

شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلو

## بسم الله الرحمن الرحيم





MONA MAGHRABY



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلو



شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية التوثيق الإلكترونى والميكروفيلم

## جامعة عين شمس التوثيق الإلكتروني والميكروفيلم قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



MONA MAGHRABY





# EARLY DETECTION OF ALZHEIMER'S DISEASE USING MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING

By

#### Eman Nabeel AbdAllah Marzban

A Thesis Submitted to the

Faculty of Engineering at Cairo University

in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

in

**Biomedical Engineering and Systems** 

## EARLY DETECTION OF ALZHEIMER'S DISEASE USING MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING

By

#### Eman Nabeel AbdAllah Marzban

A Thesis Submitted to the

Faculty of Engineering at Cairo University

in Partial Fulfillment of the

Requirements for the Degree of

#### DOCTOR OF PHILOSOPHY

in

#### **Biomedical Engineering and Systems**

Under the Supervision of

#### Prof. Dr. Ayman Mohamed Eldeib

Prof. Dr. Yasser Mostafa Kadah

Biomedical Engineering and Systems Faculty of Engineering, Cairo University Biomedical Engineering and Systems Faculty of Engineering, Cairo University

#### Assoc. Prof. Dr. Inas Ahmed Yassine

Biomedical Engineering and Systems Faculty of Engineering, Cairo University

FACULTY OF ENGINEERING, CAIRO UNIVERSITY
GIZA, EGYPT
2020

# EARLY DETECTION OF ALZHEIMER'S DISEASE USING MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING

By

#### Eman Nabeel AbdAllah Marzban

A Thesis Submitted to the

Faculty of Engineering at Cairo University

in Partial Fulfillment of the

Requirements for the Degree of

#### DOCTOR OF PHILOSOPHY

in

#### **Biomedical Engineering and Systems**

Approved by the
Examining Committee

Prof. Dr. Ayman M. Eldeib, Thesis Main Advisor

Assoc. Prof. Dr. Inas A. Yassine, Advisor

Prof. Dr. Ahmed H. Kandil, Internal Examiner

Prof. Dr. Mohamed A. Eldosoky, External Examiner

Professor, Biomedical department, Faculty of Engineering, Helwan

FACULTY OF ENGINEERING, CAIRO UNIVERSITY GIZA, EGYPT 2020

University

**Engineer's Name:** Eman Nabeel AbdAllah Marzban

Date of Birth:9/11/1985Nationality:Egyptian

**E-mail:** eman.marzban@eng1.cu.edu.eg

**Phone:** +2 01003320868

Address: Zahraa ElMaadi, Cairo, Egypt

**Registration Date:** 1/3/2014 **Awarding Date:** .../2020

**Degree:** Doctor of Philosophy

**Department:** Biomedical Engineering and Systems

**Supervisors:** 

Prof. Dr. Ayman M. Eldeib Prof. Dr. Yasser M. Kadah

Assoc. Prof. Dr. Inas Ahmed Yassine

**Examiners:** 

Prof. Dr. Ayman M. Eldeib (Thesis main advisor)

Assoc. Prof. Dr. Inas A. Yassine (advisor) Prof. Dr. Ahmed H Kandil (Internal examiner)

Prof. Dr. Mohamed A. Eldosoky (External examiner)

Professor, Biomedical department, Faculty of

Engineering, Helwan University

#### **Title of Thesis:**

Early Detection of Alzheimer's Disease Using Magnetic Resonance Imaging and Diffusion Tensor Imaging

#### **Key Words:**

MRI, DTI, Alzheimer's, CAMs, Deep learning

#### **Summary:**

Recently, classification and prediction of several diseases can be performed via machine learning methodologies. Of particular importance comes the neurodegenerative diseases, those related to losing neurons and brain cognitive functions, which encompasses Alzheimer's Disease (AD). The large amount of data being readily-available and the increasing computer powers help boost the unleashed growing usage of these machine learning algorithms. The objectives of this work were 1) to find out the class activation maps (CAMs) deriving the network decision, and 2) to detect AD and its earlier pathology; namely, the mild cognitive impairment (MCI), from healthy controls (HC) in robust and low-cost network design. Both tasks were implemented using convolutional neural networks (CNNs).



### **Disclaimer**

I hereby declare that this thesis is my own original work and that no part of it has been submitted for a degree qualification at any other university or institute.

I further declare that I have appropriately acknowledged all sources used and have cited them in the references section.

Name: Eman N. Marzban	Date:
Signature:	

#### **Dedication**

It was such a great trip; through which I faced a lot of hurdles and disappointments and also, I was able to learn a lot.

It would not have been without Allah's support and my parents' that this work had ever reached fruition.

I would like to express my gratitude to my great parents and my siblings; *Raghda*, *Ahmad*, and *Nouran*, for their support in all the tight times, struggles and distresses I have been through.

"Strength does not come from winning. Your struggles develop your strengths. When you go through hardships and decide not to surrender, that is strength". A. Schwarzenegger

### Acknowledgement

I would like express my great appreciation and gratitude to my chief advisor, Prof. Dr. Ayman Eldeib, for his precious support, motivation, and advice throughout this journey. I would like to thank my supervisor, Assoc. Prof. Dr. Inas Yassine, for her support, thorough review, and valuable assistance with ideation. Words are short to describe my gratitude to my mentor Prof. Dr. Yasser Kadah for his invaluable support in the dark moments, his belief in me, and his remarkable reassurance.

I spent a great year with the German center for neurodegenerative diseases (DZNE), in Rostock, Germany, under the supervision of Prof. Dr. Stefan Teipel and Dr. Martin Dyrba. Prof. Dr. Teipel helped us always with medical perspective, interpretation, and corrections. Dr. Dyrba spared no minute to eagerly teach me whatever it takes to get the tasks done. Credits go to Dr. Michel Grothe for his kind consent to use the ADNI data he already had pre-processed.

Further, I treasure the provision I got from my great sister Prof. Dr. Raghda Marzaban, Kasr ElAiny school of Medicine.

I would like to thank my professors and colleagues from Cairo University; especially, Prof. Dr. Ahmed H. Kandil, Assoc. Prof. Dr. Tamer Basha, Assoc. Prof. Dr. Noha Hassan, Prof. Dr. Ahmed A. Morsy, Prof. Dr. Doaa Shawky, Yassin Amer, Ola Sarhan, and Ghaidaa Eldeeb.

Further, I would like to express my appreciation to my colleagues at the German center for neurodegenerative diseases (DZNE) in Rostock. Special thanks go to Fatemah Sakr, Dr. Sara Weschka, Katharina Brueggen, Ivonne Fehr, Irina Jelistratova, Dr. Ingo Kilimann, and Petr Sabik. In addition, I would like to thank Dr. Stefan Kruse, Center for the Study of Democracy (CSD), Leuphana University Lüneburg, Germany for his support and the great Statistics course held in Cairo, Egypt.

I am indebted to the compassion I had with other German Egyptian research short term scholarship's (GERSS) holders. Namely, Dr. Shahinda Rezk, Dr. Ahmed Hemdan, Dr. Nada Mohammad, Esraa Moustafa, and Dr. Sara ElMaghraby. Thanks go to Asmaa Ibrahim and Sally Badra for being always there.

Living in Rostock would have been gloomier without the Ammar's family (Fatemah, Mohammad, and little Malek). I cannot forget the emotional support I had from the cheerful smile of Monika Schmidt's, the warmth of the Pfaff's family (Henrika, Peter, and Lisa my dear friend), the golden-hearted Kristine Liebschner, Sarah Fischer, and Abhishek Dasgupta.

Part of this research project was funded by the German Egyptian research short-term scholarship (GERSS) and grants from the University Medicine Rostock. GERSS is jointly funded by the Ministry of Higher Education and Scientific Research (MHESR) and the German Academic Exchange Service (DAAD).

I would like to cordially thank the DELCODE steering committee for providing me by one of the two datasets used in this work. Further, I would like to express my gratitude for Rostock University for providing me with access to its server for implementing some tasks included in this work.

### **Table of Contents**

DISCLAIMER	I
DEDICATION	II
ACKNOWLEDGEMENT	III
TABLE OF CONTENTS	V
LIST OF FIGURES	VIII
LIST OF TABLES	XIII
NOMENCLATURE	XV
ABSTRACT	XVII
CHAPTER 1 INTRODUCTION	1
1.1 Brain anatomy and cognition	1
1.2 Alzheimer's disease (AD) and mild cognitive impairment (MCI)	2
1.3 AIM OF WORK	6
1.4 Organization of the thesis	7
CHAPTER 2 LITERATURE REVIEW	8
2.1 MEDICAL BACKGROUND	8
2.1.1 Treatment of Early AD	8
2.1.2 RISK FACTORS OF AD.	9
2.1.3 BIOMARKERS OF AD	10
2.2 Brain imaging	11
2.2.1 MRI: THEORY OF OPERATION	11
2.2.2 Brain MRI modalities	16
2.2.3 DIFFUSION TENSOR IMAGING (DTI)	21
2.3 MACHINE LEARNING IN NEUROSCIENCE	31
CHAPTER 3 METHODS	39

3.1 THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE DATASET	39
3.1.1 Introduction	39
3.1.2 INCLUSION CRITERIA FOR THE ADNI DATASET	39
3.2 THE PREPROCESSING PIPELINE: T1 AND DTI	41
3.2.1 T1 PREPROCESSING	41
3.2.2 DTI preprocessing	47
3.3 BASIC ELEMENTS OF CNNs	53
3.3.1 THE INPUT LAYER	53
3.3.2 THE CONVOLUTIONAL LAYER	53
3.3.3 The pooling (downsampling)	54
3.3.4 THE ACTIVATION LAYER	54
3.3.5 Overfitting	55
3.3.6 MATHEMATICAL BACKGROUND	56
3.4 MOTIVATION	58
3.5 THE FIRST APPROACH: INTERPRETABILITY OF CNNs	58
3.5.1 Preprocessing	58
3.5.2 The proposed design	61
3.5.3 VALIDATION ON THE INDEPENDENT DELCODE COHORT AND CHANGING THE THRESHOLD OF THE ROC CURVE	63
3.6 THE SECOND APPROACH: FUSING DTI AND MRI IN CNNs	63
3.6.1 Preprocessing	63
3.6.2 The proposed design	65
CHAPTER 4 RESULTS	68
4.1 First approach	69
4.1.1 DIAGNOSTIC PERFORMANCE	69
4.1.2 A CTIVITY MADE AND DISCRIMINATIVE DECIONS	75

4.1.3	CLASS ACTIVATION MAPPING: ANTERIOR AND POSTERIOR CIN	GULATE CORTEXES75
4.1.4	DISCUSSION	80
4.2 SEC	COND APPROACH	81
4.2.1	DIAGNOSTIC PERFORMANCE	81
4.2.2	DISCUSSION	89
СНАРТЕ	ER 5 CONCLUSIONS AND FUTURE WORK	91
REFERE	ENCES	93
APPEND	OIX A. STATISTICAL MEASURES	112
APPEND	OIX B. HYPOTHESIS TESTING	115
B.1	Definitions	115
B.2	NULL HYPOTHESIS TESTING	115
B.3	THE CHI-SQUARE TEST	116
B.4	THE STUDENT'S T-TEST	117
B.5	THE SIGN TEST	118
APPEND	OIX C. NEUROLOGICAL TESTS	119
C.1	THE GERIATRIC DEPRESSION SCALE (GDS)	119
C.2	THE MODIFIED HACHINSKI SCORE	120
C.3	THE MINI-MENTAL STATE EXAM (MMSE)/FOLSTEIN	121
C.4	THE CLINICAL DEMENTIA RATING (CDR)	121
C.5	THE COGNITIVE CHANGE INDEX (CCI)	124
1 11		Í

## **List of Figures**

Figure 1-1 The Human Brain: Functions [3]
Figure 1-2 The Human Brain: Anatomy [4]2
Figure 1-3 Postulated sequence of neurofibrillary pathology in AD [18]. The depth of the red color is proportional to the density of tangles
Figure 1-4 The brain atlas in the axial section [19]
Figure 1-5 The brain atlas in the coronal section [19]4
Figure 1-6 The brain anatomy in the sagittal section [19]4
Figure 1-7 The progress of MCI patients throughout two years. Peterson et al. [27]6
Figure 2-1 Global annual costs and prevalence of dementia [42]
Figure 2-2 AD interventions [47]9
Figure 2-3 Progression of AD biomarkers with respect to time [7]. CDR: clinical dementia rating
Figure 2-4 Hydrogen protons at normal status [81]11
Figure 2-5 When a magnetic field $(S \rightarrow N)$ is applied, all protons align and precess parallel and antiparallel to its direction [81]12
Figure 2-6 Formation of the longitudinal magnetization vector Mz [81]12
Figure 2-7 Formation of the transverse magnetization vector M <sub>xy</sub> [81]13
Figure 2-8 Protons dephase and lose energy in the form of heat dissipated to the tissues and the longitudinal magnetization vector $M_z$ regrows [81]13
Figure 2-9 Different values for repetition time (TR) and echo time (TE) [84]15
Figure 2-10 T1-weighted versus T2-weighted brain images [85]16
Figure 2-11 <sup>11</sup> C PIB distribution on lateral and medial cortical surfaces of the brain hemispheres [95]
Figure 2-12 Scans for an MCI subject who did not convert to AD during follow up [87]19
Figure 2-13 The significant changes in MO and FA. The first row is for pMCI and the second is for the sMCI [105]
Figure 2-14 Stress tensor as an example of a rank-three tensor [109]22