thus, the prediction of MS disability using brain MRI only is not an easy task. Due to the weak correlation between MRI findings and MS patient disability (Tommasin et al., 2021). However, most of the previous studies focusing on this field were working on multiple MRI scans or MRI protocols. They also used large amounts of patient information requiring multiple visits from patients' follow-ups. Past studies also tend to use supporting non-raw MRI data that require human interactions and expert knowledge. This practice tends to involve variations in terms of inter and intra-expert input as well as radiological, clinical, and general patient information, as illustrated in Section 2.7. As a result, all the previous MS prediction algorithms cannot consider as fully automated prediction algorithms. However, implementing a fully automated system to predict MS disability prediction algorithms using a single MRI scan, single MRI protocols, without patients' follow-up and also without clinical data, is challenging. All the previous mentioned related work issues and limitations are motivating us to implement a fully automated prediction algorithms based on fully automated feature extraction method and without clinic data.

As a clinically heterogeneous disease, MS brain abnormalities vary in size, shape, number, and location. In addition, MRI scans have a high variation in size, quality, Tesla, and intensity range. Most past studies (Law et al., 2019; Roca et al., 2020; Tommasin et al., 2021) that had examined this area had detected traditional brain abnormalities, such as seen lesions only, without considering the hidden or unseen brain abnormalities. Thus, automated segmentation of brain abnormalities that have high correlation to the patients' disabilities may not be an easy task although it is significant for MS patients' disability prediction.

Secondly, each location within the central nervous system is responsible for controlling a specific function of the human body. This means that the abnormalities at any central nervous system would directly affect a specific function of the human body which corresponds to that location (Filippi et al., 2019a). Furthermore, abnormalities at a specific brain region, such as the brain periventricular region, have higher correlations to the patients' disabilities than other brain regions, which have a substantial correlation to patients' disabilities when compared to other brain regions (Correale & Gaitán, 2015). Thus, identifying the location of the brain abnormalities based on brain lobes and brain periventricular region can help us to identify which human body function is affected by the abnormalities. This task is challenging because of the high variation of the human brains in terms of size, shape, and abnormality level. In addition to that, this task also requires high-quality 3D imaging. Most of the previous studies had used radiological information extracted by the expert for brain abnormalities localization (Gajofatto et al., 2013).

Lastly, traditional MRI findings have been found to be weakly correlated to MS patient's disabilities (Correale & Gaitán, 2015). Thus, most of the previous studies used supporting non-raw MRI data such as clinical, radiological and general patient information for feature extraction, which required expert knowledge and inter and intra-expert variation. Therefore, extracting and selecting a highly correlated feature to the MS patients' disabilities is active research in the past few years to facilitate MS disability prediction and to enhance the understanding of MS disease. This study aspect can also help identify an imaging biomarker for MS disease.

## 1.3 Motivation

Developing an automated method which can be used to predict MS patients' disability level is significant for the MS diagnosing stage as well as for identifying the progression of the disease. Both aspects are vital and significant for MS treatment plan, medication dose, and for assessing how much the MS patients are responding to the medication. Past studies tend to rely on manual or semi-automated feature extraction methods, which used multiple MRI scans, various MRI protocols, with patient follow ups. This is in addition to the various clinical and radiological data used to support MS patients' disabilities. These methods, as mentioned earlier, not only involved excessive and costly patient follow-ups, but also contained variations in expert input and patient information. These challenges have motivated us to design an automatic feature extraction method which can be used to predict MS disabilities by using a single MRI scan, and single MRI protocols, both of which reduce cost, time, expert knowledge, and muti-visits for the patients. However, this study tries to answer three hypotheses: First, it can automatically segment MS brain abnormalities. Second, it can automatically segment brain lobes and brain periventricular regions using 2D images. Third, it can automatically predict MS patient disability using a fully automated feature extraction method.

## 1.4 Aim and Objectives

Based on the problem statement explained, our study thus aims to design an automatic feature extraction method using brain MRI to predict MS disabilities. The following objectives were thus formulated to fulfil the aim of this study.

1. To investigate a segmentation method for MS brain abnormalities' areas of MR images by using dynamic image thresholding.

2. To design a segmentation method to approximately segment brain lobes and brain periventricular region by using 2D brain MRI.

3. To evaluate the ability of the highly selected features extracted from the segmented MS lesion based on the correlation analysis in order to predict MS disabilities by using machine learning classifiers and the regression method.

## 1.5 Scope of study

This study focuses on 2D FLAIR MRI for patients confirmed with the diagnosis of MS, with an EDSS score range of between 0 to 5, and MRI Tesla of 1.5 and 3. This study uses a dataset collected from multi-centers in Iraq and Saudi Arabia. The proposed method can automatically segment and locate MS brain abnormalities without human interactions by using our proposed dynamic image thresholding, brain lobes, and brain periventricular region segmentation.

A fully automated feature extraction is developed by considering the segmented abnormalities and the locations of the abnormalities in the brain lobes and brain periventricular region. A correlation analysis which used the Pearson correlation coefficient is then performed by using the IBM SPSS statistics version 28.0.1 (Kurtzke, 1983). The Brain Extraction Tool (BET) (Abou Elmaaty et al., 2019; Abouelmaaty et al., 2019; Artemiadis et al., 2018; Filippi et al., 2010) is then conducted for skull striping. Then using, the highly correlated feature to predict the different types of MS disabilities, including exact EDSS, and the different ranges of EDSS, with a step of between 1 to 2.5.

Two datasets were collected from Iraq and Saudi Arabia. These were used with different MRI Tesla of 1.5 and 3, with the EDSS score ranging between 0 to 5. The first dataset has rich patient meta information, including general patient information, such as gender, age, age of onset, and clinical information, like types of medicine, presenting symptoms, number of presenting symptoms, dose the patient has for co-morbidity, and whether or not the patient has abnormalities encompassing pyramidal, cerebella, brain stem, sphincters, visual, speech, motor system, sensory system, coordination, gait, bowel and bladder function, mobility, mental state, optic discs, nystagmus, ocular movement, and swallowing, during one of the neurological examinations. The first dataset was also supplied with radiological information, including manual MS-lesion segmentations representing seen lesions done by experts. Patients' meta-information for the second dataset includes gender, age, MS type, and MRI report. Appendix A illustrates patients' meta-information, and Appendix B shows a sample extracted from patients' documents.

The proposed framework is run using a CPU with the following specifications: (4th Gen Intel® Core™ i7-4700MQ (2.4GHz 1600MHz 6MB) and RAM of 16GB.

## 1.6 Contribution

This study offers a new automated feature extraction method which uses single brain MRI and single MRI protocols to predict MS disabilities. The main contributions of this study can be traced to the extraction method designed. It can be used to:

1. Automatically segment brain abnormalities by using our proposed dynamic image thresholding (DIT) method.

2. Automatically localized the brain abnormalities based on brain lobes and brain periventricular region by using our proposed brain lobes and brain periventricular region segmentation (BLBPRS) method.

3. Extract features automatically based on the DIT, and BLBPRS using single MRI scan, single MRI protocols and without patient follow-ups.

4. Predict patient disabilities (exact EDSS and different ranges of EDSS) by using highly correlated features.

## 1.7 Thesis Organization

This chapter has highlighted the background of MS, the problem statement, the motivation inspiring this study, the research aim, the research objectives, and the scope of this study, followed by the contributions derived. The remainder of this thesis is organized as follows:

Chapter 2 presents a review of the state-of-the-art of related studies of MS patients' disability prediction, diagnosis, and evaluation process. This chapter also looks at the different MRI protocols used to predict MS patients' disabilities.

Chapter 3 presents the proposed automated feature extraction method based on brain abnormalities segmentation, lobes segmentation, periventricular region segmentation, correlation analysis, and disability prediction methods.

Chapter 4 presents the results of the proposed method in detail for correlation analysis, dynamic image thresholding, brain lobes and brain periventricular region segmentation, and disability prediction algorithms.

Chapter 5 presents the conclusions and recommendations for future research work.

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