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ADiag: Graph Theory and Deep Learning Based Diagnosis of Alzheimer's Disease †

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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.
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Abstract: Alzheimer's Disease (AD) is the most widespread neurodegenerative disease, affecting over 50 million people across the world. While its progression cannot be stopped, early and accurate diagnostic testing can drastically improve quality of life in patients. Currently, only qualitative means of testing are employed in the form of scoring performance on a battery of cognitive tests. The inherent disadvantage of this method is that the burden of an accurate diagnosis falls on the clinician's competence. Quantitative methods like MRI scan assessment are inaccurate at best, due to the elusive nature of visually observable changes in the brain. In lieu of these disadvantages to extant methods of AD diagnosis, we have developed ADiag, a novel quantitative method to diagnose AD through graph theory and deep learning-based analysis of large graphs based on thickness differences between different structural regions of the cortex. ADiag is adept not only at differentiating between controls and AD patients, but also at predicting progression of Mild Cognitive Impairment (MCI) to clinical AD.

Keywords: Alzheimer's Disease; Graph Neural Network; Cortical Thickness; Network Graphs; ADNI

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1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disease affecting more than 50 million people worldwide [1]. Though AD is usually not the direct cause of death, it is causally linked to other terminal pathologies like pneumonia. The cause of AD is not precisely known, but the buildup of aggregations of misfolded proteins (beta-amyloid and tau proteins) in the hippocampus and the temporal lobe has been cited as a factor. These aggregations are neurotoxic and progressively kill cortical neurons; this process can be understood as a progressive decrease in cortical thickness.

No treatments exist yet, but timely diagnosis can contribute to an improved quality of life for the patient. These diagnostic methods, however, are extremely qualitative in nature; one such test, and a correct diagnosis is solely based on the clinician's competence and not on quantitative backing; this is the major cause of the high rate of misdiagnosis. In lieu of this, it is essential that efficient quantitative methods of AD diagnosis are developed. Quantitative AD testing is restricted to cerebral biopsy [2] and is not widely implemented: being invasive, there is a high risk of infection, which can be debilitating for senior citizens. In fact, a conclusive diagnosis of AD is done only after the patient has passed away and an autopsy has been performed. Other non-invasive quantitative methods have

been developed but are still experimental; they rely almost exclusively on supervised learning and are thus inherently data hungry and inaccurate.

Graph Neural Networks (GNNs) are a powerful tool to aid in AD diagnosis, simply because the brain can also be represented as a network graph, defined by distinct nodes (representing different structural and functional regions of the brain), and the edges, representing neuronal connections between these regions of the brain. ADiag is thus a GNN model that leverages the graph representation of the brain to diagnose Alzheimer's Disease.

2. Materials and Methods

2.1. Data Acquisition

Data used in this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) Database. ADNI was launched in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

In 2011, Cuignet et al. (2011) [3] quantitatively compared the performance of various classification methods, resulting in comparable metrics. For the purpose of this study, 260 T1-weighted cortical MRI scans were chosen as a subset of the 509 scans of Cuignet et al. (2011). These 260 scans were subdivided into three groups based on subject's MMSE and CDR scores: Cognitively Normal (CN), Alzheimer's Disease (AD), and Mild Cognitive Impairment (MCI). The MCI group was further divided into two groups, MCI conversion to AD (MCIc) and MCI non-conversion to AD (MCInc), both taken in a three-year period.

Table 1. Criteria for Subdivision into CN, AD, MCI.

Group	CDR	MMSE
CN	0	24-30
AD	0.5-1	0-22
MCI	0.5	18-24

2.2. Cortical Thickness Extraction and Graph Creation

MRI scans were registered to MNI stereotactic space, and then resampled to the Desikan-Killiany atlas. The parcelled surface was then subject to cortical thickness extraction using Freesurfer [4] suite, with the recon-all and qcache flags applied. Each cortical surface consisted of approximately 290,000 discrete vertices. Thickness features were then passed through the VisualQC pipelines to ensure the absence of irregularities stemming from bias field and abnormal signal intensity regions.

The thickness data extracted by FreeSurfer was then processed by the graph generation software Graynet [5]; here, differences in cortical thickness between functional regions of the brain were used as parameters to define the weight of the different connections. Large differences in thickness were taken to define relatively weaker connections than those defined by smaller thickness differences. Obviously, the strength of these connections was defined by the edge weight between connected nodes.

These nodes were taken to be aggregations of vertices (defined by absolute cortical thickness values); the number of vertices incorporated into each node was inversely proportional to the number of nodes in the graph, and thus the size of the graph. To preserve the detail and intricacies of the thickness disparities, we chose a relatively small number

of 250 vertices to be aggregated into each node. Furthermore, we also calculated distance between different nodes using Manhattan distance. The graph of each scan had exactly 1162 nodes, and 6,74,541 edges between these nodes.

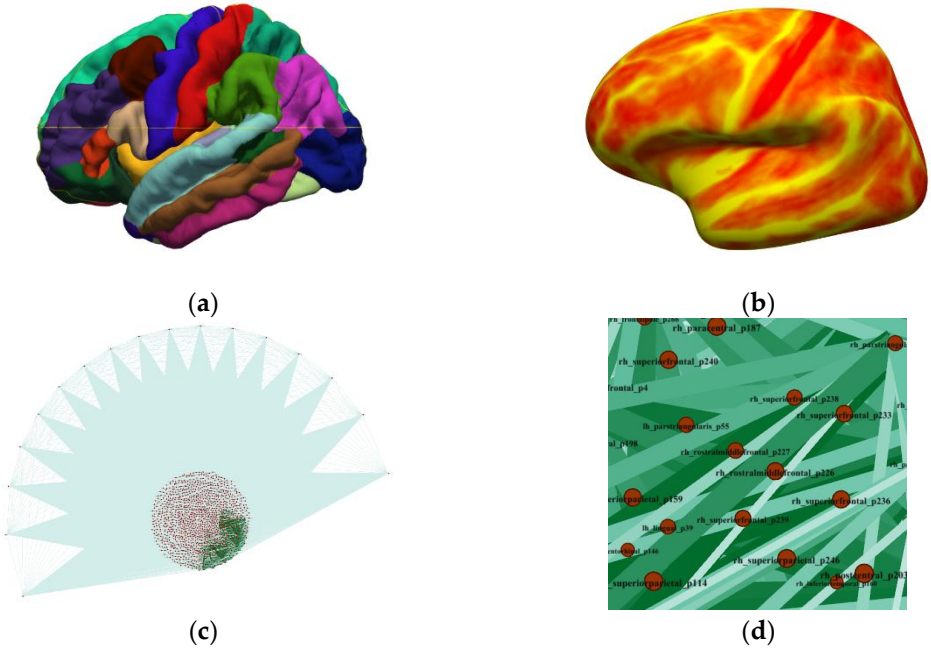
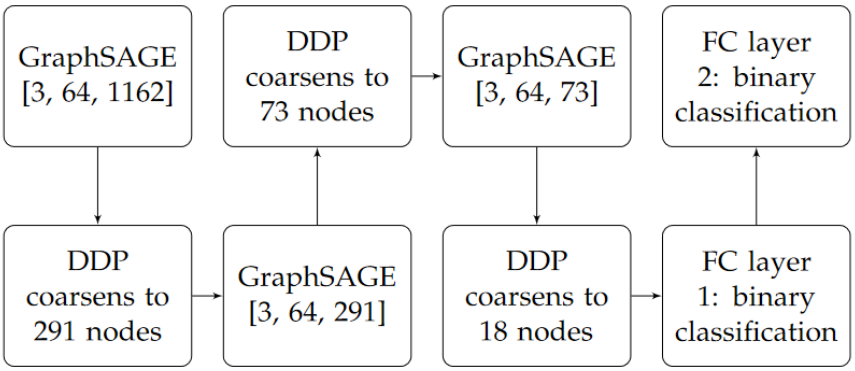


Figure 1. Preprocessing stages of MRI scan: (**a**) Parcellation of cortical surface into cortical regions based on Desikan-Killiany Atlas; (**b**) Thickness map of surface, where intensity of color equates to thicker surface; (**c**) Graph representation of cortical surface; (**d**) Close-up view - graph representation of right frontal lobe.

2.3. Graph Neural Network Structure

Our GNN deep-learning model consisted of three dense GraphSAGE [6] convolutional layers that took the number of inputs, output and hidden channels as input parameters. Each of these layers performed inductive learning on the graphs by aggregating nodal information at each successive iteration, thereby simultaneously incorporating information from far reaches of the graph and increasing the amount of information available to each node. The GraphSAGE layer has several advantages, of which two are salient: the inductive learning process allows for information-rich, aggregated representations of each node, and the neighborhood aggregation process allows for even unseen nodes to be included in the learning process.

The processed graph outputted by the GraphSAGE layer then undergoes pooling in the DDP layer [7]; the goal of the pooling layer is to methodically reduce the coarsen the graph from 1162 nodes down to 18 nodes so that it can be easily classified. Each pooling layer reduced the number of nodes by approximately 75%, such that the graph was coarsened down to 18 nodes before being fed to the fully connected layers for binary classification.



Scheme 1. Layout of Neural Network used in ADiag.

3. Results

With respect to AD vs CN, after running the model over 150 epochs, we observed a peak validation accuracy of 80.1% and a training loss of 0.71. To improve accuracy and decrease training loss, we applied batch normalization, k-fold cross-validation, and applied learning rate optimization. This increased accuracy up to 83.44%, and decreased loss to 0.695. Specificity and sensitivity values were also extremely high, with 85.7% specificity and 70.4% specificity calculated. These accuracy and loss values, however, are preliminary and will almost definitely be drastically improved with increased training data.

In classifying MCIc vs MCInc, we observed a peak validation accuracy of 75.38% and a slightly higher loss value of 0.76, even after optimization. We also observed a sensitivity of 68.6% and a specificity of 80.2%.

Analysis of connectivity patterns revealed significantly diminished interlobar connections in MCI patients, with MCIc patients showing diminished right temporal lobe (RTL) edge weights compared to MCInc. Compared to NC, AD patients had significantly weaker interlobar and intralobar edges, with the most stark difference observable in RTL edges .

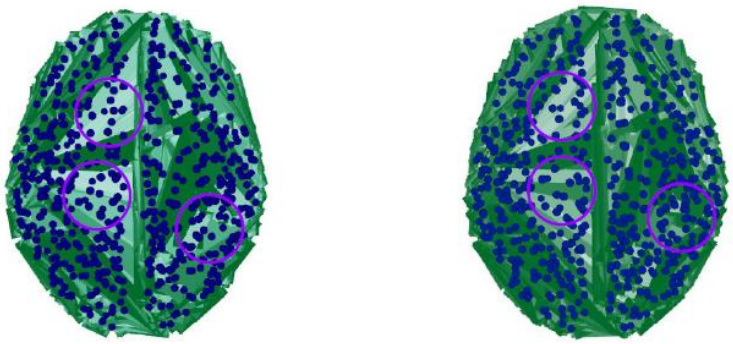


Figure 2. Side-by-side comparison of top-view AD graph (left) and CN graph (right), with visually observable edge-weight disparities circled in purple. Apart from interlobar edge-weight discrepancies, the RTL edge weight is observed to be significantly weaker in AD graph versus CN graph.

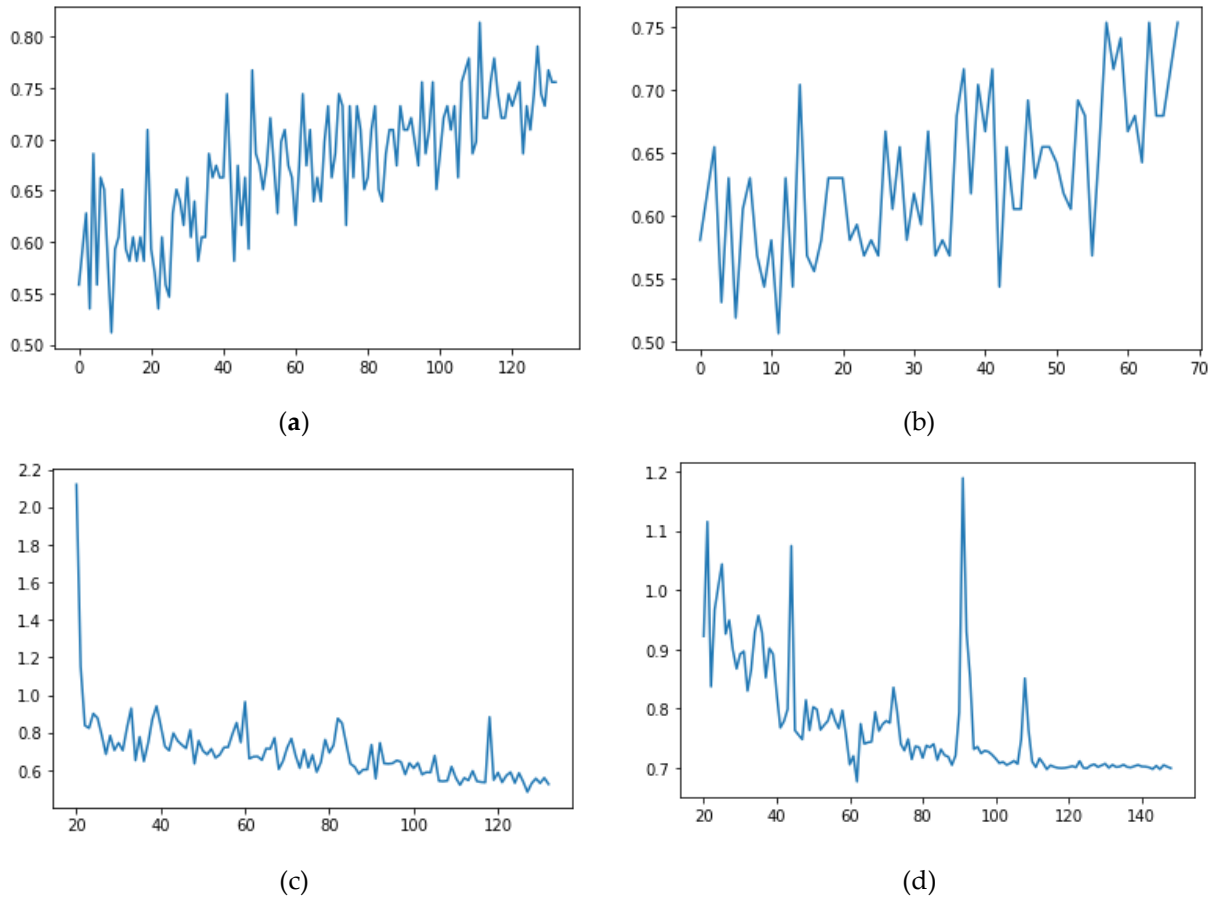


Figure 3. Side-by-side comparison of accuracy values for AD v CN (**a**) and MCIc v MCInc (**b**); Side-by-side comparison of loss values for AD v CN (**c**) and MCIc v MCInc (**d**).

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